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P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

MARKER RESEARCH PLANS DESCRIBED; NCAB MAY CONSIDER ASKING FOR SPECIAL STUDY SECTION FOR THOSE GRANTS

Recommendations for modification and expansion of cancer marker research, how the program is administered by NCI, and how it is reviewed by NIH surfaced during a presentation on markers at the recent meeting of the National Cancer Advisory Board by Robert McIntire,

(Continued to page 2)

In Brief

AUTO WORKERS NOT AT INCREASED RISK OF BLADDER CANCER, BUT TRUCK DRIVERS ARE, NEW STUDY SHOWS

AUTO INDUSTRY employment is not associated with excess risk of bladder cancer, but there is evidence of increased risk for truck drivers, a study by NCI and Michigan Cancer Foundation investigators has found. The study, published in the February issue of the *Journal of the National Cancer Institute*, suggests that exposure to motor exhausts and traffic fumes may be the primary factors involved. . . . **ANOTHER STUDY**, also by NCI's Environmental Epidemiology Branch and published February in *JNCI*, suggests that regular use of mouthwash may contribute to oral and pharyngeal cancers. However, the same issue includes a report by the American Health Foundation that its study found no dose response relationship, and that reports of increased incidence could be confounded by use of tobacco and alcohol. AHF concluded that it was not possible in its study to attribute causal significance to the association between daily mouthwash use and oral cancer in women. The fact that other studies have found an association of mouthwash with oral cancer in nonsmoking and nondrinking women suggests that further studies are needed, the AHF report said. . . . **BERNARD FISHER**, director of oncology at the Univ. of Pittsburgh and chairman of the National Surgical Adjuvant Breast & Bowel Project, will receive the Joseph H. Morton Memorial Award from the AMC Cancer Research Center this month. The award will be presented at the meeting of the International Assn. for Breast Cancer Research in Denver March 20-24 for his "sustained and outstanding contributions to the conquest of cancer". . . . **TOM PETRI**, Republican congressman from Wisconsin, has introduced legislation to abolish the federal tobacco subsidy and regulation of tobacco farming. He is counting on support from health groups as well as farmers who are severely limited or frozen out of tobacco growing by the regulations. . . . **REWARD FOR** information leading to arrest and conviction of the person who murdered Fred Conrad has been increased from $15,000 to $50,000. Charles LeMaistre, president of the Univ. of Texas Cancer Center, where Conrad was vice president for patient care, said a drive to secure the reward money had been undertaken by friends of Conrad who are determined the "senseless murder" will not go unsolved.

MCINTIRE SAYS BEST USE FOR MARKERS NOW IS TO MONITOR COURSE OF THERAPY

(Continued from page 1)

chief of the Diagnosis Branch in the Extramural Research Program of the Div. of Cancer Biology & Diagnosis.

McIntire told the Board that he had several recommendations, "not really recommendations to the Board, but recommendations for our program—things that we are either in the process of doing or hope to be doing in the near future." They were:

- Expansion of the study to select a battery of appropriate markers for small cell and non-small cell bronchogenic carcinoma to include selection of groups of markers for other major tumor types.
- Emphasize through the grants program that studies be carried on during periods of active therapy, "so we can most accurately find those markers that correlate with change in tumor size."
- Increase the availability of tumor marker assays in cancer centers, "so that the appropriate markers could be done wherever protocols have appropriate patients for them. I think at the present time many of the markers have to be sent to various institutions around the country, and perhaps the results are not coming back as rapidly as they might, or they're not obtained as frequently as might be optimum."
- Evaluation of the new monoclonal antibodies. "I think that because of the upsurge in research in markers, due to the ability to make potentially more specific antibodies with monoclonal hybridoma techniques, we're seeing that people are perhaps evaluating these antibodies in a much more careful fashion than they have in the past, using tissue sections to carefully look at specificity and looking at all normal tissues throughout the body to look for potential areas of cross reactivity."
- Use markers in in vitro systems and with transplants of human tumors to nude mouse systems, "so that the metabolism of the markers could be studied, to get a more accurate idea of the correlation between tumor size and concentration of the marker in whatever biological fluid is being monitored."
- Increase the availability of sera for the testing of the monoclonal antibodies, which are coming along with such rapidity, "and just basically to improve the evaluation of markers."

Board member Rose Kushner was critical of what she said was the "unfocused" manner in which grant applications for marker research are assigned to study sections. "For two years now I have been watching the pink sheets (review summary statements) come through and seeing that marker research, which has a very clearly defined clinical application, is helter skelter throughout the study sections of NIH. Monoclonal antibodies, which at this point are a marker for early detection of a recurrence or a metastasis, may have therapeutic applications some day. The enzymes and the histochemical things and the biochemical things and the biological things are all scattered in various areas."

Kushner said she had asked McIntire if it would be possible to create a new study section, either within the NIH Div. of Research Grants or NCI, specifically for tumor marker research. It should include clinicians, Kushner said, "who would have an appreciation of the value clinically, rather than just as a pathological oddity, or a biochemical oddity."

Kushner charged that Hoffmann-La Roche and "all the big pharmaceutical companies are advertising markers which are very expensive and are at this time really not useful for routine care. But people are paying for them."

Board member Victor Braren commented, "Unfortunately, for the general public, there has been a very bad thing happen, in my opinion, in prostatic cancer. A company was allowed to market what they told the public was "the male Pap test." This was an unfortunate demonstration to the laity because in fact the determination of the serum acid phosphotase can in no way be parallel to the Pap test. That advertising has since been removed from the market."

Kushner offered a motion that the Board "pursue whatever avenues need to be pursued to create a new study section, whether it be ad hoc or newly chartered, specifically for tumor markers."

McIntire said a staff review still in progress had counted about 180 applications in marker research during a one year period. He expected the total to reach about 270 when the count is completed, and said they were reviewed by about 30 different DRG study sections.

NCI Director Vincent DeVita asked how many of those applications would be attempts to apply markers in some clinical studies, as opposed to development of the marker. "One of the problems we face is that development of the marker occurs whenever there happens to be somebody working in that area. It could be a microbiologist or a biochemist. The clinical evaluation may not belong in any of it."

McIntire said he guessed that less than half of the markers being studied now are "reaching any sort of clinical applicability where they're at the point of attempting to correlate them with the cancer in the patient."

Board member Janet Rowley suggested that more information was needed to determine if a problem in review exists, "whether it's best dealt with by some kind of special study section or whether there are alternative mechanisms that might be more effective for achieving the same end."

Sheldon Samuels pointed out that some markers are associated with diseases other than cancer. "Shouldn't there be an NIH committee that looks

at the marker issue, rather than just the cancer marker issue? It seems to be much broader than that."

McIntire agreed and noted that many marker grants have dual assignments with other institutes. "Our main interest is in those that have some correlating effect with what's happening in the patient, so we could perhaps have a study section that would deal only with those related to cancer."

McIntire said, "We have gathered a large amount of information. We haven't quite completed it, and we haven't had time to analyze it. But within a short time we should know how many studies, how many grants might be appropriate for their own study section. We could even discuss the applications with you, and begin to work out some recommendations. I would prefer to proceed with perhaps a little more factual knowledge about what is actually coming through the system before we make the attempt for a remedy."

Board member Robert Hickey said, "I think it's incumbent upon us to let the scientific community know that we are deeply interested in markers, and proceed on that basis. A certain amount of information has been harvested here and needs to be analyzed."

Board member Roswell Boutwell said, "Based on my experience on study sections, if you bring in things that are so multidisciplinary (as the marker studies described by McIntire), you have many people on the study section who just aren't acquainted with immunology, biochemistry, or cytogenetics, or the various areas and disciplines that are represented. In many ways, it's better if the applications go to a study section that is appropriate to the specific discipline in the developmental stage. So I think more study is necessary before I could vote for a special study section."

Morris Schrier suggested tabling the motion "until we received the printed information so that we can vote intelligently about it."

Kushner then changed her motion to "ask NCI staff to consider ways of studying markers and approaching and focusing on the matter of marker research, including the possibility of a special study section, but not exclusively that, and then report back to the Board with its recommendation."

DeVita suggested that McIntire ask DRG staff about the situation. "If they in fact see a need for it, I'm sure they'll be cooperative and give this at least a try."

Kushner's motion was approved unanimously.

In the discussion following McIntire's presentation on the status of marker research, Harold Amos, member of the President's Cancer Panel, asked, "Is it a fair assumption to make that one of the real problems in marker research is the refinement of the assay for markers to detect subspecies of the apparent enzyme?"

"That's been one of my favorite hypotheses because I think that we have really only gotten the first blush of success with markers," McIntire answered. "The reason is because each investigator uses his or her own antibody and the one getting the negative results could have an antibody that is unsuccessful in picking up the particular marker that is associated with the malignant condition."

"I think that one of the issues in marker research is that everyone would like to have a marker, so there's a lot more spray research than depth research," Amos said. "Is there something that can be done to encourage that?"

"Yes, I think the solution will come through the development of monoclonal antibodies because we're no longer dependent on the life span or blood supply of a rabbit," McIntire said. "We now have unlimited resources for producing antibodies which can be shared around the world by every cancer center or investigator who wants them."

McIntire said the application for tumor markers which he thinks "is most important for us at our present stage is to use them for monitoring the clinical course of treatment. Another available utilization now is the localization of metastatic disease. This generally uses a marker in a reverse fashion, where an antibody to the marker is labeled with the radioactive compound injected into the patient. Then, using nuclear scanning techniques, we try to demonstrate the presence of small metastatic disease that may not be clinically apparent.

"Markers can also be used in a prognosis way and to help in the staging of patients for proper treatment protocol inclusion. Markers can be used as a way of classifying tumors over and above the traditional morphologic classification systems that we're using now. An example of this might be the use of estrogen receptors in breast cancer as a type of classification of the tumor.

"The last three points of applications are ones that I think are more for the future. These are ones where we're looking for cancer in patients who may have signs or symptoms, but at the present state of medical tradition require a histologic diagnosis rather than a serologic diagnosis.

"Then there is the very difficult problem of defining patients who have no symptoms, who are in a group of individuals who may be at high risk, but otherwise have no symptoms as being those that have cancer in that group.

"The screening for premalignant lesions is, I think, some way off in the future and perhaps we ought not to worry so much about that at the present time."

McIntire said cancer markers are analogous to chemotherapy because they are used in close conjunc-

tion with patient observation; may require modification or change; may be improved by utilizing appropriate combinations; and are essential to base selection on both the type of malignancy and the unique aspects of the patient's disease.

Characteristics of an ideal cancer marker are that they are produced and secreted or released by tumor cells; are accessible in a body fluid; have a reasonable degree of specificity for cancer; provide correlation with size of tumor; and are available for quantitative assay.

McIntire defined markers as substances found in blood, urine, and other biological fluids (including saliva, effusions, etc.) that are abnormally elevated or decreased due to the presence of malignant disease.

Example of markers include:

Hormones and precursors and subunits, enzymes and variant isoenzymes, modified nucleosides and bases, glycoproteins (pregnancy proteins, fibronectin, etc.), glycolipids and lipoproteins, oncofetal and tumor associated antigens (CEA, AFP, POA, etc.), regulatory peptides (enkephalin, somatostatin, bombesin, etc.), serum proteins (immunoglobulins, ferritin, pre-albumin, circulating immune complexes, etc.), polyamines, hormone receptors, cell surface constituents (lymphoid markers, histocompatibility AGS, etc.), cell mediated immune function (LAI, lymphocyte proliferation, etc.), blood carbohydrates (red cell antigens, etc.), nuclear proteins (nonhistine protein AGS, nucleolar AG, etc.) antigens detected by monoclonal antibodies, viral antigens (EBV, herpes, hepatitis B, etc.), cytogenetic markers, trace metals, and protease inhibitors.

NCAB SHAPING UP, BUT REGRESSES, FAILS TO MAKE TWO KEY DECISIONS

Those who have had occasion to sit in on meetings of the National Cancer Advisory Board since the six Reagan appointees took their seats last October have been at various times amused, outraged, discouraged, dismayed, flabbergasted, and entertained by the antics of the body which is charged with advising the government on the most extensive and expensive biomedical research program ever undertaken.

"It's a travesty," one observer commented after the November meeting. "These people sound as if they have no idea why they are here. They certainly don't rank with the quality of scientists we have had in the past."

The criticism may have reached the ears of some of the members (and not all of it was directed at the new members). Or, perhaps the learning process has had an effect. In any event, the Board showed signs at the February meeting of shaping up.

The members heard presentations on the cost of cancer and on tumor markers and participated intelligently in the discussions which followed. They thrashed out a reasonable compromise on the Organ Systems Program (which probably did not make anyone happy but which appears to be workable), with new member Victor Braren playing a prominent leadership role in helping to bring it off.

Five of the six October appointees attended the grueling two day weekend session of the Committee on Organ Systems Programs when the compromise was drawn up, along with most of the other Board members, and nearly all of them attended the night meeting of the Budget Committee. In fact, the committee meetings and the three day session of the full Board saw the best attendance by members since the NCAB was established by the National Cancer Act of 1971. Ann Landers was the only absentee.

Members demonstrated without a doubt that they take their appointments seriously, they will work hard, and they can grapple with the tough issues.

The seventh Reagan appointee, Roswell Boutwell of McArdle Laboratory, brought his solid scientific credentials to the scene. He replaces Gerald Wogan, a solid scientist himself whose resignation had raised fears that Reagan might fill that seat with someone unfamiliar with cancer research.

It was not until the agenda item entitled, "The Role of the Board," came up that the nonsense returned.

Barbara Bynum, who as director of the Div. of Extramural Activities is the executive secretary of the Board, made a careful presentation on the legislative mandates and departmental decrees which outline the Board's responsibilities. She presented members with two issues for them to resolve:

—Should individual members receive and/or review only selected grant summary statements, or continue receiving all of them with the inferred responsibility of reviewing them all?

—Should certain committees of the Board be abolished?

In the fashion which has been typical of this Board, no firm decision was reached on either of those questions.

The issue of reviewing all the summary statements came up after the October meeting, when Chairman Tim Lee Carter was appalled by the two foot high stack of paper sent to each member. Bynum sent a questionnaire asking members their preference on (1) receiving and reviewing all; (2) receiving all and reviewing only selected statements; (3) receiving and reviewing only selected statements.

Those who said they wanted to continue receiving and reviewing all of them were Angel Bradley, Braren, Robert Hickey, Gale Katterhagen, Rose Kushner, Morris Schrier, William Powers, and Kash Mostofi (an ex officio member representing the Armed Forces).

Those who said they would like to continue receiving all of them but would be happy to review only selected ones were Ed Calhoon, Carter, Maureen Henderson, Geza Jako, Janet Rowley, and Irving Selikoff.

LaSalle Leffall said he would settle for receiving and reviewing only selected summary statements.

Ex officio members Allen Heim, of FDA, and Denis Prager, of the White House Office of Science & Technology Policy, offered to save NCI a tidy sum on paper and duplicating costs by not getting or receiving any statements. Prager later saved the government his entire salary by resigning.

Bynum had obtained a legal opinion from the HHS general counsel that it would be all right for members to receive only selected statements provided that was acceptable to the director of NIH.

Kushner said that now that legality of the issue had been determined, she would accept assignment of some grants.

"Reading them is one thing; detailed review is something else," Henderson said. "Those of us who read them all can continue."

"I think it is poor practice to assign reviews," Sheldon Samuels said. "People would select those topics about which they have some knowledge. They will never get to our most important function, the review and approval of policy."

"The Board does not review grants as an initial review group but as a review of policy," Bynum agreed.

"I would like to emphasize that you are guardians of the peer review system," NCI Director Vincent DeVita said. "You are not required to read all applications. There are 1200 per meeting. That's a heavy workload."

"I like the idea of assigning all 1200," Cancer Panel member Harold Amos said.

Boutwell said he would like to receive them all.

Braren proposed that each Board member receive all or selected statements as he/she chooses, and review all or selected as each prefers.

Rowley asked if anyone opposed trying for a meeting or two some selective review.

"I would prefer to be responsible for all," Powers said. "I particularly do not want to be singled out for review of an area because of expertise I may have in that area."

"I don't think a certain number should be given to some people," Carter commented. "If we do, something could go wrong. We may have difficulty if we let a few people deal with a few grants. I would rather be responsible for all."

Rowley suggested that every member get all the statements, with some assignment to individuals for more careful review.

At that point, Carter launched into a diatribe in which he charged that some members had accused him of being "unfair and dictatorial" in committee assignments (the discussion of the fate of certain committees had preceded the discussion on grant review. No such charges were made during that discussion).

"If any member thinks he has been treated unfairly, or has not been assigned to the committees he asked for, he has only to come to me," Carter said, crashing his gavel on the table.

No formal action was taken on the review issue. So NCI staff determined later that, for the May meeting, those members who asked to receive all summary statements will get them, and those who asked for selected ones only would have that request honored. Each member will be assigned specific statements for more detailed review.

DeVita and some Board members have referred in previous meetings to overlapping functions of some NCAB committees and those of the Board of Scientific Counselors of the Div. of Resources, Centers & Community Activities, and possibly other division BSCs. The NCAB committees were established to help the Board develop policy on specific programs, and in some cases to conduct detailed review of grants in specific areas. When many of those programs were assigned to DRCCA, they came under the purview of the DRCCA Board.

Bynum presented the Board with a list of committees staff suggested could be abolished. They were Centers & Construction, with an ad hoc committee to be established for construction only; Environmental Carcinogenesis, to be abolished after the Board takes final action on the report in which the committee will present a definition of quantitative risk assessment; Cancer Control & the Community; and Organ Systems.

The compromise on the Organ Systems Program included a provision asking that the Board's Organ Systems Program Committee be kept in existence, so that took care of that issue.

Henderson offered a resolution to abolish the "duplicating committees. I suggest that the board of scientific counselor meetings are of interest to this Board, and encourage members to attend rather than have overlapping committees."

Carter asked Henderson to present the resolution in writing, "for consideration later."

"There is a limited number of committees which should be standing," Henderson continued. "We should identify as essential, the committees on Planning & Budget, Activities & Agenda, and Special Actions."

Hickey, who chairs the Committee on Review of Contracts & Budget of the Director, said that committee was essential.

Braren suggested that Bynum should continue her presentation "and we can take up the question of committees later." However, the Board never returned to that question, leaving it unresolved.

Staff later decided that the committee structure would have to remain in place at least until the May meeting, when the issue will be brought up again.

Other issues which went unresolved, after being presented by Bynum, included:

—Should there be a limit on committee membership, and how many committees could a member serve on?

—Should some committees include in their memberships only NCAB members? (Some have brought in outside consultants for specific roles.)

—What records should be kept of meetings?

The Board did take action of these questions:

—When should members be compensated for attending committee meetings?

—To what extent is it appropriate to compensate members who are attending committee meetings only as observers?

DeVita pointed out that the NCAB charter "is something we prepare, and you can have whatever committees you want. You will not offend NCI staff by saying you want a committee. They meet and function under the chairman of the Board. Some committees of the Board were established to cover programs in the Office of the Director. When those programs went to divisions with boards of scientific counselors, those Board committees no longer were necessary, although you can have overlap if you feel it is useful. You can have any committee you want, and have any meetings you want."

Carter commented that some members had discussed with him the question of whether per diem and expenses would be paid for members attending committee meetings. "It should be paid," he said.

"I'm surprised that it's not," DeVita said.

The Board digressed into a discussion which turned emotional and resulted in another gavel slamming exhibition by Carter.

"Can we summarize the responsibilities of the Board?" Selikoff asked. "Are we the public's representatives to NCI?"

"As I interpret it, we are," Carter said. "There's no question, we represent the people."

"We bring perspective, but we serve as members collectively, not delegates or representatives," Henderson said.

"The public sometimes believes we are their representatives, keeping an eye on things," Selikoff said. "Is the Board responsible for evaluating, considering, establishing programs and priorities?"

"Any person who holds a position of trust in the United States government represents the people," Carter shouted, slamming down his gavel.

Bynum quietly pointed out, "During the meetings, you are technically employees of the government."

"This issue deserves closer analysis than the emotional rhetoric we're getting," Amos said. "The Board has 18 appointed members. You are being asked to use your experience and knowledge. You are not representing some charge from a vague public or a general public will."

"I hate to enter into an already over-belabored debate," Samuels said. "There is no public. There are publics."

"Different people were appointed for different reasons," Kushner said. "I'm a political appointee. There was pressure on President Carter from women's groups to get representation on the Board by someone who had breast cancer. I do have a constituency. I try to be parochial."

"Most of us here have a constituency," Carter said.

Selikoff attempted to return to the question of how the Board should function, but Carter rudely and inexplicably cut him off by slamming down the gavel and shouting, "We represent the people. This is a democracy, not a communist dictatorship."

Richard Bloch turned the discussion back to the issue of payment for attending committee meetings (Not an inconsequential issue. Per diem is at the highest rate paid top government executives, now more than $200 a day, plus expenses including travel from anywhere in the U.S., hotels, and meals).

"Every member can attend all committee meetings and be paid, if it is approved by Dr. Carter," DeVita said.

"I don't agree with this discussion," Amos said. "Dr. Carter is the chairman, but the chairman functions as mandated by the members. We don't have time at Board meetings to discuss every problem and issue, so we need committees. It is inappropriate for those decisions to be made by the chairman. The decision on how many committees each can serve on is something for us to determine." (Perhaps that was what brought on Carter's outburst, noted earlier.)

Braren's motion that attendance of members at committee meetings be cleared with the Board chairman, with the assistance of staff, was approved, with Henderson, Rowley and Kushner opposed.

NCI CONTRACT AWARDS

Title: Screening of congeners and detailed evaluation of antitumor agents

Contractor: Southern Research Institute, $809,555.

The Cancer Letter _Editor Jerry D. Boyd

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