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RAUSCHER TO BECOME ACS VP FOR RESEARCH NOV. 1; SEARCH STARTS FOR NEW NCI DIRECTOR

Frank J. (Dick) Rauscher Jr. sent a letter to President Ford this week, resigning as director of the National Cancer Institute. He was leaving "for personal reasons," Rauscher told the President. On Nov. 1, Rauscher will join the staff of the American Cancer Society as senior vice president for research.

Rauscher made the decision last week to accept the ACS offer after it became apparent that Congress would take no action on bills to raise his salary and that of all NIH institute directors. His salary at ACS will be approximately twice the $37,800 government pay, the top federal civil service figure. He also will be able to lecture and write for pay, something he was prohibited from doing as NCI director.

It was solely for financial reasons that Rauscher decided to make the

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In Brief

MONEY BILL AWAITS PRESIDENT'S DECISION; M.D. ANDERSON TO DEDICATE NEW FACILITIES

HEW APPROPRIATIONS bill finally made it through Congress, when both houses agreed to a compromise on the abortion issue. If the President signs it, NCI could have its 1977 money at the start of the fiscal year. Even if there is a veto, Congress will vote on the override before it adjourns early in October. Only if a veto is sustained will there be a considerable delay, although recision requests could hold up some funds for a couple of months. . . . **M.D. ANDERSON** will wrap up its $60 million expansion program with ceremonies Oct. 2. A new hospital wing, clinic building, chapel, radiation therapy center and two more floors of facilities for cancer research will be dedicated. The new wing, the Lutheran Hospital Pavilion, adds 330 beds in single-occupancy rooms, bringing MDA's capacity to 600 beds. The new clinic will accommodate 1,200 outpatients daily. The UICC Committee on International Collaborative Activities will meet at MDA Sept. 29-30, and the President's Cancer Panel will meet there Oct. 1. . . . **NCI STAFF** appointments in the Div. of Cancer Research Resources & Centers: Barbara Stanford, to chief, Cancer Biology Branch; Robert Woolridge, to program director for Detection & Diagnosis; and William Straile, to director of the National Pancreatic Cancer Program. . . . **HOWARD SKIPPER**, president and director of Southern Research Institute, has resigned from the National Cancer Advisory Board. . . . **AMERICAN SOCIETY** of Therapeutic Radiologists meeting is scheduled Oct. 13-16 in Atlanta at the Hyatt Regency. . . . **MORTIMER LIPSETT**, former chief of the NCI Endocrinology Branch and more recently director of Cancer Center Inc. in Cleveland, is the new director of the NIH Clinical Center. Griff Ross, who has been acting director, was appointed deputy to Lipsett.

FINANCIAL PRESSURES FINALLY FORCE RAUSCHER TO RESIGN, JOIN ACS

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move. Three children in college and two more who soon will be there have pushed his family's finances to the limit. Even so, he delayed the decision for months, hoping that Congress would give him a raise.

"I really hate to leave," Rauscher told *The Cancer Letter.* "I think I have the best job in the federal government." He is proud of the accomplishments of the National Cancer Program but feels that "we are just beginning to see the results" of the massive increase in cancer research and control brought about by the National Cancer Act of 1971. Leaving at a time when he expects major advances in treatment and diagnosis, in prevention, in basic science to come along was a painful decision.

The ACS job is one of the few, if not the only one, that will permit him to remain in the Cancer Program. He had determined that he would not take a position with a university or commercial organization that was receiving substantial support from NCI, to avoid even the appearance of an ethical problem. One job he seriously considered, with the giant Whittaker Corp., would have kept him completely away from the Cancer Program (and away from the country most of the time, which is one reason he turned it down).

With ACS, Rauscher will remain an active participant in the Cancer Program. His talent as an enthusiastic and articulate supporter of the program—perhaps his No. 1 attribute—will still be available to stimulate and encourage his fellow scientists, the medical community, the public, and Congress.

Rauscher will be running a $33 million research program at ACS—small compared with NCI's budget in FY 1977 of $815 million—but still probably the second largest cancer research program in the world.

Benjamin Byrd Jr., ACS president, said in a statement issued by the Society that "Dr. Rauscher's outstanding record in cancer research and leadership makes him eminently qualified for his position at the American Cancer Society." Byrd noted that ACS was a pioneer in both basic and clinical cancer research and that "Dr. Rauscher's appointment would further advance the society's varied and imaginative research program and bring new initiates to the search for causes and cures of cancer."

Byrd emphasized the long partnership of ACS as a voluntary private agency with NCI and said this collaboration would be strengthened. Rauscher has served as a member of various ACS advisory committees.

Arthur Holleb has been senior vice president for research and medical affairs at ACS. He will surrender the "research" portion of that job to Rauscher, permitting him to devote full time to clinical matters.

Holleb said the appointment of Rauscher to head ACS research programs affirmed the importance of this aspect of ACS activities "with the single biggest expenditure of the Society—over $30 million." Holleb also pointed out that Rauscher "has steadfastly adhered to the precept of attaining proper balance between basic and clinical research, both being essential for the progress of cancer control."

Rauscher, 45, received his bachelor's degree at Moravian College and his PhD in microbiology from Rutgers Univ. He went to work for NCI in the Laboratory of Viral Oncology in 1959, later was deeply involved in establishing the Special Virus Cancer Program and was chairman of that program from 1964 to 1970. From 1969 to 1972 he headed the Etiology Div., now the Div. of Cancer Cause & Prevention.

Rauscher's scientific credentials were firmly established when he discovered a new leukemogenic mouse virus and its induced disease. The Rauscher virus produces lymphoid leukemia in mice and rats in 12 days. The very short latent period and the high potency and stability of the virus permits studies on its chemotherapeutic, biochemical and physical properties in one-fourth the time required for other lab model systems. The Rauscher virus has been supplied to more than 800 labs throughout the world, and more than 1,000 scientific papers have been published about it.

After the National Cancer Act became law late in 1971, setting up NCI in a special category with a certain degree of independence from both NIH and HEW, many Cancer Program advocates felt the new big effort should start with new leadership.

The Act created the President's Cancer Panel, and one of its duties spelled out in the law is to advise the President on the selection of the NCI director. Panel Chairman Benno Schmidt, with the concurrence of fellow Panel members and with the counsel of others in and out of government, submitted Rauscher's name to President Nixon. Rauscher was appointed May 5, 1972.

Now Schmidt has the job to do again. "I'm terribly sorry to see Dick Rauscher leave," Schmidt said. "He has done an absolutely outstanding job. He was ideally qualified for the job and will be very difficult to replace."

Schmidt said Rauscher has gained "tremendous respect, in Congress, the White House, the scientific community and members of the public who have gotten to know him and his work. He is such an eminently decent human being, he can make decisions people do not entirely agree with, without incurring their animosity.

"I hate to see him leave, but it is not fair to urge him to stay when he has reached the limit of his resources."

Rauscher gave six weeks notice, to give Schmidt and the Panel enough time to find a successor and permit the President to make a new appointment by Nov. 1, if he so desires.

Schmidt said he did not want to comment on any aspect of the search for a new director until after he

has heard from the White House. He did indicate his mind was open on the question of whether the appointment should come from within NCI or from outside government. "There are a number of people eminently qualified in both places," he said.

COMMITTEE HOLDS UP ON FCRC RFP, ASKS FOR SIX MONTH DELAY ON NEW CONTRACT

NCI executives who decided it would be a good idea to convene an ad hoc committee to help write the workscope for the RFP in the recompetition of the contract for operation of the Frederick Cancer Research Center now may be having second thoughts about it.

The committee held its first meeting last week and did not even look at the draft of the workscope drawn up by NCI contract staff. Instead, the members spent most of the day trying to determine what their role should be. Most of them felt that the job of writing the scope of work that will guide the successful contractor for another five years really should involve a full-scale review of the FCRC operation, its relation to NCI and the scientific community, and the goals set out for it by NCI and the National Cancer Advisory Board.

The committee adjourned without reaching any conclusion, except to tentatively agree to meet again in November. The members asked NCI staff if they would consider delaying the RFP for six months to permit more thorough review of the entire operation.

The present contract with Litton Bionetics Inc. expires Sept. 25, 1977. NCI had planned to issue the RFP late in October, complete review of the proposals in the spring, and complete negotiations for the new contract by early summer.

If the six-month delay is granted, it probably would mean that the LBI contract would be extended for at least six months and perhaps for an entire year.

NCI could delay the RFP for a month without disrupting the schedule too much. This would give the committee another chance to go over the workscope in November, if the members agree to limit their advice to that task.

William Payne, scientific coordinator for NCI at Frederick, said a staff meeting will be held in a few days to decide what to do about the committee's request.

The committee is chaired by James Liverman, assistant administrator for environment & safety at the Energy Research & Development Administration. Other members are Harold Amos, Harvard, member of the National Cancer Advisory Board; Gloria Heppner, Roger Williams General Hospital in Providence, R.I.; Timothy O'Connor, Argonne National Laboratory; Wade Parks, NCI Viral Oncology Program; Sidney Weinhouse, Fels Research Institute; Bernard Weinstein, Columbia Univ.; Hilary Koprowski, Wistar Institute; Frank Dixon, Scripps Clinic & Research Foundation; and John Burns, Hoffman-LaRoche. Dixon and Burns missed the meeting.

James Peters, director of the Div. of Cancer Cause & Prevention which is responsible for the major part of the work at Frederick, commented somewhat ruefully to the committee, "When you ask for advice, you're going to get it. And when it comes from an august group like this, it is hard to ignore."

Peters said the goal of FCRC is to "become a center of excellence" with its basic science program and to support the National Cancer Program. "The die is already cast. NCI divisions have invested time, effort and money in Frederick and are fairly satisfied with what has happened so far. I don't think we'll want to make sweeping changes."

O'Connor asked, "Are we getting full national value for the $25 million we're spending there each year, relative to putting that money into grants or contracts elsewhere? Why is it desirable to go there? Because of an advantage as an administrative tool? Because of scientific excellence?"

Peters answered that technical excellence was one reason, along with "the ease with which we can implement something. We can achieve something there that we couldn't anywhere else. We certainly couldn't do it here on the NIH campus. We don't have the positions or the space." Peters said that FCRC offers the capability of quickly following opportunities. "When we have a major advance, it is a place to go to get tests underway in a few days (as opposed to nine months or more with a contract elsewhere). If we get an epidemiological lead, when we need to test a compound right now, we can do it immediately."

Peters said NCI hoped the committee would answer these questions: "Are we asking the right questions in the RFP? Are we asking of proposers the questions we need to take FCRC in the direction we want to go?"

FCRC has two major roles, the largest of which is as an extension of NCI programs and a resource for NCI divisions. The other is the basic research program, in which the contractor proposes the nature, approach and emphasis of the research.

The basic research effort during the year just ending was funded at $2.9 million, 12% of the total. The resource-program extension efforts were: viral oncology, $7.7 million, 32%; chemical carcinogenesis, $6 million, 25%; animal resources including animal production, animal holding, and diagnostic animal health and quarantine, $2.5 million, 11%; biohazards and environmental control, $.6 million, 3%; cancer treatment (chemotherapy fermentation and biological markers), $3.5 million, 15%; special histopathology service, $.17 million, less than 1%.

In addition, support services are provided for studies being conducted by the National Institute of Neurological & Communicative Diseases & Stroke in the amount of $.3 million.

Funds come out of the budgets of the appropriate

NCI programs. In some cases, Frederick competes with other contractors for a job and does not always win.

The NCI contracts office has been contacted by 20 organizations which have expressed interest in the recompetition. Representatives of seven organizations, including LBI, attended the committee meeting. They were Dynalectron Corp., which operates a number of government owned facilities including the White Sands Proving Ground in New Mexico; EGG/ Mason Research Institute, which narrowly lost out to LBI four years ago; Microbiological Associates, one of the five finalists in the first competition; Information Applications Associates; and Program Resources Inc.

The proposed workscope drafted by NCI fills 70 pages and is broken down by program areas. Excerpts from the draft follow:

VIRAL ONCOLOGY

The overall objective of the Viral Oncology Program at FCRC is to conduct investigations on oncogenic and suspected oncogenic viruses and their interactions with host cells to: (1) determine whether viruses comparable to those known to induce cancers of laboratory and domestic animals are associated with, indicative of, or, in fact instrumental either alone or as co-carcinogens in inducing the development of cancer cancers (2) define the character and mode of action of virus and/or viral components in their relationships to such cancers, and (3) to devise therapeutic and preventive measures for their control. Functional laboratory elements within the VO/FCRC program will conduct basic, exploratory and applied research on programs that are or could be vital to the Cancer Program. Moreover, as a highly important support activity a substantial resource effort will be maintained for the purpose of providing critically needed working materials for the Virus Cancer Program both within and outside FCRC.

As work in given areas is performed, particular research or resource goals may receive changes in emphasis; objectives may be modified and/or previously established ones postponed or eliminated. Taking into account, however, that major portions of the viral oncology program have been newly restructured for FY77, there is no appreciably outstanding requirement for substantive changes in work scopes in initiating program in FY 77-78.

RNA Virus Laboratory—Research in this area will be directed toward achieving objectives within several project elements designed to elucidate the potential role of RNA viruses as etiological agents in human cancer. Investigative research will be conducted on host range, natural history, replication cycles, and and molecular biology of both B and C types. Among studies to determine species distribution, attempts will be made to detect related viruses and/or viral-induced components in human materials. Some redirected effort should be concerned with the development of methods for studying chemical and viral-chemical co-carcinogens.

DNA Virus Laboratory—The contractor will engage in a series of studies for the purpose of determining the carcinogenic or co-carcinogenic role of DNA viruses in the neoplastic process. Basic research will be conducted with herpesviruses of human and non-human primate origin in in vivo and model in vitro systems to elucidate mechanism of action in tumorigenesis and cell transformations. Biological, serological and biochemical techniques will be designed and/-or perfected to identify significantly active (e.g., transforming or other) regions of herpesvirus, to detect genomic fragments and proteins that might be found specifically in transformed cells, to characterize factors released from tumor cells in vivo and/or in vitro as markers of oncogenesis, and to investigate the feasibility of using specific viral or viral induced component reagents to search for evidence of these in humans and to attempt to correlate their presence with the incidence of human cancer.

CHEMICAL CARCINOGENESIS

At FCRC the Chemical Carcinogenesis Program has as a primary objective the development of a unique national resource capable of initiating and evaluating a broad range of approaches to effectively identify human carcinogens. To do this requires a coordinated interdisciplinary approach which consciously emphasizes the integration of basic and applied research. Broadly, the areas of research being supported are:

1. Development of methods and testing to identify environmental chemicals which are carcinogenic or co-carcinogenic.

2. Investigation of host-chemical interactions with the aim of being able to alter host susceptibility and response after exposure.

3. Attempts to elucidate mechanisms of carcinogenesis on the premise that an understanding of the process will permit the manipulation of factors which will block or reverse tumor formation.

Bioassay Research—The FCRC Bioassay Program has had three significant taks: (1) conduct research to evaluate and improve methods currently being used for the major portion of routine bioassays; (2) conduct a limited number of routine bioassays in which chemicals of special interest are tested to meet specific needs; and (3) provide testing support for other FCRC research programs.

In Vitro Carcinogenesis—Interest has increased over the past several years in exploiting a number of in vitro cell systems to develop rapid, reliable and probably relatively inexpensive procedures for screening chemicals for potential carcinogenicity. The In Vitro Carcinogenesis Program at FCRC has concentrated on standardizing a hamster embryo cell transformation system.

Proposed work will include standardization of the cell system, investigate criteria in addition to morphology which may be reliable indicators of in vitro

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$_3$H 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 = 7.0×10^{-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 proposql 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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