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BEAHRS REPORT URGES MAMMOGRAPHY CONTINUATION, SAYS BCDDPs EFFECTIVE IN DETECTING EARLY CANCER

The Breast Cancer Detection Demonstration Project should be continued with the existing guidelines for use of mammographymodified slightly, a working group headed by Oliver Beahrs of the Mayo Clinic has recommended to NCI.

The report of the Beahrs group was scheduled to be presented this

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In Brief

JOB DISCRIMINATION SURVEY REPORT NOT READY UNTIL NEXT MONTH; SACCHARIN DATE EXTENDED

SURVEY REPORT on cancer patient job discrimination (***The Cancer Letter,*** Aug. 19) is not ready, probably won't be until after project director Larry Burke of NCI's Div. of Cancer Control & Rehabilitation returns from Russia Oct. 5. Statistician Jerry Metter is still gathering additional information from the four contractors who conducted a nationwide survey to determine if employers discriminate against cancer patients in hiring and promotions. . . . **ELI GLATSTEIN,** of Stanford Univ., is the new chief of radiation therapy in NCI's Div. of Cancer Treatment. Former chief Ralph Johnson is now at the Univ. of Florida. . . . **FDA HAS EXTENDED** the time for comments on its proposal to ban saccharin from foods and permit its sale only as an over the counter drug. The previous comment period expired Aug. 31; those wishing to be heard now have to Oct. 3 to submit statements in writing to Hearing Clerk (HFC-20) FDA, Rm 4-65, 5600 Fishers Ln., Rockville, Md. 20857. . . . **NATIONAL CONFERENCE** on the Lymphomas and the Leukemias, sponsored by NCI and the American Cancer Society, will be held Sept. 29-Oct. 1 at the Waldorf-Astoria in New York. Henry Kaplan of Stanford will deliver the opening address. Sessions are scheduled on acute lymphocytic leukemia, myelogenous leukemia, lymphocytic and histiocytic lymphomas and Hodgkin's disease. Purpose of the conference is to improve the quality of patient care by bringing to the general medical community the most authoritative information currently available on management of the diseases, the sponsors said. There is no registration fee, but advance registration is requested: S.L. Arje, ACS, 777 Third Ave., New York, NY 10017. . . . **FOUNTAIN SUBCOMMITTEE** on Intergovernmental Relations will hold a hearing Sept. 21 on fluoride as a possible carcinogenic threat in drinking water. Some conservative groups have fought the practice in many communities of adding fluoride to the water supply. NCI has never tested it as a carcinogen because of the vast amount of epidemiological data which have pretty well established that fluoride is not a carcinogen—it occurs naturally in the water of many areas of the country. But because of the controversy, NCI is considering putting it on test.

BCDDP ADVISED TO TIGHTEN GUIDELINES FOR MAMMOGRAPHY ON WOMEN 35-39

(Continued from page 1)

week to the NIH consensus meeting on breast cancer screening. The panel of lay persons, scientists and clinicians which was to hear and consider evidence on mammography was asked to formulate a recommendation on its continuing use today (Friday, Sept. 16), the last day of the meeting.

The panel's recommendation and a complete report on the meeting will appear next week in ***The Cancer Letter.***

The Beahrs group made an extensive review of data collected within the BCDDP and made nine recommendations including the one that the project be continued.

The group recommended that mammography be continued as a routine screening modality for all women 50 years of age and older. The recommendation added that mammography should be used to screen women ages 40 to 49 only when the women have a personal history of breast cancer or a history of breast cancer in first degree relatives (mother or sisters), and women ages 35 to 39 only when they have a personal history of breast cancer.

The group's recommendations for continued use of mammography are identical with guidelines now in effect within the BCDDP for women 40 years of age and older. For women 35 to 39 years of age, current BCDDP guidelines also allow use of mammography to screen women who have a history of breast cancer in first degree relatives, while the Beahrs group recommends that use of mammography in this age group be restricted to those who have a personal history of breast cancer.

Thermography, another modality used for screening in the BCDDP, which records heat patterns on the surface of the breast, "does not appear to be suitable as a substitute for mammography in routine screening in BCDDP," the report states.

All nine conclusions and recommendations of the Beahrs group follow:

1. That the BCDDP be continued as a demonstration program for the remainder of the planned five annual screenings.

2. That physical examinations be continued in BCDDP as a routine screening modality for all ages.

3. That mammography (or xeroradiography) be continued in BCDDP as a routine screening modality for all women 50 years of age and older; women at ages 40 to 49 only when they have a personal history of breast cancer or a history of breast cancer in first degree relatives (mothers or sisters); women at ages 35-39 only when they have a personal history of breast cancer.

4. That thermography be discontinued as a routine procedure in the BCDDP for all ages.

5. That a concurrent review of pathology for minimal cancers be activated: also a concurrent review of mammography and monitoring of quality of the physical examination. Existing monitoring and control measures for radiation dosage should be maintained.

6. That the informed consent provide women having routine mammography a reasonable basis for weighing radiogenic risks against known benefits or against benefits not established but which BCDDP experience suggests might result from including mammography.

7. That follow-up after the planned five annual screenings be restricted to breast cancers detected. Follow-up should be for a minimum period of 10 years after diagnosis; the minimal cancers form a unique group of cases for the study of the natural history of breast cancer.

8. That randomized controlled studies in breast cancer screening be started on questions not answerable from BCDDP. These include magnitude of benefit and net benefit-risk in use of mammography, benefit in screening at ages 40-49, effect of increasing the interval between screening.

9. That the working group continue its review of various issues related to BCDDP.

The Beahrs Working Group was established in January by NCI's Div. of Cancer Control & Rehabilitation. It was asked to review the current BCDDP to determine (1) what scientific information is now available from the BCDDP, which was established as a demonstration project rather than as a controlled, clinical trial; (2) whether the projects provide any suggestive evidence that could guide the development of a clinical trial; and (3) if appropriate, develop a plan for such a clinical trial and consider the use of the BCDDP to conduct such a trial.

Copies of the Beahrs report are available from the Office of Cancer Communications, NCI, Bethesda, Md. 20014.

The report says that the 27 BCDDP centers "are demonstrating that large numbers of women can effectively be brought into a screening program for cancer of the breast. All of the projects will shortly complete the second of five annual screenings. The first of the projects to be started are now carrying out the fourth screen.

"There is evidence that the combined modalities of physical examination and mammography in the BCDDPs are effective in detecting early disease among women under 50 years of age and at older ages. Over a third of the cancers were minimal and at least 70% had no axillary nodal involvement. This is promising in view of the evidence from many clinical sources that the treatment of early disease (small tumors, no lymph node involvement, and other prognostic indicators) leads, on the average, to better survival, although measures of benefit cannot be derived.

"The working group believes that the BCDDPs are

fulfilling a basic objective of the project in detecting breast cancer in an early stage of disease in a large group of women volunteering for screening. The projects are serving a demonstration function and the experience cannot answer questions regarding large scale applications of screening for which special research is needed, i.e., independent benefit of mammography, efficacy of screening under age 50, or frequency of screening.

"Over the years since mammography was first proposed, the procedure has improved substantially, both with respect to the quality of the image and the reduction of radiation exposure to the breast tissue necessary to achieve that image. The exposure to the mid-breast (absorbed) is less than one rad per examination in all projects. Among the breast cancers detected, after the first two screenings, 45% had positive findings only on mammography, 47% on both physical examination and mammography, and 6% on physical examination alone. There are problems in interpreting the results of screening in the absence of information about the procedures followed in completing report forms. Nevertheless, it is apparent that mammography was a major factor in the detection of minimal cancers, and was effective in case detection among younger and older women.

"The area of physical examination has some limitation based on the physical characteristics of the breast parenchyma, the size of the breast, the size and exact location of the tumor within the breast and the experience of the examiner whether physician, nurse or trained paramedical personnel. As smaller and smaller lesions are identified on screening among the total lesions detected, the lower will be the percentages diagnosed by physical examination. The degree to which the proportions of cancers with negative physical findings reflect this situation is not known. In any event, the quality of the physical examinations needs to be monitored.

"Thermography was positive in 43% of the breast cancers detected during the first two screenings but very few were negative in the initial interpretation of the mammography and physical examination findings. Further, a large proportion of minimal cancers would have been missed if mammography had been excluded and thermography alone had been used in conjunction with the physical examination (37% in the first screening and 44% in the second). Accordingly, thermography does not appear to be suitable as a substitute for mammography for routine screening in BCDDP.

"Consideration of continuation of mammography has in the background the HIP study finding of an appreciable benefit at ages 50 and over from screening with mammography and physical examination of the breast. The BCDDP experience reinforces the expectation that screening with these two modalities is effective at these ages. However, information with sufficient precision cannot be derived from findings in BCDDP to determine the differences between (a) the net benefit, taking into account radiogenic risk, when mammography is included and (b) the benefit from screening with physical examination alone. For long-term policy in screening this question needs to be answered but it is prudent for the remaining BCDDP examinations to continue the inclusion of mammography as a routine screening modality for women aged 50 and over.

"The situation is different under age 50. Reduction in mortality due to screening has not yet been demonstrated and because of their younger ages, these women are at risk for radiogenic effects of mammography over a longer period than the older women. The data from BCDDP suggests that mammography may be more effective in detecting cancers early than in the HIP study; further radiation exposure has been significantly reduced. But in the absence of a specific measure of benefit that can be attributed to mammography and the need to avoid radiation exposure given at low levels unless there is benefit, routine use of mammography in BCDDP should be restricted under age 50.

"In the case of women still aged 35-39, factors that lead to severe restrictions are the low detection rate in BCDDP and the relatively young age (45-49) when the women pass the 10-year latency period and radiation effects due to mammography may begin. Mammography should be used in the screening program routinely only when there is a personal history of breast cancer.

"For women aged 40-49, a factor to be taken into account is that the detection rate assumes increasing significance among them, and familial history of breast cancer would place them at an exceptionally high risk. A very small benefit in the high risk group may lead to a net benefit, whereas a small hazard from radiation following the use of mammography in the entire group of women aged 40-49 may not justify the routine use of mammography in screening. The possibility that women with a positive family history of breast cancer are more susceptible to radiation than normal women has been advanced, but this is still highly theoretical and is not ready to be accepted as a basis for decisions in screening. The routine use of mammography in BCDDP for women aged 40-49 years is, therefore, viewed as appropriate for those at high risk evidenced by a personal history of prior breast cancer and ahistory of breast cancer in mothers or sisters.

"On a non-routine basis, mammography should be used for women with clinical indications."

The working group included three subgroups. The epidemiologic and biostatistical review subgroup, chaired by Sam Shapiro of Johns Hopkins, included Samuel Greenhouse, George Washington Univ.; Jeffrey Krischer, Univ. of Florida; A.B. Miller, Univ. of Toronto; Marvin Schneiderman, NCI; David Schottenfeld, Memorial Hospital, NYC; and Donovan

Thompson, Univ. of Seattle.

The clinical review subgroup, chaired by Charles Smart, Latter-Day Saints Hospital, Salt Lake City, included Anne Carter, State Univ. of New York (Downstate); Robert Crichlow, Dartmouth; Richard Gold, UCLA; Robert McDivitt, Univ. of Utah; and Justin Stein, VA Hospital, Long Beach, Calif.

The pathology review subgroup, chaired by McDivitt, included Lauren Ackerman, State Univ. of New York (Stony Brook); Krischer; Paul Rosen, Memorial Sloan Kettering; Shapiro; and Louis Thomas, NCI.

UPTON TELLS CLEARINGHOUSE TO BASE RISK ASSESSMENT ON BIOASSAY DATA

NCI Director Arthur Upton told the Clearinghouse on Carcinogens Executive Subgroup Monday that he expected the Clearinghouse to make a risk assessment on chemicals tested in NCI's Bioassay Program. The assessment of risk to humans should be based only on the results of those tests and should not involve use of other data, Upton said.

The Clearinghouse should develop some guidelines to use in making its evaluation, Upton said. Clearinghouse Chairman Arnold Brown appointed a committee to start work on guidelines—Cuyler Hammond, Marvin Kuschner, William Lijinsky, Verald Rowe, Sheldon Samuels and Brown.

The Executive Subgroup was meeting to consider Clearinghouse objectives, now that it has been in existence for nearly a year. Upton was attending his first meeting of the Clearinghouse since he became director.

"I ask you, Dr. Upton," Brown said. "What kind of advice do you need from the Clearinghouse? Is risk assessment part of the advice you need?"

It was a question more controversial than it may appear. Some scientists and NCI executives fell that the institute's function should not go beyond making the bioassay reports available and let them speak for themselves, leaving it up to the regulatory agencies to make a risk assessment. On the other hand, deliberations of the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on certain chemicals reveal that some believe the NCI bioassay results should be augmented by other findings which bear on whether or not a substance may be a risk to humans.

Upton said that for the Clearinghouse to "look beyond the bioassay itself, to include data from all other tests . . . would be a herculean effort, for which the Clearinghouse is not equipped." But NCI has become "a repository of knowledge and ideas, and is increasingly turned to for advice," Upton said. "Today, we need yes or no answers. The tests are set up that way."

Upton agreed to Brown's summation of the discussion, that a statement of principles or guidelines should be developed on how a single bioassay could be evaluated; that if the Clearinghouse cannot make a risk assessment on the NCI test alone, it will make no assessment at all; and that consideration of "world wide" data along with NCI tests "is more properly applied elsewhere," notably the regulatory agencies.

The subgroup unanimously approved a resolution urging NCI in its carcinogenesis testing program "to take necessary measures to integrate short term assays into the chemical selection and experimental design processes." The resolution commented:

"During the past several years, a considerable research effort has been underway to develop and to validate short term assays for predicting the carcinogenicity of chemicals. NCI's in vitro program has taken a lead role in this important area of research. This statement deals with use of short term tests in the Bioassay Program and is not formulated for regulatory guidance.

"Short term assays can be broadly divided into three major categories. Namely, those in which there is (1) induction of neoplastic transformation of mammalian cells in culture, (2) mutagenic or cytogenetic changes in microorganisms or mammalian cells, and (3) interactions between chemicals and target macromolecules, e.g., unscheduled DNA synthesis. These assays are still in the process of being defined and evaluated in terms of their usefulness, reproducibility, and comparability to known in vivo carcinogenicity systems. Data thus far obtained indicate a good correlation exists between in vitro and in vivo results, although no single assay is totally satisfactory for predicting the carcinogenic potential of all carcinogens tested. This does not detract from their usefulness since combinations of assays provide a higher level of reliability.

"Notwithstanding the limitations imposed by the current state of the art, there still appears to be an immediate, practical application for short term assays. At present, microbial mutagenicity assays offer a rapid and inexpensive approach to acquire information useful in selecting and ranking chemicals for long term carcinogen bioassay. The concomitant or sequential use of DNA repair and mammalian cell transformation systems should enhance the selection process. Results from these short term assays should eventually provide important information that may be useful in assisting in the evaluation of marginal data on carcinogenicity.

"It is recognized that short term assays are still in the process of evaluation. Further, it is acknowledged that short term assay data, by themselves, are inadequate to define the carcinogenicity or lack of carcinogenicity of a given chemical. Still, it is the sense of the Clearinghouse on Environmental Carcinogens that short term assays are sufficiently developed to provide information useful in the selection of chemicals for carcinogen bioassay and in their later evaluation."

Subgroup member Joseph Highland first objected

to the resolution. "I'm not saying they are substitutes for long term testing, but I am saying we shouldn't eliminate their use to provide some guidance . . . I would argue this statement is so qualified and so hesitant to take a stand that it would not be useful to regulatory agencies."

Div. of Cancer Cause & Prevention Director James Peters commented, "Your point is well taken. But I wonder if this is the proper document for that. It seems to me this document is addressed to program (NCI staff) for program guidance. The regulatory problem could be addressed with another document."

Highland argued, "If a chemical is positive in the Ames test and positive in a cell transformation test, a regulatory agency should require monitoring, at least, until it gets long term test data."

Brown noted that, while the resolution is directed officially to program, "it does represent an official position taken by a government agency," and presumably could be used to influence a regulatory decision.

Virginia Dunkel, coordinator of NCI's In Vitro Carcinogenesis Program, agreed that the program "could seriously start using short term tests" to assist in chemical selection test design, but probably on a limited basis compatible with resources available to support such tests.

Brown presented a statement of objectives of the Clearinghouse and each of the subgroups which he said the entire Clearinghouse would be asked to consider at its plenary session Oct. 31:

BROAD OBJECTIVE: To advise the NCI Bioassay Program on its efforts to identify and to evaluate environmental carcinogens to which humans may be exposed.

Chemical Selection Subgroup

Function is to advise on subjects affecting chemical selection—appropriateness of testing specific chemicals, systematic approach for identifying representatives of large, environmentally important chemical classes for evaluation. The subgroup reviews past and current testing priorities to advise on appropriate balance in the selection of new chemicals. Advice to the Experimental Design Subgroup is particularly important in regard to exposure routes, grade and composition of test chemicals and other matters that impact on study design development.

1. Advise on critical data elements and procedures necessary to evaluate candidate chemicals.
2. Advise on approaches for the selection of classes of chemicals requiring evaluation.
3. Advise on approaches for rank ordering individual chemicals and classes of chemicals.
4. Advise on the utility of and extent that short term tests can be used in the chemical selection and ranking process.
5. Advise on and nominate candidate chemicals and classes of chemicals that should be evaluated.
6. Advise on the need and priority to test chemicals recommended by the NCI Chemical Selection Working Group.
7. Advise on the need to test chemicals appearing as low-level environmental contaminants.
8. Advise on the need to test mixtures.
9. Advise on the need to test for incomplete carcinogens.

Brown had as Task 10, to advise on chemical probes that could be used to gain better understanding of bioassay test systems and results. But David Clayson, chairman of the Chemical Selection Subgroup, objected, commenting that more groundwork is needed before that would be feasible. Brown agreed to drop it from the list for now.

Experimental Design Subgroup

Function is to advise on experimental designs compatible with objectives and goals of the Bioassay Program. It also advises on studies specifically designed to provide better understanding of present bioassay models and more meaningful interpretation of test results. The subgroup advises on new model systems and experimental designs as the state of the art permits.

1. Advise on appropriateness of current bioassay methodology.
2. Advise on specific experimental designs to test chemicals based on the rationale for their selection.
3. Advise on experimental approaches that could be used to gain a better understanding of bioassay test systems and results.
4. Advise on experimental approaches to test complex mixtures, incomplete carcinogens, and chemicals appearing as low-level environmental contaminants.
5. Advise on the utility and extent of short term tests as an adjunct to the standard bioassay.

Data Evaluation/Risk Assessment Subgroup

Function is to advise on all subjects that affect data evaluation and risk assessment. An important aspect is the assessment of past studies to determine how future ones can be better designed to facilitate their evaluation. Advice of this nature is provided to the Experimental Design Subgroup. Risk assessments are generally limited to the data developed in NCI sponsored bioassay studies.

1. Develop guidelines for evaluating and interpreting bioassay studies.
2. Advise on new approaches for data evaluation, e.g., statistical methodologies.
3. Advise on completeness and integrity of bioassay reports.
4. Advise on appropriateness of conclusions and interpretations drawn by program staff on results of bioassay studies.
5. Advise on data elements necessary for meeting Program goals, e.g., pharmacokinetics, metabolism, dose-response, etc.
6. Develop approaches for estimating carcinogenic

potency.

7. Develop approaches for quantifying human risk based on biological and mathematical considerations.

Executive Subgroup

Function is to advise on subjects outside of the mandates of the other subgroups. It also is responsible for dealing with issues of common interest to the subgroups and coordinating their efforts.

1. Provide overall coordination and direction to the other subgroups.

2. Advise on program goals and objectives, structure, use of resources, priorities, and other areas deemed appropriate.

NCI'S RESPONSE TO GAO EPPLEY REPORT: GIO GORI DOESN'T PULL ANY PUNCHES

The General Accounting Office report on NCI's contract with Eppley Institute has been submitted to NCI and Eppley, to permit them to develop their comments. This is standard practice, when the congressional agency completes an investigation of an Executive Branch operation. The usual response from the bureaucrat who was investigated is rather namby-pamby, as he attempts to strike a conciliatory note. That won't be the case with NCI's response, if the answer by Gio Gori, who is project officer on the Eppley contract, is permitted to go to GAO.

GAO forbids release of its reports until the responses have been collected, and sometimes only after approval for release is obtained from the congressman who initiated the investigation (in this case, Rep. David Obey). GAO's NIH chief, Matt Solomon, did discuss the material that would be included (***The Cancer Letter,*** July 15).

However, ***The Cancer Letter*** has obtained a copy of Gori's response, along with other material to be included in NCI's answer. Gori, who is deputy director of the Div. of Cancer Cause & Prevention, did not pull any punches, pointing out that if the steps apparently demanded by GAO in the report are permitted to become policy, it could establish "a dangerous precedent" with "intolerable restrictions" on biomedical research:

"Throughout the report the impression is given of major improper financial transactions. However, even a cursory summation of the findings reveals that between 1 and 2% of total funding may be open to some question of accuracy and propriety, but not of willful wrongdoing.

"This would not appear sufficient grounds for the stern and alarmistic tone of reprimand that pervades the report.

"NCI in particular is scored for not becoming aware of these problems, implying that NCI should routinely adopt an investigative attitude toward its contractors, and ignoring that regular audits were conducted by independent auditing agencies, without resulting in the dramatic charges of the GAO report.

"It goes without saying that no error, however small, should be condoned, but because of the minor relative import of the infractions noted, the tone of the report could give a feeling of partiality. Probably, a group of reviewers with a more equitable attitude would have concluded that the conduct of the contract was rather good.

"The report states that improper review procedures were adopted, but fails to state what proper procedures are. Internal NCI guidelines are just that: guidelines. Exceptions to these guidelines are from time to time authorized by senior NCI management, which promulgates guidelines and modifies them as appropriate. Guidelines have never been static at NCI, and have always operated within the framework of legal requirements. The Eppley review procedures represented the best judgment of management at the time.

"The report seems to indicate that no precise authority for funding decision exists at NCI, when it is clear that for the Eppley Institute that decision rested with the Associate Director for Carcinogenesis (who at that time was Umberto Saffiotti).

"The GAO report insists on the six month comprehensive progress report requirements. As such, it fails to recognize what was repeatedly explained to the investigators, namely, that the accrual of information in bioassay research is very slow (2-3 years), making semiannual reports rather superfluous, costly and repetitive efforts, of great hindrance to the contractor and of little or no use to NCI. This is particularly true because initiation and finalization of individual bioassays are staggered in almost random fashion throughout the year. Of greater value to NCI are interim individual reports on individual bioassays. We supplied the GAO investigators with several thousand pages of such interim reports, either as publications or as manuscripts, and the charges that NCI was or is unaware of the results of the Eppley research are incorrect.

"The report implies that NCI should closely monitor the conduct of daily research and bioassay activity at Eppley. This ignores the traditional practices of research monitoring at NIH, within the context of academic freedom in the U.S. Perhaps these entire practices should be reviewed and questioned, but hardly a case can be made against a single institution.

"The report implies that NCI should monitor and demand strict adherence to the letter of the contract in all project activities. This ignores the variable and unpredictable nature of research, the relative mobility and pay scale differential of scientific personnel, the changing and free patterns of scientific collaboration between scientists in an institution. Also, it fails to recognize that NIH has traditionally allowed some discretion in the administration of research fund

allocation within a contract to the recipient institution. This has been precisely in recognition of the uncertainties of science and as a means to allow judgment in the pursuit of novel and promising ideas.

"The insistence of the report on the issue of value added or dollar return for a research investment, has dubious legitimacy within the context of a policy of federal investment in biomedical research. As such, the report could easily be classified as anti-science or anti-intellectual, a charge that GAO probably wishes to avoid. Research productivity is sometimes measured in terms of publications. In this respect, it is interesting to note that in FY 1973 the Eppley Institute received 9.2% of the collaborative research funds of the Carcinogenesis Program ($2.3 million of $25 million), and contributed 28% of the publications from the same collaborative program (52 of 185 publications). Similar ratios are apparent for the following years.

"The report makes charges and recommendations that apply to research management at NIH, and not only to the particular instance of the Eppley contract which we feel is not a bad example of research administration.

"The strict financial and scientific monitoring that the report suggests goes against the established practices of a healthy degree of scientific and academic freedom in the conduct of biomedical research sponsored by NIH, and of assuming a high degree of trust, fair dealing, integrity and legitimacy in the relationships between NIH and the academic institutions of this country.

"What concerns one most is:

"1. The report would force a detailed fiscal, administrative and scientific supervision of biomedical research contracts (and perhaps grants by extension) far beyond what the personnel capacity of NIH is, and to an extent that would encroach on the academic freedom and free development of scientific inquiry.

"If the current system of administration provides less than 2% of the fiscal error, the NCI-NIH should point out that it appears quite satisfactory.

"2. The report seems to demand a justification for tangible dollar value added as a result of a given research investment. This provision would set a dangerous precedent for the entire scientific establishment.

"I feel that NCI and NIH should respond vigorously now to these charges and demands: accepting them would be an admission of guilt and would establish a dangerous precedent that may produce intolerable restrictions on biomedical research in general."

DCCP administrative officer John Miller answered what apparently was GAO's charges that the contract was inappropriately reviewed in 1973:

"Our position in the congressional hearings and in other settings has repeatedly been that we did not pretend to have committee review of the technical aspects of this contract in 1973. References to an ad hoc committee or any other committee for technical review are incorrect. A number of consultants and expert reviewers did review certain technical aspects of the contract and provide comments to the associate director for carcinogenesis who formulated a recommendation to the CCPMG.

"On page 7 of the draft the statement is made that, 'Technical reviews. . . did not comply with normal procedures used by NCI at the time because the reviews were made by an ad hoc committee rather than by standing committees chartered by NCI for the purpose.' As stated above, it was not an ad hoc committee but further, NCI procedures at the time did not clearly require a standing committee for renewal review. According to page one of the Orange Book procedures, effective Jan. 1, 1973, procedures confine dual committee review on a mandatory basis to initial awards rather than routine renewals of contracts."

Another part of NCI's response points out the changes that have taken place in the Carcinogenesis Program which have affected Eppley:

"Since completion of the GAO investigation at Eppley Institute in March 1977, considerable changes have taken place in the way NCI directs and monitors the testing of chemicals for carcinogenicity, not only at Eppley but at every institution where such studies are supported by NCI. The changes, which were initiated long before the GAO investigation, were made possible by (1) the creation of a separate Carcinogenesis Testing Program, which began functioning in July 1976, to give emphasis to this newly developing field of research, (2) the appointment of an entirely new NCI staff (including its director when Saffiotti was replaced) who were selected because of their expertise in testing chemicals for carcinogenicity, and (3) the creation of an advisory committee, the Clearinghouse on Environmental Carcinogens, to insure that NCI-supported testing of carcinogens would serve well the nation's interests.

"The impact of these changes on Eppley Institute has been great. The new Carcinogenesis Testing Program staff conducted a site visit in March 1977 to re-evaluate the capability of Eppley to test chemicals for carcinogenicity. The site visitors rated Eppley in the top 25% of laboratories in the country that perform such work. Subsequently, Eppley Institute's proposed research in carcinogenesis testing was reviewed and approved by a technical review committee for scientific merit and by the NCI program committee for priority, need, and relevance.

"A major change has taken place in the selection of chemicals for testing. The Eppley Institute staff, with the concurrence of the NCI project officer, now choose from a list of chemicals that have been selected by NCI with the approval of the Clearinghouse. This insures that the chemicals have a high priority for testing and that the work at Eppley is coordinated with that in the rest of the world to avoid unnecessary duplication of effort. At present,

three chemicals that are representatives of chemical classes in which Eppley has demonstrated experience and expertise have been assigned to Eppley for testing. Two other chemicals are under joint consideration.

"Another major change is in the design of experiments. After the chemicals have been selected, the proposed experimental protocols from Eppley are reviewed by the same NCI group which designs all of NCI's testing experiments. Included in the considerations are such variables as the choice of animal species, the number of animals, the routes of exposure, the purity of the chemical, the vehicle, and the setting of doses. The chemicals are supplied by NCI to Eppley with the exception thus far of one, agaratine, which has to be synthesized by Eppley chemists. When the preliminary tests for dose setting are completed by Eppley, the data are reviewed by NCI to insure proper dose setting before long term experiments are begun.

"As results of experiments become available, the Eppley data are reviewed by toxicologists, pathologists, and statisticians who comprise the NCI data evaluation group. For example, we have just reviewed Eppley's experiment on dilantin. Our evaluations plus Eppley's data are then shared with the federal regulatory agencies as well as with the Data Evaluation/ Risk Assessment Subgroup of the Clearinghouse.

"It should be apparent that the efforts of Eppley Institute in carcinogenesis testing have been incorporated by NCI (with the concurrence of Eppley) into the national effort to protect the public from potentially carcinogenic chemicals. The combination of demonstrated research excellence at Eppley Institute and the direction and surveillance provided by NCI guarantee quality research."

CONTRACT AWARDS

Title: Prototype Comprehensive Network Demonstration Projects for head & neck cancer
Contractor: Univ. of Wisconsin, $108,545.

Title: Implementation of Clinical Oncology Program
Contractor: St. Mary Community Hospital, Walla Walla, Wash., $287,687.

Title: Development of new methods of single cell separation
Contractor: Block Engineering Inc., Cambridge, Mass., $620,961.

Title: Metabolism of carcinogenic compounds
Contractor: Fred Hutchinson Cancer Center, $38,260.

Title: Estrogen replacement after premenopausal oophorectomy and the risk of breast cancer
Contractor: Boston Univ., $118,750.

Title: Studies and investigations on the effects of estrogen and progestin on the biological behavior of the mammary gland during the neonatal period
Contractor: Baylor College of Medicine, $70,100.

Title: Studies and investigations on prevention of the formation and of the progression of preneoplastic lesions of the mammary gland
Contractor: IIT Research Institute, $257,000.

Title: Serum collection from volunteer participants in the Breast Cancer Detection Demonstration Projects
Contractor: Cancer Research Center, Columbia, Mo., $342,900.

Title: Carcinogenesis in vitro: Initiation and promotion, modification
Contractor: Univ. of Southern California, $116,033.

Title: Use of physico-chemical parameters in obtaining structure activity relationship with potentially cancer related endpoints
Contractors: Case Western Reserve Univ., $98,678; and Stanford Univ., $82,747.

Title: Data management system and statistical support for NCI serum panel
Contractor: Small Business Administration, $49,832.

Title: Environmental occurrence of N-nitroso compounds, supplemental
Contractor: Massachusetts Institute of Technology, $85,127.

Title: Changing sensitivity to carcinogenesis of the mammary gland
Contractor: New York State Dept. of Health, $173,100.

SOLE SOURCE NEGOTIATIONS

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

Title: Screening, indexing, and abstracting of cancer-related literature for input to the ICRDB program data bases, modification
Contractor: The Franklin Institute, Philadelphia.

Title: Latin American cancer research information project, modification
Contractor: Pan American Health Organization.

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