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NEW MEXICO, MISSOURI, COLUMBIA NEXT FOR REVIEW AS COMPREHENSIVE CENTERS; UCLA DECISION IN OCTOBER

Three centers aiming for comprehensive cancer center designation will be site visited by members of the National Cancer Advisory Board and NCI staff within the next six months—the Univ. of New Mexico,

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In Brief

HSAs WOULD DELAY NCI AWARDS BY NINE MONTHS; MARY LASKER NAMED TO CARTER HEALTH GROUP

HEALTH SERVICE Agency impact on the Cancer Program "would be devastating," NCI Deputy Director Guy Newell told the President's Cancer Panel last week. Newell said additional reviews by local and regional HSAs would add a minimum of nine months to any program. Director Frank Rauscher noted that this would mean it will take 1½ years to fund a project: "We couldn't start at the beginning of the fiscal year and get the money out during that fiscal year." When the HSAs are activated, they will have the power to review all federally funded health programs, including NCI grants and contracts. Proposed HSA regulations will be published soon in the *Federal Register*; NCI and NIH will suggest changes which, if adopted, will exempt most of their activities. If HEW refuses to go along, Cancer Program advocates will have to carry the fight to Congress and try to get an exemption written into the National Cancer Act. . . . **MARY LASKER**, health philanthropist and a member of the National Cancer Advisory Board, has accepted appointment to Jimmy Carter's "Task Force for Health". . . . **R.W. LAMONT-HAVERS**, NIH deputy director, has resigned to become deputy for research and administration to the general director of Massachusetts General Hospital. He will help formulate and coordinate research policy. Highly respected by NIH staff, Lamont-Havers is another casualty of the salary freeze on government scientists and top executives. . . . **GROUNDBREAKING** for the Yale Comprehensive Cancer Center Oct. 7 will be an occasion for a symposium on "Retrospective Perspectives—The National Cancer Act of 1971." Center Director J.W. Cole and Yale President Kingman Brewster will open the program, followed by Cancer Panel Chairman Benno Schmidt speaking on "Five Years into the National Cancer Program;" and National Cancer Advisory Board Chairman Jonathan Rhoads, talking on "Some Advances in Clinical Practice, 1971-1976." Robert Berliner, dean of the Yale School of Medicine, will moderate a question and answer session. Connecticut Gov. Ella Grasso will preside at the groundbreaking, with remarks by Robert Wakely, chairman of the Connecticut Cancer Consortium. The program will conclude with addresses by Lewis Thomas, president of Memorial Sloan-Kettering; Harold Amos of Harvard and an NCAB member; and Arthur Holleb, American Cancer Society senior vice president.

SAN FRANCISCO, NEW ORLEANS LISTED BY RHOADS AS NEEDING COMP CENTERS

(Continued from page 1)

the Missouri Cancer Program, and Columbia Univ. Although it isn't likely all three will be recognized at once as comprehensive centers, the next to achieve that status quite possibly could include one or more of them.

UCLA, which has been teetering on the brink of comprehensive recognition for a year or more, could have its situation resolved by the end of next month. NCI Centers Program staff members will visit UCLA in October. The UCLA Cancer Center was provisionally approved by NCAB for comprehensive designation last year, pending resolution of certain administrative problems. No further Board action will be necessary on its application.

New York Univ.'s chance of achieving comprehensive status now is further clouded by the fact that Columbia feels it is ready. NYU had an NCAB site visit last year, was advised that it had a lot to do before recognition would be conferred. The Board agreed that it would have to review the NYU application again after the deficiencies were corrected. However, a Centers Program staff member told ***The Cancer Letter***, "we haven't heard from them."

If Columbia becomes comprehensive, and with Memorial Sloan-Kettering one of the original comprehensive centers, it might be several years before New York City would get a third center with formal comprehensive recognition, considering congressional interest in broad geographic distribution.

NCAB Chairman Jonathan Rhoads referred to the geographical problem in a discussion at Monday's Board meeting. "I think our record is not bad on distribution, considering everything," Rhoads said. "There are two metropolitan areas which should be represented. The San Francisco Bay Area is one, and an organization is being perfected there (the Northern California Cancer Program). We'll likely have an application there. The other metropolitan area that should be represented is New Orleans."

Benno Schmidt, chairman of the President's Cancer Panel, suggested that Congress should be made aware that budget constraints have made it necessary to limit comprehensive recognition to those institutions which have already met the requirements and demonstrated the scientific capability of comprehensive centers.

"It's easy to say, there ought to be a center here and a center there, without taking the budget into effect," Schmidt said. "As a practical matter, to be a comprehensive center, an institution already would have to be receiving the kind of support (through program project and regular research grants and possibly other NCI support) a comprehensive center receives."

Board member Denman Hammond, chairman of the Board's Subcommittee on Centers & Construction, agreed that "only those already with major commitments of resources, human and programmatic, should be considered for comprehensive recognition." Hammond pointed out that in 1970 and 1971, before the National Cancer Act became law, the budget for program projects already was substantial. "The heart of the Centers Program now is the core grant," Hammond said.

Board member Frank Dixon disagreed. "I'm not so sure the core grant is the guts of the Centers Program," Dixon said. "It is the toughest to review. There's a lot of slosh in it. It is just as possible to have good science; good patient care, good clinical research, and all the rest, with a program project as it is with a core grant."

"The center directors would disagree with that," said Hammond, who is director of the L.A. County-U.S.C. Comprehensive Cancer Center.

"Sure," Dixon said. "If I was a center director, I would think so, too. The core grant has money I could play with. Everyone would be working for me."

Meanwhile, NCI and Hammond's subcommittee continue to wrestle with questions related to the direction of the Centers Program, particularly the definition and types of cancer centers, their location and regional responsibility, and the goals of the Cancer Centers Program.

An NCI committee of staff members has been meeting to discuss those questions, which were raised in the lengthy report by former Centers Program Director Simeon Cantril before he left NCI. Two other issues NCI committee is considering are the responsibility of NCI and centers to each other, and the organization locale of the Centers Program within NCI—that is, whether or not it should be moved out of the Div. of Cancer Research Resources & Centers.

The committee will hold its last meeting later in September and will present its report to the NCI director by mid-October.

DCRRC Director Thomas King told Hammond's subcommittee that the staff committee agreed that the primary responsibility of NCI to centers is to provide core support, and for five years instead of three as at present, and that the responsibility to NCI is for the centers to develop their own resources so as not to be permanently dependent on NCI for support.

Cancer Panel member R. Lee Clark felt that this was too restrictive of the responsibilities. "The sponsorship by NCI of centers is not limited to core support," Clark said. "The selection of comprehensive centers involves great expense and a great deal of labor. The responsibility of NCI is to see to it that centers are used in the Cancer Program to the maximum extent. It is the centers' responsibility to carry out the goals of the National Cancer Program."

Hammond suggested that a memo be sent to all

centers asking for their comments on the five topics being considered by the staff committee.

Hammond previously had asked members of his subcommittee to comment on Cantril's report and recommendations (See ***The Cancer Letter***, July 2, for a description of the recommendations). Only a few members had responded, Hammond said, but he hoped to have a complete report ready by the subcommittee's November meeting.

"It's hard to disagree with any of the recommendations," said subcommittee member Werne Henle.

Hammond admitted that "it might be like agreeing with apple pie and motherhood," but noted that 20 statements in Cantril's recommendations have elicited some disagreement from those subcommittee members who have responded.

The 18 existing comprehensive centers are facing a rigorous review over the next four years to determine if they should continue in that status. NCI staff presented the subcommittee with a list of suggested dates for NCAB site visits which will be part of that review:

Duke, Feb. 1977; USC-LAC, March 1977; Hutchinson, April 1977; Mayo, May 1977; Georgetown-Howard, June 1977; Colorado, July 1977; Illinois, Aug. 1977; Alabama, Jan. 1978; Hopkins, Feb. 1978; Roswell Park, March 1978; Texas, April 1978; Yale, May 1978; Farber, June 1979; Florida, Aug. 1979; U.Pa.-Fox Chase, Oct. 1979; Ohio State, June 1980; Wisconsin, July 1980; and Memorial Sloan-Kettering, Aug. 1980.

The subcommittee endorsed the principal of Board site visits to review already designated comprehensive centers and requested the staff to implement the review schedule.

Centers Program staff is planning to distribute a "Cancer Center Profile" to every center with a core grant. It would be a questionnaire which would provide what Bernard Keele, assistant to Centers Program Director William Walter, called "an inventory of data about centers. We need some mechanism to define what is in centers," Keele said.

Keele distributed a draft of the questionnaire and emphasized that it may be substantially revised before it is sent out to the centers.

Some of the questions are routine, but most of them, taken together, seem to provide an outline of what NCI thinks the centers should be doing and how they should be organized. The foreword notes that some of the seven sections may not be relevant to a particular center.

Section I asks the type of center, organizational setting—freestanding, university, consortium; center affiliates, number of patients, list of occurrence of cancer by organ site in the catchment area, other demographic data.

Section II involves program plan and objectives. Questions include: Do you have an organized planning process? Permanent planning committee, ad hoc planning groups, continuous or intermittent? Indicate the status of the program plan. List the objectives to be accomplished, including time frame for starting and completing, clinical research, nonclinical research, control/outreach, education/training, and include criteria for measuring the completion of each. Describe the planned approaches to accomplishing each objective. Explain your understanding of the concept of cancer centers as a National Cancer Program resource, and how your center participates in the program.

Section III, centers organization, is concerned with two major items—commitment of the parent institution to the initiation and maintenance of a cancer center, and the autonomy of the center as reflected by authorities and prerogatives delegated to the center director. Specifically identify the commitments, in funds, personnel, space and equipment. Describe any constraints.

Section IV, center resources, asks details on personnel, budget-fiscal management, and space and equipment.

Section V, nonclinical research programs, asks for lists of ongoing projects in seven research areas—epidemiology, carcinogenesis, viral oncology, cancer biology, immunology, preclinical treatment research, and nutrition. It also asks for lists of projects that will be activated within three to five years, for a description of "the most notable achievements in nonclinical research at the center in the past three years," and for a statement of what achievements have been transmitted directly to clinical research. Awards to and publications by staff, funding obtained through competitive review, visiting scientists, education and training responsibilities of the nonclinical research scientists, and lists of all trainees and graduates over the previous three years sponsored by nonclinical scientists.

Section VI, clinical research and cancer care programs, asks for lists of ongoing projects in diagnosis, treatment and rehabilitation, for projects planned to be activated within five years, for the total number of new cases, those entered into research protocols, inpatients and outpatients. Details on review are asked, along with the same type of information on training, funding, awards, etc. asked of the nonclinical research program. Descriptions are asked of the multimodality aspects of nonresearch patient care and of the relationship of nonresearch patient care with cancer control activities.

Section VII involves community outreach, essentially, the total cancer control component of the center program. Lists are asked of all ongoing intervention projects, education-training projects, names of hospitals in the center's patient catchment area, affiliation arrangements, participation of community health providers, and "specific, quantitative evidence that the cancer control/outreach program of the center has had an impact on the cancer problem" in its area.

PAY INCREASE BILL KILLED BY HOUSE COMMITTEE; RAUSCHER RESIGNATION NEAR

Frank Rauscher's days as director of NCI and the National Cancer Program appear to be numbered.

The House Commerce Committee last week voted 13-13 on a bill that would raise Rauscher's salary and that of all other NIH institute directors, the NIH director, and the assistant secretary for health, to $52,000. The tie vote effectively killed the measure, since a majority vote is required to report out a bill.

A last-ditch effort was being planned by cancer program advocates to get an amendment tacked onto some other bill already on the floor, but that would take some tricky parliamentary maneuvering and its chance of success was slim.

Rauscher has maintained all along that, once congressional action on a pay raise is ruled out, he would leave. His resignation now appears imminent, probably in a matter of days.

NCAB HUNG UP ON REMOVING $5 MILLION CORE LIMIT FROM ACT, DELAYS REVISIONS

The National Cancer Advisory Board took its first crack at drafting suggested revisions for the National Cancer Act next year but could not get past the issue of deleting the $5 million limit on funds for centers.

The Act now contains an ambiguous section which could be interpreted as meaning that no center could receive more than $5 million from NCI in a year. NIH legal staff has interpreted that to mean no more than that for core, program projects, regular research grants and other funding mechanisms. NCI has avoided the problem by using other authority in other sections of the Public Health Service Act, so the NIH legal opinion has not been tested.

NCI would like to have the $5 million limit removed in any case, even for core grants. An NCAB subcommittee chaired by Harold Amos worked up a list of recommended changes (*The Cancer Letter*, Sept. 3), and Amos was scheduled to present them to the Board Monday.

Amos and Robert Schonfeld, chief of NCI's Program Liaison Branch, managed to get agreement on the first item—authorization totals for the 1978, 1979 and 1980 fiscal years. The subcommittee had recommended $1.073 billion, $1.139 billion and $1.214 billion, but Amos reported that Board member Mary Lasker, who was not at the meeting, had insisted on more. The Board agreed, although scaling down Lasker's figures to $1.1, $1.2 and $1.3 billion respectively.

Board member Laurance Rockefeller said, "We all want as much as we can get and spend well. But how much can we ask for without a boomerang? Overreaching can be counter-productive."

Director Frank Rauscher agreed, contending that the appropriations committees, which pay no attention to authorizing figures, are embarrassed if the authorizing committees go too high. But Rauscher admitted that NCI could spend "very well" the entire amount suggested by Lasker for each of the years.

Panel Chairman Benno Schmidt said, "Mary operates on the philosophy that the more you ask for, the more you'll get, and that you should ask for all you need. My philosophy is don't put people in an untenable position."

Disagreement on removal of the core grant limit was expressed by Board member Frank Dixon. "As a non-center spokesman, if we didn't have in the Act the $5 million limit, we should embrace it and get it in. If an institution can't become self supporting, can't do what it needs to do on $5 million, then it shouldn't receive any money."

Board Chairman Jonathan Rhoads suggested that "if we tell Congress we want to drop the $5 million limit, that suggests we want to spend more." The change would be primarily to legalize a situation that already exists and would not necessarily permit more spending.

Amos suggested that no action be taken, leaving the limit as it is, reasoning that Congress might react to a request to remove the limit by spelling out that it does apply to total support and not just to core grants. He put the suggestion in the form of a motion but later agreed to table it.

Schmidt said that terms such as core support are not familiar to most congressmen. "We're going to wind up getting an overall limit. But we should face it now, and get it out of the Act."

Board member William Powers commented that the subcommittee did not necessarily seek final Board action on the recommendations, and the Board agreed to hold any further consideration until its November meeting.

CONFEREES STILL ARGUING MONEY BILL AND ARE RUNNING OUT OF TIME

House and Senate conferees on the HEW appropriations bill still had not yet resolved the bitter dispute over the abortion issue by press time this week, and time is starting to run out on Congress.

Both houses are determined to adjourn by Oct. 2, with the election following only a month later. But they have to get the appropriations bill to the President more than 10 days before adjournment to prevent a pocket veto. That would take away the opportunity for Congress to override.

If the bill goes to the White House no later than Sept. 20, that would leave enough time for an override vote. Indications are that President Ford will veto it, but there seems to be enough support to override, as Congress did on fiscal 1976 appropriations.

NCI Director Frank Rauscher told the National Cancer Advisory Board Monday of his plan to reprogram $10 million from construction grants (*The*

Cancer Letter, Aug. 20), provided the congressional appropriations committees give him authority to do so.

Board member Philippe Shubik said he was "terribly upset" by the cutback on construction. "Most medical schools can't do much for the cancer program without new buildings," Shubik said.

Chairman Jonathan Rhoads replied that Panel member Lee Clark has an answer. "He introduced (at the Univ. of Texas System Cancer Center) the concept of zero budgeting to space. He asked investigators to justify the space they asked for, from the first square foot up."

"That quieted a lot of discord," Clark said.

OBEY BLASTS NCI FOR HOLDING BACK ON TRANSFER OF $3 MILLION TO NIOSH

Congressman David Obey (D.-Wisc.) resumed his attack on NCI last week in a news release in which he charged that "National Cancer Institute defiance of a congressional directive has delayed study of several suspected cancer-causing chemicals in the workplace, including a dry-cleaning agent which unreleased NCI tests have linked with cancer in animals."

The complete news release appears below, followed by a chronology of events related to Obey's charge and correction of some misstatements in the news release:

"Obey, a member of the Labor-HEW Appropriations Subcommittee, said that NCI has refused to obey language in the fiscal year 1976 Labor-HEW appropriation requiring it to provide $3 million toward an $8 million occupational cancer program being conducted under the auspices of the National Institute for Occupational Safety & Health. He said NCI told NIOSH that there would be no money for the program in fiscal year 1976 or the transition quarter, which ends Sept. 30, at a meeting between the directors of the two institutes held Tuesday, Sept. 7.

"Obey said that the NCI decision has stymied research that could lead to regulation of a number of chemicals suspected of causing cancer in workers including perchloroethylene, a widely used drycleaning agent.

"Obey stated that an investigation by his office has revealed that while no data exists on the effects of perchloroethylene on the more than 300,000 workers who are exposed to it on a daily basis, results of tests conducted by NCI more than two years ago but still unreleased indicate that the chemical causes a high level of liver cancer in mice.

"Obey said that the unreleased NCI data on perchloroethylene shows that 32 of the 49 male mice exposed to low dosages of the chemical developed liver cancer. He said the experiments showed that at both high and low dosages, male and female mice developed liver cancer at four to six times the rate of mice who were not exposed.

" 'There is no way that the Occupational Safety & Health Administration can develop regulations to protect workers without this kind of scientific information,' Obey said. 'NCI has prevented them from having this animal test data by failing to report the test results, and has prevented NIOSH from learning about the effect of this chemical on human beings by defying the Appropriations Committee directive.'

"Obey added that such action on the part of NCI 'explains why we are now protecting workers from only 16 of the nearly 1,500 workplace chemicals suspected of causing cancer, and why we have adopted new regulations on only one cancer-causing chemical in the last three years.'

"Obey said that perchloroethylene is one of more than 200 chemicals on which NCI has completed tests but failed to issue a report. He added that 129 of those chemicals have been off test for more than a year, some of them for more than five years.

"Among the other efforts which will be delayed or curtailed by NCI's refusal tp provide occupational cancer funds are:

"—A follow-up medical examination of Kepone workers to determine the long-range health effects of exposure.

"—Development of test procedures for 14 known cancer-causing agents regulated by the Occupational Safety & Health Administration.

"—A health study of miners exposed to short asbestos fibers similar to those dumped into Lake Superior by Reserve Mining Company.

"—A study of the health effects of pesticide exposure which are thought to include cancer, kidney disease and blood disorders.

"—Studies to determine what methods are now available to protect workers from cancer-causing agents in the foundry, smelting and textile finishing industries.

"—Development of methods to measure the workplace levels of known cancer-causing agents.

"Obey said his subcommittee required that the occupational cancer program be funded by both NCI and NIOSH in order to encourage the two institutes to work together and to 'get NCI involved in the practical problem of workers who are dying from exposure to unregulated chemicals.

" 'It's hard to believe that with a $775 million budget, NCI spends less than 6% on its own carcinogenesis program for testing chemicals and then refuses to provide a mere $3 million for a program to protect workers from cancer-causing agents, even when directed to do so by Congress,' Obey said.

"Obey concluded that NCI's refusal to provide funds for the occupational cancer program indicates 'blatant insensitivity to workers and all Americans exposed to potential cancer-causing agents, and an arrogant disregard for the conditions under which Congress made the money available to the National

Cancer Institute in the first place. There is no way the federal government can regulate industries which expose workers and the general public to chemicals like Kepone unless NCI stops playing an obstructionist role and starts assisting in this research.' "

Now for the facts:

1. In the House report on the fiscal 1976 appropriations bill, the committee directed that "up to $3 million" be transferred to NIOSH—not the flat $3 million as stated in the news release.

2. Language in House and Senate committee reports on bills do not have the full force of law behind them. The reports are not incorporated into bills, but generally are designed to show congressional intent. Agencies are not required to follow such directives, but they are expected to make reasonable efforts to do so. Anytime Congress absolutely insists that a certain amount of money be spent on a specific item, it is included in the bill as a line item.

3. NCI did not "refuse to obey" the directive. In December, 1975, after Congress passed the appropriation bill but before it was enacted over President Ford's veto, NCI and NIOSH executives met to discuss it. NCI agreed to help fund NIOSH projects in occupational carcinogenesis provided that NCI could review them for program relevance, need and priority.

4. Nothing more was heard from NIOSH until last June when it submitted a list of proposed projects to NCI which would cost an estimated $2.4 million. NCI's response then was that since it was so late in the fiscal year, its money had already been obligated. NCI suggested that the projects be considered for funding with fiscal 1977 money.

5. By then, the House report on the 1977 appropriations bill was written, including a directive that $3 million from FY 1977 money "will be" transferred by NCI to the NIOSH program.

6. A few weeks ago a member of Obey's staff discovered that NIOSH had not yet received any 1976 money from NCI (1977 money is not yet available, since Congress has not passed the appropriations bill). Subsequently, NIOSH Director John Finklea renewed his request to NCI, telling NCI Director Frank Rauscher that proposals on the list of $2.4 million in projects had been reviewed, cleared and were waiting for funding.

7. NCI took another hard look at the list and at its own budget and came up with $920,000 of reprogrammed money out of the Div. of Cancer Cause & Prevention. The money was transferred to NIOSH this week.

8. The balance of the projects on the list, plus about $4 million in additional projects will be submitted to NCI by NIOSH for funding with 1977 money. Rauscher told the President's Cancer Panel last week that $3 million would be transferred to NIOSH when it becomes available.

There is little question that pressures from Obey stimulated NCI to scratch around and find the $920,000 in 1976 money. Obey's news release was sent out before that had been done. But it was inaccurate for Obey to claim that NCI had defied Congress, that Congress had directed that a total of $3 million be transferred from 1976 funds (rather than "up to $3 million"), and that NCI, instead of NIOSH, should be blamed for not moving faster.

Use of terms such as "blatant insensitivity to workers" and "arrogant disregard" of Congress sounds more like a politician hunting for headlines than someone interested in the facts.

One question remains unanswered: If Obey felt that it was so vital for NIOSH to have $8 million for the occupational cancer program, why didn't he put the entire amount directly into the NIOSH appropriation? NIOSH is an HEW agency, under the Center for Disease Control, and its appropriation was contained in the same bill as NCI's.

The explanation that the subcommittee wanted to encourage the two institutes to work together and to "get NCI involved in the practical problem of workers who are dying from exposure to unregulated chemicals" seems rather lame. NCI has no regulatory authority nor any health delivery function. Obey's little game of handing $3 million to NCI with instructions to give it to NIOSH instead of giving it directly to NIOSH did nothing to speed up implementation of the projects.

The three studies funded by NCI were for studies on the mortality of pesticide formulations; mortality of miners exposed to amphibole, an asbestos-like material; and for development of analytical methods for evaluating carcinogens.

NCI did not have to be coerced into cooperating with another federal agency. The Cancer Act requires NCI to be the lead agency in federal cancer-related activities, and in fact NCI already supports those activities with more than $20 million a year.

Rauscher told the National Cancer Advisory Board Monday that he considers the funds transferred to NIOSH "money well spent." He pointed out that NIOSH has "the right of entry" to obtain medical records, a power NCI does not have.

Delays on releasing results of carcinogen tests were due in part to personnel shortages caused by the Administration's job freeze, part to problems in the Carcinogenesis Program which brought about the reorganization of the program last spring.

ABSTRACTS OF PAPERS PRESENTED BY BREAST CANCER TASK FORCE

Following are abstracts of papers presented at the Sept. 8 meeting of Breast Cancer Task Force contractors. The papers describe ongoing research being performed by the Task Force and have not been published elsewhere.

IN VITRO GROWTH STUDIES OF NORMAL AND TUMOR CELLS — Aaron Bendich and Ellen Borenfreund

The growth properties of normal cells can be modified by their exposure in culture to DNA or to DNA-containing moieties such as viruses or sperm. In model systems, sperm were found to penetrate tissue-cultured rat liver epithelial cells or Chinese hamster bone marrow fibroblast-like cells, and altered progeny were obtained with cultural characteristics which resembled those of tumor cells. The changes included the formation of giant and multinucleate cells, loss of contact inhibition, increase in plating efficiency, heteroploidy, formation of polynucleate cells after Cytochalasin B treatment, and acquisition of the ability to grow in soft agar. These properties appeared to be acquired in a stepwise sequence and resembled those also seen after treatment of normal cells with carcinogens. These cultural growth properties are also shown by the established human mammary tumor cell line, SH-2. When exposed in vitro to mouse or to human sperm, penetration of the SH-2 cells occurred. Upon subsequent growth, the replicating cells showed an increased plating efficiency in liquid and in soft agar medium, and the proportion of multinucleate cells due to Cytochalasin B was increased. However, these effects were decreased when the cells were treated instead with DNA isolated from calf thymus or human spleen. The studies indicate that the in vitro growth parameters of mammary tumor cell lines, which may be an in vitro measure of malignant potential, can be modified by exposure to these external agents.

We have found that hamster cells acquire the ability to express mouse or rat fetal antigens after interaction with mouse or rat sperm, respectively. The reappearance of fetal antigens is a characteristic of animal and human tumors. Accordingly, we examined the SH-2 cells after incubation with mouse sperm but mouse fetal antigens could not be detected in the progeny. Several lines of human breast tumor cells were tested for the presence of ectopic human fetal or placental antigens with the hope that one or another might prove to be a useful tumor marker. Although many of the tumor lines showed no reaction when tested with antisera prepared against various fetal and placental antigens, a few gave positive tests as did a few primary breast tissue explants. The results suggest that the turning-on of a fetal expression may be a mark of tumorigenesis, but that one specific for mammary carcinoma is still not at hand.

Primary explants of normal and tumor breast tissues were examined by [^{3}H] thymidine autogradiography to compare the dynamics of their cell replication in vitro. No characteristic differences have been found. However, only a small proportion of the epithelioid cells replicated in either case, and it is therefore apparent that improved culture conditions will be needed to provide normal or tumor cell lines for further study and to help determine whether in vitro parameters are appropriate monitors for in vivo disease.

GROWTH CHARACTERISTICS OF CONTINUOUS MOUSE MAMMARY TUMOR CELL LINES — Janet Butel

The purpose of this project is to determine the effect of nucleic acid preparations on the biological properties of mammary cancer. Our approach to date has been three-fold: (1) To establish in tissue culture clonal cell lines derived from mouse mammary tumors induced by various agents, (2) To characterize these cell lines and determine which growth parameters correlate with transplantability in syngeneic hosts, and (3) To examine the uptake and fate of exogenous DNA in the cells.

Cell lines have been established from transplantable BALB/c mammary tumors which originally arose in response to (a) a hormone (estradiol), (b) a carcinogen (DMBA), (c) a virus (MTV-L), or (d) spontaneously, as well as from (e) a transplantable C_3H mammary tumor. Two or three clonal lines have been derived from each parental line. Several growth properties have been monitored in vitro, including saturation density, colony formation on plastic, and colony formation in methylcellulose. None of these properties was observed to invariably correlate with transplantability of the cells in syngeneic mice.

Studies have recently been initiated to examine the cultured tumor cell lines for altered surface properties associated with transformation (e.g., fucolipid composition, fucolipid metabolism, and glycopeptide size distribution). Preliminary results suggest that the MTV-L/BALB parental line has a fucolipid composition and fucopeptide size distribution characteristic of DNA and RNA virus transformed cell lines. In contrast, in the ESD/Balb-C13 line these membrane parameters are not as greatly altered.

The intracellular fate of isotopically labeled, exogenous viral (SV40) and cell (BSC-1) DNAs was followed kinetically in the murine mammary carcinoma cells, as well as in transformed cell lines of diverse origin. Exogenous DNAs become rapidly and quantitatively associated with the nuclei of normal murine mammary gland cells and those of the other tumor cell lines. In contrast, all of the mammary carcinoma cell lines tested thus far possess a reduced ability to transport exogenous DNA from the cytoplasm into the nucleus, suggesting that this defect in DNA transport may be characteristic of mammary carcinoma cells.

FACTORS EFFECTING GROWTH OF MAMMARY GLAND AND MAMMARY TUMORS — Frank Stockdale and H.W. Hsueh, Stanford Univ. Medical Center

We have found a factor(s) in serum which initiates DNA synthesis in normal mouse mammary gland and in mouse mammary tumor epithelium. This factor—mammary serum factor (MSF)—is relatively heat stable and has been partially purified by ionic exchange chromatography, gel filtration, and isoelectric focusing. This partially purified MSF has a molecular weight of approximately 11,000 and an isoelectric point of 5.5 to 6.0. MSF can be isolated from a variety of sera, but it is most active on mouse mammary epithelium when isolated from mouse or rat sera. Its activity decreases at least 50% in the sera of hypophysectomized rats with estrogen, prolactin, or growth hormone. No detectable change in MSF serum activity occurs with pregnancy or lactation. Very high concentrations of serum are required to initiate DNA synthesis in mammary epithelium from late pregnant and lactating mice. In this respect, mammary epithelium from late pregnant and lactating mice is very much like mouse mammary tumor epithelium—both are much less responsive to mammary serum factor than epithelium from non-pregnant or early-pregnant mice, but are equally responsive to insulin.

Present work focusing on both the biochemical and biological characteristics of MSF is as follows:

1) Further characterization of mammary serum factor.

2) The effects on mammary gland growth in animals injected with mammary serum factor. Epithelium from mammary glands of non-pregnant mice injected subcutaneously on three successive days with 1 mg. of partially purified MSF has a higher initial rate of DNA synthesis in response to both insulin and serum in vitro than saline-injected control mice.

3) Hypothesis that the mammary gland consists of more than one preliferative cell population. We have found there are two operationally different populations of epithelial cells in normal mouse mammary gland and mammary tumors. The differences in response to the two mitogens we have studied, MSF and insulin, suggest either two proliferative types of epithelial cells, or a single type which is resting in two different phases of the cell cycle prior to mitogen exposure. Our studies suggest that the relative proportions of the two operationally different growth types of epithelium change during pregnancy and mammary tumor development.

4) Growth promoting substances from normal and malignant mammary epithelium. Both mammary tumor epithelium and normal mammary epithelium produce mitogenic substances in vitro. The response of normal epithelium to these mitogens suggests tumor cells produce more mitogen or a more active mitogen. The sera from mice bearing various sized tumors and varying numbers of tumors is currently under analysis to determine if tumors in vivo produce growth-promoting materials which reach the general circulation and affect the growth of mammary tumors.

FACTORS MODIFYING RODENT BREAST CARCINOMA CELLS IN VITRO AND IN VIVO — P.O. Kohler, D. Medina and J.S. Norris, Baylor College of Medicine

The effects of stromal and fibroblast-like cells have been studied on the growth and differentiation of rodent breast carcinoma cells in culture. We have developed multiple cloned strains of preneoplastic and neoplastic rodent breast epithelioid cells including 4 from the R3230-AC rat tumor, 6 from new DMBA induced tumors in Sprague-Dawley rats, 9 from GR mice and 8 from BALB/c mice. Ultrastructural studies on many of these cells have demonstrated the presence of desmosomes and microfilaments. We have also isolated normal fibroblasts and 12 cloned strains of malignant fibroblast-like cells from the same animals. Several of the strains isolated from both rat and mouse carcinoma and hyperplastic alveolar nodule cells formed tumors on reinjection into appropriate host animals.

The presence of saturable high affinity ($Kd = 7.0 \times 10^{-10}$ M) estradiol binding in some of the epithelioid cell lines has been demonstrated by the whole cell binding technique. Verification of this technique for mammary carcinoma has been accomplished by utilizing the human

MCF-7 cells developed by Marvin Rich. No saturable progesterone binding has been demonstrated although non-saturable uptake has been demonstrated in all cell lines tested.

The cultured epithelioid cells have been tested for effects of stromal or tumor fibroblast-like cells by a variety of techniques. No clear effect on morphology, hormone-binding or growth has been demonstrated in organ culture or monolayer co-culture. However, fibroblast-like cells appear to inhibit estradiol binding when grown on the opposite side of Nuclepore filters in a special Mark II Rose chamber. In contrast, epithelioid GR mouse tumor cells appear to exert a toxic effect on GR mouse fibroblasts grown on the opposite side of the filter as demonstrated by the scanning electron microscope.

We have also examined the interactions of mouse mammary nodule cells and normal mammary cells on the neoplastic transformation in vivo. Nodule line D1 has a low tumor potential, nodule line D2 has a moderate tumor potential, and line C4 has a high tumor potential. The first two nodule lines (D1, D2) arose in hormonally-stimulated BALB/c mice (pregnancy, pituitary isograft), whereas line C4 arose in a DMBA treated BALB/c mouse. Nodule lines were established by serial transplantation of samples of the nodule tissue in the mammary fat pad. The experiments involve making "single" cell suspensions of mammary cells using a procedure developed by Prop and modified by DeOme. Dissociation led to enhanced tumor potential, even in the low oncogenic line D1. Additional experiments have shown that results cannot be explained on quantitative differences between the number of cells injected as compared to the number of cells in a small implant.

The interaction of normal mammary cells on the tumor potential was examined in nodule line D2. In these experiments, 3 groups of mice were injected in the mammary fat pad with either 10^5 D2 cells, 10^5 D2 cells plus 10^5 normal mammary cells (pregnant), and 1.4×10^5 D2 cells plus 0.7×10^5 normal mammary cells. The presence of normal cells inhibited markedly the tumor potential of normal cells. The experiments are encouraging since they indicate that normal mammary cells can inhibit the neoplastic transformation in nodule cells.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg., NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CB-74093-31

Title: *Cell-mediated immunity to rodent tumors*
Deadline: *Jan. 3, 1977*

NCI is seeking a laboratory to perform in vivo and in vitro studies of cell-mediated immunity in rodents to tumor associated antigens of virus-induced tumors. Since these studies are to be performed in close collaboration with the NCI staff, the facility must be within 30 minutes of normal driving distance from the NCI Bethesda campus.

Contracting Officer: Robert Townsend
Biology & Diagnosis
301-496-5565

CONTRACT AWARDS

Title: Human melanoma: Evaluation of BCG immunotherapy of patients without detectable disease after removal of tumor containing lymph nodes
Contractor: UCLA, $332,723.

Title: Chemical characterization of purified thymic products or other agents promoting lymphocyte differentiation
Contractor: New York Univ., $113,209.

Title: Analysis of serum requirements for in vitro immunological studies
Contractor: Univ. of California (Berkeley), $72,370.

Title: Detection of antigen binding activity of transplantable T-cell tumors
Contractor: Yale Univ., $57,620.

Title: Breast cancer detection demonstration project
Contractor: Rhode Island Hospital, $265,910.

Title: Replication of oncogenic RNA viruses
Contractor: Columbia Univ., $486,670.

Title: Research on cancer incidence and patient survival data
Contractor: Connecticut State Dept. of Health, $587,536.

Title: Immunotherapy with in vitro lymphocyte sensitization
Contractor: Stanford Univ., $126,509.

Title: Tumor registry program and allied activities
Contractor: Univ. of California (San Francisco), $136,704.

Title: Pharmacologic and carcinogenic studies in neonatal primates and maintenance of a primate breeding colony
Contractor: Hazleton Laboratories, $15,000.

SOLE SOURCE NEGOTIATIONS

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

Title: Clinical oncology program
Contractor: Institute for Medical Research of Santa Clara County, Calif.

Title: Facility to provide and maintain subhuman primates for cancer research
Contractor: Litton Bionetics.

The Cancer Letter—*Editor* JERRY D. BOYD

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