THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 3 No. 19
May 13, 1977

The Cancer Letter, Inc.
Subscription $100 per year

1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

NCI STAFF SUGGESTS NEW COMMUNITY ONCOLOGY, PAIN CONTROL, NURSE, PATHOLOGY CENTER PROJECTS

A variety of new programs, including a Community Clinical Oncology Program that may not be rated high enough by NCI staff to be funded, have been proposed by the Div. of Cancer Control & Rehabilitation for initiation with fiscal 1978 money. The proposals will compete for $4.7 million which DCCR Director Diane Fink said will be

(Continued to page 2)

In Brief

ONE MORE COMMITTEE REVIEW NEEDED FOR L.A., RHODE ISLAND; ANIMAL TESTS IN FACTORIES(?)

LOS ANGELES and Rhode Island proposals for implementation of their Community Based Cancer Control Programs will get at least one more review by NCI's Community Activities Review Committee. ***The Cancer Letter*** reported (April 29) that Div. of Cancer Control & Rehabilitation staff could proceed with contract negotiations without further review by the committee; however, the committee will conduct a mail review of the final proposals. Approval of both is still nearly certain. . . . **ENVIRONMENTAL CARCINOGENESIS** experts Ernst Wynder, Arnold Brown and Henry Pitot, were talking. Wynder: "Certain carcinogens are not carcinogens by themselves, but become clinically active only when certain modifying factors are present. Cigarette smoking is associated with bladder cancer. The Japanese have little bladder cancer but smoke heavily." Brown: "Sheldon Samuels (AFL-CIO representative on the National Clearinghouse for Environmental Carcinogens) suggested we ought to place experimental animals in factories, like canaries in mines. . . . I'm concerned about spending $200,000 each on animal tests. They are more than carcinogenicity tests but are toxicity tests. I would like to have normal livers and bladders looked at even when there are no gross tumors. It would be an extra burden on pathologists. Throwing away information so expensively gathered is not intellectually satisfying." Pitot: "One way to get around the burden on pathologists is to use PhDs in pathology. Also, we need to look at animals earlier. We can get answers before 24 to 36 months." James Peters, director of the Div. of Cancer Cause & Prevention, added that the National Center for Toxicological Research uses "parapathologists," and that "it seems to be working". . . . **BENNO SCHMIDT**, chairman of the President's Cancer Panel, suggested that "if we just increased the budget of the National Institute of General Medical Sciences enough, we would not have to fund basic research through the National Cancer Institute." Alan Rabson, director of NCI's Div. of Cancer Biology & Diagnosis, said, "I would have to agree with that." "I know you would have to agree," said Schmidt, who also knows that NIGMS Director Ruth Kirschstein is Mrs. Alan Rabson.

DCCR TO HAVE $4.7 MILLION AVAILABLE FOR NEW PROJECTS; DECISION BY JULY 1

(Continued from page 1)

available for new programs from the 1978 budget.

A list of project ideas developed by DCCR staff was submitted to the Cancer Control & Rehabilitation Advisory Committee for its consideration. The list also included current projects with estimated 1978 funding for each and where each will fall in emphasis—high, low or present status.

Committee members were asked to submit written comments, and some will be asked to attend a meeting with staff later this month to help work out priorities. Fink said she hoped the division's planning could be completed by July 1, so that RFPs and RFAs (requests for grant applications) could be ready to go out "as soon as possible." The 1978 fiscal year starts Oct. 1.

The Community Clinical Oncology Program proposal was one of 10 drawn up by the Treatment, Rehabilitation & Continuing Care Branch. Estimate for 1978 funding was $1.5 million for the clinical oncology project, the highest of the 10. But Donald Buell, program director for medical oncology who drew up the proposal, told ***The Cancer Letter*** that two other projects he had suggested, in pain control, deserved higher priority than community clinical oncology. Buell also felt that a proposal to support development of a master's program in nurse oncology could be rated higher.

DCCR already is supporting a Clinical Oncology Program with six contracts, at San Jose, Grand Rapids, Indianapolis, San Antonio, Allentown, and Walla Walla. A seventh is still in the planning phase, at Ada, Okla. Those were limited to community hospitals with no affiliation with universities or cancer centers, with the goal to establish multidisciplinary cancer management. Contractors were required to develop management guidelines, demonstrate support from community physicians, obtain multidisciplinary representation, plan rehabilitation programs, and coordinate community resources.

The new proposal would enable entire communities to organize programs, and would encourage cancer centers or universities to work with community hospitals "to establish community wide, coordinated oncology programs to implement modern diagnostic and staging techniques, proven modalities of therapy and advanced rehabilitation and continuing care techniques," according to DCCR's description of the objectives.

Buell said he had envisioned from five to 10 contracts, with each receiving $75,000 the first year for planning and $150,000 the second and third years for implementation, with local matching funds the last two years.

"But we have to decide if we could demonstrate something with the new program in addition to what we are getting from the original one," Buell said. That is the key to whether or not it will ever see the light of day.

The description of activities that would be required of the contractor makes it seem like a mini version of the Community Based Cancer Control Program but without the prevention and public education aspects and without the absolute demand for full community participation:

—Plan a community wide clinical oncology program organizing existing resources to ensure sound multidisciplinary evaluation and treatment of patients with cancer.

—Develop through community physician participation sound management guidelines for the 10 to 15 most frequently seen cancers.

—Provide evidence for full community participation. Where this is not possible or appropriate, justification must be presented.

—Organize hospital and community resources to provide comprehensive rehabilitation and continuing care for cancer patients.

—Evaluate the program for acceptance, utility and success using the tumor registry and appropriate quality control and data management techniques.

Many of the proposals which get approval for 1978 funding will turn up as RFPs, leading to contracts. Some may be channeled into Cancer Research Emphasis Grants—DCCR is under pressure to spend at least 25% of its extramural funds through grants, and Fink said it might be as high as 30% next year. The division also funds investigator-initiated grants, and in fact is supporting seven grants for research on various aspects of pain control, totaling between $500,000-$600,000.

Staff planners estimated they could spend, with high priority, $400,000 in 1978 on new miscellaneous rehabilitation grants and another $400,000 on new psychosocial rehabilitation grants.

Buell's two proposed contracts on pain are:

—A study of cancer pain, $150,000 in 1978. Objective is to document and eliminate the problem of cancer pain, its magnitude and consequences, determine the current patterns of pain care and secure the data base necessary to plan effective programs in cancer pain control.

The contractor would plan and implement methods to obtain valid data on the epidemiology and natural history of pain in patients with cancer; assess the choice, timing, and range of pain treatment methods currently in use; determine the degree of disability attributable entirely or predominantly to pain associated with cancer; and make recommendations for a coordinated approach to pain management for cancer patients.

—Pain control in cancer, $600,000 in 1978. Objective is to demonstrate that a planned, prospective, combined modality approach to cancer pain results in more effective pain control and significantly de-

creased disability when compared to traditional pain management.

The contractor would organize pain management teams to implement planned programs of pain control; describe the composition of the team based on the needs and resources of the institution, assuring multidisciplinary participation; describe the patient population to be served; devise and implement both in-patient and outpatient pain management plans; describe a plan that insures a prospective approach to pain management for the individual cancer patient; and devise and implement methods for evaluating the success of the multidisciplinary pain management approach.

Other new projects suggested by the Treatment, Rehabilitation & Continuing Care Branch included:

—Improved program for terminal care in cancer, $1.5 million in 1978. Objective is to utilize existing knowledge about the deficiencies in resources for terminal care to plan and implement a solution and to identify or recognize problems.

The contractor would provide the continuing care of a select population of terminal cancer patients for the purpose of study and field test. A sufficient sample size 300-700 of patients with end stage disease must be available. Though home care of the patient is to be emphasized, space, staff and facility for inpatient care must be designated. Management guidelines for the effective management of clinical symptoms common to terminality must be developed and utilized throughout the contract period.

—Training at the master's level in oncology nursing, $600,000 in 1978. Objective is to educate nurses at the master's level in oncology nursing as clinicians and practitioners who will be capable of practicing a wide range of skills consistent with an expanded role of the nurse, to function in a complex clinical situation and in a number of settings as a collaborative member of the cancer team, to alleviate the deficits in availability and quality of cancer patient care.

The contractor would develop guidelines and delineate role for oncology nursing practice at this level so that activities are well defined to avoid legal and ethical conflicts with nurse practice acts; develop curriculum and objectives which would include a core unit of instruction and preceptorship in clinical oncology nursing; develop measurable outcome criteria for this practitioner; and recruit students and implement the program.

—Outpatient drug contract, $30,000 in 1978. Objective is to identify drugs employed in treatment, continuing care and rehabilitation of cancer patients, determine the extent to which costs of these drugs are reimbursed by third party payers, the extent to which positive incentives exist to prescribe the most appropriate drugs in the most appropriate setting, determine incentives needed to change inappropriate care and mechanisms to implement these incentives.

The contractor would undertake a literature search and consult with oncologists to identify the most commonly prescribed cancer control drugs, compile a data base, and evaluate relative treatment costs utilizing various regimens.

—Analysis of outpatient/ambulatory health care, such as home health care for cancer patients, $25,000 in 1978. Objective is to demonstrate that home health care and related outpatient services, especially in the case of terminal illness, can be of equal or superior quality and lower cost than comparable inpatient services, and to identify associated key variables and critical attributes.

This pilot study effort would estimate the cost and assess the efficacy of alternative care modalities (e.g., home health, acute hospital, and nursing home) for various disease sites.

The Prevention Branch came up with suggestions for three "Model Primary Cancer Prevention" programs for comprehensive cancer centers, Community Based Cancer Control Program contractors, and state health departments:

—Comprehensive centers would be asked to integrate cancer prevention into the health care and educational system; reduce the cancer impact by education; disseminate information and knowledge on chemical carcinogens or suspected carcinogens to the practicing medical community and the public; and develop awareness mechanism and alert system to the medical community and the public about the possibilities of avoiding the exposure to environmental carcinogens and suspected carcinogens.

Monographs on key carcinogens, cancer control and prevention strategies and health and smoking educational programs developed under several separate contracts supported by DCCR will be used to demonstrate the feasibility to base cancer control programs in comprehensive cancer centers.

CBCCP contractors would be asked to perform the same tasks, using the same monographs, as the comprehensive centers, with the objective of demonstrating the feasibility of basing cancer control programs in community cancer control efforts.

The staff estimated each of the programs would cost $150,000.

—State health departments would be asked to develop and implement prevention programs to serve specific needs of communities served by comprehensive centers. They would develop occupational and environmental prevention programs. Staff allocated $150,000 for this effort.

The Prevention Branch also suggested that state of the art workshops in prevention be organized in 1978, on smoking cessation, public education strategies in smoking, bladder cancer detection and prevention, and ultrasound in detection and prevention.

The big new project suggested by the Detection, Diagnosis and Pretreatment Evaluation Branch was for development of a network of nine anatomic pathology reference centers. The project would cost

$1.35 million in 1978, the first year in three year contracts. Objective is to provide standardized review, evaluation, diagnostic terminology and clinical implications for cancer diagnosis, control and treatment, one or more site-specific PRCs to be provided for each major cancer site (i.e., cervix, breast, head and neck, clinical oncology, leukemia and lymphoma, colorectal, bladder/prostate or others) covered by current or proposed DCCR programs.

The branch also suggested a program for colorectal cancer screening planning and field trials. It would cost $100,000, to take from the planning conference scheduled for July and from state of the art conferences the best consensus items on protocols, tests, markers and procedures into a shakedown field trial prior to future possible mass screening projects.

The branch, which has funded state of the art workshops for cancer of the cervix, endometrium and bladder, in addition to the colorectal workshop, asked for funds to support similar workshops for cancer of the prostate and cancer in hard to reach persons.

MAMMOGRAPHY GUIDELINES TIGHTENED, LIMITED TO HIGH RISK GROUPS UNDER 50

New restrictions on routine mammography screening for women under 50 participating in the NCI-American Cancer Society sponsored Breast Cancer Detection Demonstration Project were recommended by the Cancer Control & Rehabilitation Advisory Committee last week.

The committee approved a motion asking the 27 BCDDP project directors to limit mammography for women under 50 to two high risk groups—those with a previous history of breast cancer, and those whose mothers or sisters had had the disease. Mammography would continue to be offered to women over 50.

Maurice Reizen, director of the Michigan Dept. of Health, was the only one of 12 committee members to vote against the motion. He did not explain his vote, but later expressed concern about "the great difficulty in reconciling routine screening without a good definition of high risk . . . blind screening is a travesty."

The committee took its action without being told that the project directors, meeting previously to consider mammography risks in light of the three NCI-commissioned studies of the controversy, had reached the same conclusion the committee did.

Diane Fink, director of the Div. of Cancer Control & Rehabilitation, told the committee that "we need some advice on where we go from here" with BCDDP. She offered four alternatives:

—Continue under the interim guidelines adopted last August, in which routine mammography screening for women under 50 was dropped but younger women were permitted to receive mammography if their physicians so requested, and if they were in certain high risk groups. In practice, almost any woman who requested a mammogram received it, presumably after the possible risk had been explained to her.

—Discontinue all mammography for women under 50.

—Discontinue all mammography for women under 50 except for those in more limited high risk groups.

—Discontinue all mammography in the program.

Fink said that since adoption of the interim guidelines, 75% of the women under 50 in projects returning for their annual examinations received mammography. Of those over 50 returning for exams, 92% received mammography.

Committee members were surprised that the percentage was so high among younger women, considering the furor that erupted last year when the reports about radiation hazards possibly outweighing the benefits were made public.

Fink said that the figures were compiled during the transition period, starting immediately after the interim guidelines were announced. The figure from the first of this year at one center had dropped from 90% to 65%.

Richard Costlow, chief of the Detection, Diagnosis & Pretreatment Evaluation Branch, told ***The Cancer Letter*** that the younger women possibly opted for mammography because most of them may have felt they were at high risk, which is why they enrolled in the project.

Costlow also pointed out that the figures could be somewhat misleading. The ages used in reporting data are those at the time of entering the project. Thus, some women who were in their late 40s when they enrolled are now over 50 and are receiving annual mammograms. They would be included among the 75% of women under 50 receiving mammography since last August.

Oliver Beahrs, head of the general surgery section at the Mayo Clinic and vice chairman of the committee, is chairman of a group that is evaluating all aspects of the BCDDP, including radiation exposure. The group is scheduled to make its report in June.

Beahrs said that he was not ready to present any conclusions from the study, but that based on interpretation of data from the HIP (Health Insurance Plan of New York) study, which formed the rationale for the BCDDP, the value of mammography to women over 50 had been demonstrated. "Until our data is evaluated, it is obvious to our committee that mammography plus physical examination be continued for women over 50," Beahrs said. "Also, mammography should be continued for women at high risk under 50."

Beahrs pointed out that women with a previous breast cancer had an increased risk of 12-20% of getting another cancer. The risk of a woman whose mother or sister had breast cancer is two to four

times that of the population at large, he said.

Saul Gusberg, committee member and chairman of the Dept. of Obstetrics & Gynecology at Mount Sinai, asked if cystic disease could be considered an increased risk factor. Beahrs said that "that risk is soft. We believe it is increased, but not to the magnitude of other factors. I would be inclined not to include those with cystic disease as those to be routinely screened."

Fink brought up the question of informed consent, which she said has caused "mass confusion." Some critics have charged that informed consent procedures have been lax. She said that all of the 27 projects have had institutional review and clearance, meeting NIH requirements.

There have been four versions of the informed consent form participants must sign. The first two did not mention radiation risk, Fink said, but the third revision, in May 1976, did.

"The new form we are using now had more authors than the Bible," Fink said. Critics of the program, including John Bailar of NCI and Sidney Wolfe, director of the Health Research Group, participated in the latest revision.

The "consensus" meeting on mammography, originally planned by NCI for July to consider all the various recommendations including the report of the Beahrs group, has been moved back to September. It will be conducted now by NIH, to give whatever consensus it achieves added clout.

Fink said the new guidelines would remain in effect until then.

In Congress

SENATE PASSES EXTENSION ACT 92-1; KENNEDY PLANS SACCHARIN HEARING

The Senate passed the Health Assistance Programs Extension Act last week, which includes a one-year extension of the National Cancer Act. The vote was 92-1, the dissenter being William Proxmire (D.-Wisc.), who said the authorization levels were too high.

The Senate bill authorized $1 billion for NCI in fiscal 1978 plus another $100 million for cancer control. The bill passed by the House would limit NCI, including cancer control, to $937 million. Conferees were tentatively scheduled to meet next week.

The Senate bill includes four changes sought by the National Cancer Advisory Board—relaxing the $5 million limit on cancer center core grants, to permit additional amounts to cover inflation; adding basic research to clinical research as activities of centers eligible for federal support (they already had this authority under other provisions of the law, but NCAB felt it needed added emphasis in the Cancer Act itself); increasing the number of consultants NCI can hire from 100 to 200; and authorizing reimbursement for travel expenses incurred by consultants moving to and from assignment locations.

Sen. Edward Kennedy singled out the issue of NCI consultants in describing the bill on the Senate floor. "The (Human Resources) committee believes that the use of consultants is an ideal way to attract high caliber people to government service for a short period of time given the enormous discrepancy between the public and private sectors respecting such medical, scientific and professional personnel," Kennedy said. "The bill provides a means of rapidly terminating employment as projects are completed, as well as precluding the buildup of government employees.

"The National Cancer Institute has already used up its existing quota of 100 consultants. Therefore the committee believes its amendment is justified and will enhance the effort to combat cancer."

That was the only reference to the Cancer Program in the debate, which did not last long.

Other congressional actions included:

—The Senate Human Resources Committee was scheduled to complete this week markup of S. 705, to revise and strengthen standards for regulation of clinical labs.

—The House Health Committee was scheduled to markup this week H.R. 4759, to regulate recombinant DNA research.

—Kennedy's Health Subcommittee scheduled hearings June 7 and 8 to evaluate information upon which FDA based its decision to limit the use of saccharin.

—Sen. Donald Riegle (D.-Mich.) introduced a bill (S. 1330) to amend the Toxic Substances Control Act to provide for a method "of effectively responding to toxic chemical contaminations."

RALL ARGUES THAT ANIMAL TESTS ARE PREDICTIVE OF HUMAN CARCINOGENESIS

A number of reports on various aspects of carcinogenesis were presented at the American Cancer Society Science Writers Seminar, including one by David Rall, director of the National Institute of Environmental Health Sciences on the value of animal tests. Rall's report and summaries of others follow:

DO ANIMAL TESTS PREDICT FOR CARCINOGENESIS? – David Rall, director, National Institute for Environmental Health Sciences

In order to prevent exposure of human populations to chemical carcinogens, laboratory or experimental animal systems must be used that will predict human carcinogenicity. Until recently, however, control has not followed until human epidemiological evidence of carcinogenicity has been developed.

The question as to whether to institute control measures based on laboratory evidence or based on human evidence is a public policy decision. Although the public will make it—through its surrogates the politicians—the decision must be based on good scientific evidence. The critical question is: Do tests in laboratory animals predict for cancer in man?

Attempts to correlate quantitative aspects of carcinogenicity between laboratory animals and man are difficult for many different reasons. The long latent period between exposure and outcome, the very fuzzy estimates of exposure, the confounding factors of diets, the background of environmental carcinogens, and so forth. A less obvious problem is that a successful carcinogenesis screening program tends to obfuscate the predictive relationship. If screening is successful and does

identify a carcinogen and if that carcinogen then is prevented from entering the environment, no human cancer can be associated with that chemical. This hinders attempts at correlation. The proper statement is that there is no evidence for man. Often one hears instead the statement that there is no evidence that this compound is carcinogenic for man. A successful carcinogenesis screening should yield animal + human ? for many chemicals and this can obfuscate possible correlations.

But let's look at the available data. An NAS/NRC committee on pesticides bravely attacked this problem. Six compounds—benzidine, chlornaphazin, aflatoxin B_1, diethylstilbestrol, vinyl chloride and cigarette smoke—were reviewed. The milligram per kilogram total lifetime dose was calculated for the experimental animals and for man. Various assumptions had to be made, particularly about occupational exposures. For benzidine, chlornaphazin and cigarette smoke the milligram per kilo lifetime exposures estimated for man and for the most sensitive animal species were close, within one order of magnitude. With the other compounds the differences appear greater. Feeding studies in mice project a somewhat higher incidence in man from alfatoxin B_1 exposure than was reported by Linsell, perhaps tenfold greater; but again I would view this as not a large difference.

The most sensitive animal tests project a cancer incidence rate 500 times higher than has so far been reported in man by epidemiological studies for vinyl chloride. I think it is too early to tell. The only human tumor considered was hepatic hemangiosarcoma, but Wagoner, et al., have suggested that there is an increased incidence of some of the more common tumors. Further, many of these workers are still at risk.

In comparing lesions in the offspring of diethylstilbestrol treated mice and women, I would like to add some data that John McLachlan and coworkers at NIEHS have recently published demonstrating that in the pregnant mouse 2.5 ug/kg per day of diethylstilbestrol for six days during the critical period of that mouse's gestation will cause the development of vaginal carcinoma in 2% of the female offspring. The most sensitive patient reported by Herbst received early in her pregnancy one and a half milligrams per day or 25 micrograms per kilo per day. One patient, 25 micrograms per kilo per day—a daughter with adenocarcinoma; a series of mice, two and one half micrograms per kilo per day—and about 2% incidence. I think again that is very close.

Consider benzo(a)pyrene (BaP). In inhalation studies in the rat at 10 milligrams per cubic meter per day for one hour a day Laskin reports that only a very rare pulmonary tumor occurs. The addition of sulfur dioxide to the inspired air results in a significant tumor incidence.

Hammond, et al., have reported that roofing workers who inhale a mixture of compounds, including a known amount of BaP, have up to twice the normal rate of lung carcinomas. The mice in Laskin's experiments received 60 milligrams per kilo per year for one or so years—the men, 60 micrograms per kilo per year for 10 or 20 years; and they both showed an increased tumor incidence. I suggest this reflects what we all know. There are a lot of other carcinogenic compounds in the effluent from the tar. But these comparisons are interesting.

One more—with aflatoxin B_1. In a series of experiments six rats were given by tracheal instillation 18 milligrams per rat or 54 milligrams per kilo of aflatoxin B_1. Four out of those six rats developed hepatic tumors. Also reported was a human inhalation exposure of plant material contaminated with aflatoxin, including B_1. The men received about 10 milligrams per man per year for possibly 10 years or about one and a half milligrams per kilo. Of these, 11 out of 55 developed liver tumors. This is suggestive—but I would say with those two data points, hardly conclusive.

What can we conclude from this? I do not know what you can conclude, but I conclude that laboratory animal carcinogenicity tests predict well for man and that such tests do offer a mechanism by which the prediction of human carcinogenesis is possible before human exposure and with reasonable accuracy.

NEW REACTIONS OF CARCINOGENIC ALKYLATING AGENTS WITH NUCLEIC ACIDS — Bea Singer, Univ. of California (Berkeley)

A number of new and chemically interesting reactions of carcinogens with nucleic acids have been discovered in our laboratory. N-nitroso alkylating agents, which are powerful carcinogens in animals, have a great affinity for alkylating nucleic acid oxygens. They react under physiological conditions with all the ring oxygens and phosphodiesters of both DNA and RNA; and in the case of RNA, also with the ribose oxygen. In contrast, alkylating agents which are very poor carcinogens react primarily with nitrogens. The extent of oxygen reaction increases with agents of increasing carcinogenicity and we postulate that the various oxygen modifications, many of which are likely to be mutagenic, are an important influence in initiating neoplastic transformation.

USE OF LYMPHOMA CELLS TO STUDY MECHANISMS OF MUTATION AND REGULATION OF CELL GROWTH — Philip Coffino, Univ. of California (San Francisco)

We have made and isolated mutant lymphoma cells that are defective in a key regulatory enzyme, cyclic AMP-dependent protein kinase. Study of mutant enzymes has revealed that mutations can arise in animal cells via changes in the DNA that codes for a protein. These studies have illuminated the mechanisms of action of mutagens and may lead to development of a system for screening environmental carcinogens. We have shown that cyclic AMP regulates cell growth and other metabolic processes in these cells by activating protein kinase.

CANCER RESEARCH IN A CLOSED POPULATION — James Holland

A center for mesothelioma treatment research has been established at the Mount Sinai School of Medicine & Hospital. Mesothelioma is a neoplastic disease of the pleural or peritoneal membrane affecting either or both chests and/or the abdominal cavity. It can infiltrate, invade, metastasize and kill. It is a highly malignant neoplasm.

Mesothelioma is a new type of cancer having first been described by Klemperer and Rabin at Mount Sinai in the 1930s. It has become increasingly frequent since that time and is still increasing at a rapid rate. This increase is demonstrably related to environmental contact with asbestos and nearly 80% of patients with mesothelioma give a definitive instance where close contact with asbestos industrially or by other environmental contacts has occurred. Contacts of workers, including children in the home, have developed mesothelioma with an average latency of more than 25 years.

Broad scale use of asbestos in the environment for construction, fire retardation, insulation and other uses implies that continuing and expanding exposure will be an inevitable phenomenon in industrialized countries. The appearance of mesothelioma without recognizable exposure may constitute background exposure, with a low incidence rate among the general population. Alternatively, uniquely susceptible individuals may be developing mesothelioma from minimal exposure.

Treatment opportunities for patients with mesothelioma are at present limited. Surgery is necessary for biopsy diagnosis. Because of the nature of the pleural membrane and of the peritoneal membrane, they cannot ordinarily be entirely removed surgically. Radiotherapy is of value in tumor control but ordinarily the effect is temporary and incomplete. Chemotherapy offers major promise for present and future accomplishments. There are 50 drugs of known activities against specific varieties of cancer, and only a few of these have been tried in patients with mesothelioma. Regression of mesothelioma has already occurred with drug treatment in isolated cases for longer than 5 years, but systematic study of appropriate drug treatment for mesothelioma has not been undertaken because of the rarity of the neoplasm.

Part of the refractoriness of mesothelioma to treatment has been the late stage of its development when first diagnosed. Studies of early diagnosis using biochemistry have not been systematically employed. Mesothelioma produces unique carbohydrates in many instances which have been found in fluid accumulating in the pleural or peritoneal cavity. Systematic search for these carbohydrates in abnormal quantity has not been made in the blood plasma. This could provide an early means of diagnosis. Systematic inspection of the pleural cavity using new fiberoptic instrumentation and of the peritoneal cavity has not been employed. Systematic use of computerized axial tomography has not systematically been used to detect masses in the pleural and peritoneal cavities. These techniques will be applied in patients already ill and in others exposed to high risk of mesothelioma in the Mesothelioma Treatment Center.

The existence of a "closed" population of patients at exceptionally

high risk based upon unique exposure provides a particular challenge for diagnostic and therapeutic research. Among the population at risk only certain members will develop mesothelioma. Studies of the entire population, or of a meaningful sample of it, provides the possibility of identifying in advance characteristics of people who eventually will de-develop the tumor. Biochemical studies of abnormal plasma carbohydrates in patients with advanced disease could, if reliably established, be undertaken in individuals at high risk looking for biochemical clues of disease, before systematic onset in a closed population. Since all subjects exposed to an environmental carcinogen do not develop the cancer, efforts will be made to define immunologic characteristics, and biochemical characteristics, to seek prediction of those who eventually do succumb. Thus, broad study of immunologic competence of subjects exposed to asbestos will be made. Differences will be sought in immune function between those who develop mesothelioma and those who do not. Since the denominator in the general population is so large, broad studies of immunologic function on a systematic basis cannot be easily undertaken in the general population.

In a closed population of limited size, however, the possible role of immune defenses in susceptibility to cancer development could be assessed for mesothelioma. In other closed populations exposed to other carcinogens (for example asbestos exposees who smoke have a markedly increased risk of bronchogenic carcinoma, whereas those who do not smoke, do not), we might be able to identify general principles that relate to cancer development.

Psychologic characteristics of patients with cancer have often been mistakenly assumed to be identical with the precancerous personality of the same individual and thus, related to etiology and pathogenesis. It is critical to study personality characteristics prior to the development of cancer to determine if common factors of personality and behavior exist, which factors indirectly may alter hormones, nutrition, carcinogenic exposure (cigarettes, alcohol) and other causes of, or triggers to cancer development. Personality assessment will also be undertaken in the closed population.

Major progress has been made in leukemia. Chemotherapy in man is based upon experimental models in animals, where new drugs could be tested and studied under laboratory conditions. It is possible to induce mesothelioma in experimental animals. The Mesothelioma Research Center will initiate experimental therapeutic studies in such animals bearing the homologous human tumor. It should be possible to prescreen compounds for study in man with greater likelihood of discovering drug activities of importance for mesothelioma patients. Drugs will be selected from other animal tumor systems or from other human tumor experience.

The recognition of occupational hazards for asbestos workers has constructively been met by the union, the industry and by governmental interest to stimulate and support an integrated scientific effort in therapy, diagnosis and understanding of the patheogenesis of mesothelioma. Information gained in mesothelioma should be relevant in principle to cancer as it occurs in the general population, with implications, dependent on findings, for immunological, psychological, diagnostic, biochemical and therapeutic aspects of cancer management.

DNA REPAIR IN CARCINOGENESIS – James Regan, Oak Ridge National Laboratory

Physical carcinogens, such as ultraviolet radiation and ionizing radiation, and chemical carcinogens, such as the active forms of methylcholanthrene and benzo(a)pyrene have the ability to cause damage in the DNA of human cells. Fortunately, human cells possess repair mechanisms to deal with these damages, to remove them or bypass them, and to replace the damaged portions of DNA with new undamaged nucleotides, the building blocks of DNA. There are two general types of DNA repair which have been studied over the past 12 or so years. The first of these is termed prereplication repair. Prereplication repair occurs in DNA that is already made. This DNA is sometimes referred to as "old" or parental DNA. A second type of repair is called postreplication repair. Postreplication repair occurs in DNA that is in the process of being made, that is, new or so-called nascent DNA.

The interaction of active forms of chemical carcinogens with the DNA of cells may be intimately related to the primary carcinogenic event. Using a unique assay system for DNA damage repair in human cells we have examined an array of chemical carcinogens and found two forms of DNA repair in human cells; "short" repair where the size of the repaired region of the DNA is short, i.e., only a few nucleotides are removed and replaced with new ones, and "long" repair where the repaired patch may involve 100 or more nucleotides. Chemical carcinogens are readily classifiable as those that induce short repair and those which induce long repair. The process of short repair resembles the repair seen in human cells after ionizing radiation damage; the long repair process appears similar to, or is identical with, the excision repair process for the removal of ultramiolet-induced pyrimidine dimers in human cells. Chemical carcinogens which induce long or UV-like repair in normal human cells cause DNA damage that is not repaired in cells from patients with the repair-deficient mutation, xeroderma pigmentosum.

Raymond Waters and I, together with Giampiero DiMayorca, N. Bouck and N. Mishra of the Univ. of Illinois School of Medicine, have examined postreplication repair in normal rat cells and rat cells infected with Rauscher leukemia virus. The infected cells were much more readily transformed into cancer cells by the chemical carcinogen, 4-nitroquinoline oxide (4NQO). The infected cells were also much more sensitive, in terms of cell killing, to 4NQO than the uninfected cells. These results suggested a possible repair defect in these cells. We subsequently found that postreplication repair of 4NQO damage was markedly slower in the cells bearing the leukemia virus than in the normal cells. Thus the leukemia virus may act as a cocarcinogen by somehow interfering with postreplication repair; consequently the cells are much more susceptible to transformation by a chemical carcinogen. To our knowledge this is the first evidence for an association between the presence of a leukemia virus in a cell and a repair defect.

ONCOGENIC PROPERTIES OF HUMAN CYTOMEGALOVIRUS: EVIDENCE FOR ASSOCIATION WITH CARCINOMA OF THE PROSTATE – Laszlo Geder, E.J. Sanford, J.E. Dagen, T.J. Rohner Jr. and Fred Rapp

Persistent infection of human embryo cells with a genital isolate of human cytomegalovirus resulted in oncogenic transformation of these cells. Virus-specific antigens were detected in the cells by immunologic techniques. Progressively growing tumors were induced by these cells in weanling athymic nude mice.

Prostate cancer patients have increased immune response to antigens of cytomegalovirus-infected and -transformed human cells compared to control groups. These results confirm the oncogenic transforming capacity of human cytomegalovirus. This finding, supported by immunological evidence, indicates that an association between cytomegalovirus and cancer of the prostate may exist.

ESTROGEN AND ENDOMETRIAL CANCER – Saul B. Gusberg, Mount Sinai School of Medicine

Constant stimulation of the uterus by estrogen endogenously produced or externally administered can increase the risk of endometrial cancer either by initiation or stimulation.

For many years, investigators have correlated indirect evidence of a cancer relationship in human subjects with observations of the powerful growth promoting properties of estrogen on animals. This circumstantial evidence devolved about the increased risk of endometrial cancer noted in clinical situations where there was constant stimulation of the endometrium (lining of the uterus) without modification by progesterone; it implied failure of ovulation in premenopausal women or some unusual hormonal stimulation in postmenopausal women.

The discovery of adenomatous hyperplasia as an endometrial cancer precursor in 1947, and its relation to constant estrogen stimulation lent further support to this hypothesis. This was followed in our laboratory in the early 60s by the demonstration of similar tissue growth characteristics in those women harboring endometrial cancer following long term estrogen administration and an analysis of the cumulative risk for endometrial cancer in those subjects with adenomatous hyperplasia at the menopause, reaching 30% at 10 years over controls. Unfortunately, at this time the wave of "Feminine Forever" engulfed us.

The modern era of hormonal metabolic technology (1960s) allowed us to demonstrate that the postmenopausal woman did produce estrogen in her body by conversions from an adrenal steroid precursor

(MacDonald, Siiteri, and Longcope), and that, in fact aging women, especially obese ones, produced a considerable amount. Further, it was demonstrated in several laboratories including our own that those women with endometrial cancer converted the prehormone to estrogen at about double the rate of controls, and that many had the cellular receptors to activate estrogen in their tumor tissue, event at an advanced age.

Publications of several case control studies recently has directed increasing attention to this problem by emphasizing the increased risk to those postmenopausal women on long term estrogen medication. The risk to individuals on long term estrogen medication from carefully controlled case studies has been shown to be 4.5% to 14% greater than in the control subjects.

We can evaluate the risk/benefit ratio to patients on estrogen, administer this powerful hormone for short term use under controlled conditions for real symptoms, monitor those at high risk by tissue sampling now possible as an office procedure, and teach women that the Pap Smear, very efficient for cancer screening, is inadequate for endometrial cancer. We have tools now for the control of both uterine cancers.

CORTISONE INDUCED RECRUITMENT OF MALIGNANT CELLS IN TISSUE CULTURE – Charles Nabors Jr., Univ. of Utah

The mechanisms by which the growth of cells is controlled has been shown to play a key role in the development of malignancies and the loss of normal cell growth. Furthermore, recruitment of quiescent cells to an actively cycling state has been shown to increase the sensitivity of malignant cells to chemotherapeutic agents. Studies reported here involve one mechanism by which this may be achieved.

Early studies in our laboratory involved the evaluation of anti-inflammatory activity of various natural and synthetic steroid hormones. The criterion used in our bioassay system was growth inhibition of L-929 fibroblasts by steroid hormones. When these malignant cells were utilized as a bioassay system, we found that not all corticosteroids inhibited cell growth. The most intriguing of these findings involved the fact that while hydrocortisone was very toxic to fibroblasts in culture, cortisone was not. Cortisone permitted greater cell proliferation than in controls. The activity of hydrocortisone to kill fibroblasts in tissue culture paralleled its topical clinical anti-inflammatory potency. Studies in this laboratory and others showed that cortisone lacks the active anti-inflammatory, gluconeogenic and lymphocytolytic potency of the cortisol molecule. When the interconversion of these two hormones was blocked by the addition of a 2α-methyl substituent, the cortisone molecule was shown to be devoid of these types of biological activity. Furthermore, it was demonstrated that long-term cultures lacked the 11β-hydroxydehydrogenase enzyme necessary to convert cortisone to cortisol.

More recently, this finding has been applied to a new straing of malignant cells in tissue culture (NAU-77). Cells were grown from a beagle fibrosarcoma which had metastasized to the lungs. This type of tumor occurs frequently in beagles. Samples of metastatic nodules were cultured in RPMI medium 1640 containing 10% fetal calf serum. This cell line is now in its 64th pass in culture and has an average generation time of 19 to 24 hrs. These cultures are not density inhibited and may be stimulated to further proliferation by the addition of fresh medium after becoming confluent. Cytogenetic studies on these cells have shown that they are aneuploid, having 61 to 98 chromosomes while normal dog cells have 78. These chromosomes are largely metacentric and the cells have a distinctly metastatic appearance. Furthermore, attempts have been made to isolate virus from the original tumor, metastatic nodules and the cultured cell strain. Thus far no virus has been discovered in any of these samples.

Although recruitment of leukemic cells has been shown to be mediated by humoral factors, parallel investigations with cortisone and cortisol in diploid cells have shown opposite results. Several investigators have shown that hydrocortisone stimulates proliferation of density inhibited 3T3 fibroblasts while cortisone inhibits proliferation and stimulation of DNA synthesis. Furthermore, the stimulatory ability of cortisol was not observed in virus transformed 3T3 cells. However, the cells that we are reporting on are transformed malignant cells and the opposite results obtained with cortisone may well relate to the malignant condition. Unlike the diploid cells, the NAU-77 cells are not density inhibited, being inhibited only by medium depletion. Future studies on these cells will include further evaluation of the growth fraction, and the potentiation of cytotoxic agents in normal and cortisone-stimulated cells. Augmentation of cell killing in this tissue culture system may provide a model for in vivo studies on chemotherapy.

CONTRACT AWARDS

Title: Cancer control program for clinical cooperative groups—Radiation Therapy Oncology Group (RTOG)
Contractor: American College of Radiology, $1,318,128.

Title: Evaluation of thermography in mass screening for breast cancer
Contractor: Health Insurance Plan of Greater New York, $353,596.

Title: Incorporation of nine alteration/renovation projects as necessary for the performance of the cancer research program being conducted at the Frederick Cancer Research Center
Contractor: Litton Bionetics, $181,503.

Title: Immunotherapeutical trials with human tumors
Contractor: Fred Hutchinson Cancer Research Center, $77,414.

Title: Systems analysis and information services resources for registries of human clinical protocols in cancer therapy
Contractor: Informatics Inc., $78,421.

Title: In vitro sensitization of human lymphocytes
Contractor: Sidney Farber Cancer Institute, $64,648.

Title: Mechanisms for cell-mediated destruction of tumor cells
Contractor: Johns Hopkins Univ., $57,090.

Title: Cell surface membrane components organization and dynamics
Contractor: Johns Hopkins Univ., $65,094.

SOLE SOURCE NEGOTIATIONS

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

Title: Cervical Cancer Screening Program
Contractor: Arizona State Dept. of Health; and Utah State Dept. of Health.

Title: Etiologic studies of cancer in New Jersey
Contractor: New Jersey Dept. of Health.

The Cancer Letter—*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., 1411 Aldenham Ln., Reston, Va. 22090.