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BREAST CANCER TASK FORCE MUST TAKE MORE ACTIVE ROLE IN RFP DEVELOPMENT, NEW CHAIRMAN INSISTS

Pietro Gullino, new chairman of the Breast Cancer Task Force, opened the first joint meeting of the task force committees last week with what probably was the understatement of the year: "As most of you know, we are changing slightly the BCTF modus operandi," Gullino said.

Gullino then handed each member present a 104-page syllabus outlining the "slight" changes, including supporting documentation. The changes include new chairmen, non-NCI investigators, for each task force committee; a stepped up schedule of meetings—six two day sessions a year; and, most important, greater emphasis on detailed input from committees in developing task force RFPs.

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In Brief

FDA TO REVIEW PRECLINICAL TESTING, PHASE I PROTOCOLS AT OPEN ADVISORY GROUP MEETING

GUIDELINES for testing oncologic drugs, including preclinical testing and phase I protocols, will be discussed at the Nov. 20-21 meeting of FDA's Oncologic Drugs Advisory Committee. Discussion of Lomustine, for which Bristol Labs has an NDA, and review of package inserts for approved anticancer drugs also are on the agenda. The meeting will be open from 9 a.m. to 3 p.m. Nov. 20, and 9 a.m. to 1 p.m. Nov. 21; conference room J, Parklawn Bldg., 5600 Fishers Ln., Rockville, Md. The closed sessions will include review of INDs and NDAs under consideration. See story starting on page 6 of this issue describing newly-emerging difficulties NCI and clinical investigators have been having with FDA over INDs and the proposed guidelines. The first hour of the Nov. 20 meeting will be a public hearing, during which anyone may present data, views, or information, orally or in writing, concerning the issues. The new problems should generate a red-hot session . . . .

NATIONAL AWARDS, American Cancer Society's highest honor, went to NCI Director Frank Rauscher, Pierre Denoix, president of the International Union Against Cancer and director general of public health of France, and columnist Ann Landers. Rauscher was honored "for his brilliant and multiple talents in cancer research and cancer control; for developing the Rauscher virus; for his inspired leadership of NCI; for strengthening clinical investigation programs; and for encouraging partnership with the private sector in all aspects of the fight against cancer." Denoix was honored "for world renowned leadership in cancer control." Landers received her award "for her powerful and inspired skills in influencing human behavior, stimulating millions of women to practice breast self-examination and encouraging Americans to quit cigarettes" and for urging readers to write congressmen in support of the National Cancer Act.

BCTF CHAIRMAN OFFERS DETAILED SUGGESTIONS FOR NEW RESEARCH

(Continued from page 1)

"One of my major concerns is the formulation of RFPs," Gullino said. "The time when the BCTF could afford RFPs formulated as generic statements on very broad problems is over. The committees must do the work necessary to justify the RFP to the scientific community. From data available in the literature, we must assemble the facts which can justify not only the committee's request for expanding work in a given area but also the reasons for giving high priority to the request.

"By necessity of limited printing space, the RFP must be formulated in a few general sentences. When scientists interested in the research area outlined by the RFP contact our administrative officers, they will receive the standard instructions together with the background information assembled by the committee in justification of the RFP. This will indicate to them what the committee believes should be done without telling them what to do.

"The freedom of the investigators to select what they consider the best approach in solving the problem presented by the RFP is essential to the viability of our program," Gullino emphasized. "The committee will select what it considers the best approaches proposed but in no way should it tell the investigators what to do. In selecting the best proposals, the scientific merit has first priority. No matter how accommodating a proposal may be for the overall program, if the objectives are not clearly stated, if the experimental approach is not carefully outlined and feasible, and if the analysis of the data to be obtained is not properly specified, the result will only be a waste of resources."

Gullino asked that each committee prepare four new RFPs by next March, estimating that BCTF would support 100 to 120 active projects.

The syllabus included Gullino's outline of four major research areas, existing projects in each, and his suggestions for work that needs to be done in each. Those areas and suggestions follow:

METASTASIS

Detection of early metastasis—Opportunities that scintigraphy may offer and the possibility of expanding them for early diagnosis of breast cancer metastasis. The need of surveying all biochemical indicators which may suggest presence of neoplastic cells before and after removal of the primary tumor, such as CEA, HCG, urinary hydroxy prline excretion, casein in serum. Emphasis should be placed on the relationship between the amount of neoplastic tissue and positivity of the reaction with the objective of developing a diagnostic tool for early detection. The importance of defining the biological clock regulating metastatic growth.

Role of diagnostic procedures and treatment in metastasis formation—An attempt could be made to define the load of circulating neoplastic cells which a patient must endure during a standard examination for suspected breast carcinoma. Since these showers of neoplastic cells seem inevitable if a diagnosis must be reached, ways of protecting the patient should be sought if the circulating load of neoplastic cells proves to be large. Nude mice bearing human transplants of mammary carcinomas could be good models for developing the technology and guiding the approach to the human problem.

The impact of various therapeutic treatments on formation and patterns of metastasis should be studied as well as the means available to predict and/or modify these patterns. Results on animal models are probably sufficient to guide the approach to the human problem. The question of prophylactic irradiation with its connotation of treatment given just in case tumor cells were present should probably be reevaluated in the light of two parameters that, in the past, were probably not considered: the effects of radiation on normal thoracic tissues, capillaries of the lung in particular; and the general response of the lymphatic system and the immunological status of the host, even after localized treatment.

Prognostic value of lymphoreticular infiltrates and metastatic potential of mammary carcinomas—Taking into consideration the relevant knowledge which is now available, it seems important to focus on the immunological milieu within human tumors. Although much is known about the interplay between antibody, blocing factors and cytotoxic cells in the circulating blood and in vitro, the actual accessibility of tumor cells by these components of the host immunological response is very limited. Focus on the measurement of what happens within the solid tumor in vivo.

Prevention of metastases: Anticoagulants and antimetastatic drugs—Does ICRF-159 influence tumor neovascularization, and if so, in what way? When neoplastic cells are lodged in a tissue, a solid tumor forms only if neovascularization occurs. Knowledge on ways and means to influence the vascular system of mammary tumor metastases seems fruitful.

Is the mammary neoplastic cell able to exert a toxic effect on the endothelium, and if so, how? Today more tools are available for approaching this question than before. Gimbrone and Alexander have described a good method of obtaining cultures of human endothelium. Populations of human mammary carcinoma cells are available in vitro and in vivo, growing in nude mice.

During both diagnostic procedures and surgery, waves of neoplastic cells appear in the circulation. Should any of the drugs or treatments suggested to effectively reduce metastases be used as preventive treatment? A careful assessment should be made because the data in the literature are contradictory and mostly concerned with animals.

Availability of human mammary carcinoma cells in culture and in nude mice might constitute a source of antigens useful for preparing antisera able to detect circulating neoplastic cells by immunofluorescence. A correlation might be sought between the number of circulating neoplastic cells before mastectomy and the metastasizing capacity of the tumors.

MAMMARY CELLS DEPENDENCE ON AND RESPONSE TO HORMONES

Dyshormonal events in breast carcinomas—Ongoing projects of BCTF program are concerned with the role of hormones in mammary gland development, the quantitation of estrogen and progesterone binding proteins, the effects of hormones on mammary cell chromatin, the role of prolactin in the pathological history of the mammary gland, and the role of hormone therapy in mammary cancer control. Gullino suggested that RFPs be developed which center on dyshormonal events in breast cancer. "There is enough information to convince everyone that dyshormonal events occur in the course of breast cancer. It is important to go one step further and try to discover if these events are due to new formation of abnormal hormones by the carcinomas and if the abnormality is due to ectopic hormones or incomplete or malformed molecules which the neoplastic cells can produce under specific circumstances. I suggest that RFPs be formulated in such a way that scientists able to handle proteins and peptides may be interested in entering this area. Constructive results will obviously improve our diagnostic and therapeutic ability besides advancing biological knowledge of mammary carcinomas."

Oral contraceptives and breast cancer—Gullino cited a long list of projects sponsored by various institutions and said he believes BCTF can add little to that at this time. "The fear that estrogen treatments can increase breast cancer to epidemic proportions is not justified," he said. If the committees feel they should support more research in that field, however, he suggested this include work to ascertain whether the hyperplastic proliferation of mammary epithelium, especially in fibroadenomas of women under oral contraceptives, may constitute a source of diagnostic errors, namely, adenomas diagnosed as carcinomas; and to follow the pathological history of the mammary gland in girls whose mothers started contraceptive medication while breast feeding them. What are the effects, if any, of early estrogenation of mammary tissues 20 and 40 years later?

Hormone receptors—New efforts should support the development of sound methods of research and simplified methods for routine clinical use; provide clinical case review for investigators who contribute data for NCI workshops; provide a model outline for case history and patient profile data for use in collaborative work; help collaborating investigators with their protocols under which ER data for workshops will be gathered. Eventually, as may be needed, identify the need for reference preparations, and facilitate their production and distribution. This might include frozen tumor pools for assay, receptor proteins, and antibodies to receptor protein.

PATHOLOGICAL HISTORY OF MAMMARY GLAND AND RISK OF NEOPLASTIC TRANSFORMATION

Mammotropic drugs and breast cancer—Determine which of the drugs with a mammotropic effect are utilized in relatively large amounts and are available without strict medical control. Collect the literature data on their effect on the breast. Decide which approach to follow when data are available. Collect available information on drugs of large consumption, such as tranquilizers, and an evaluation from the available literature of the impact that they may have on the pathological history of the mammary gland. From this evaluation a final decision should be made with reference to (a) BCTF approach to the general question of the effects of drugs with mammotropic action on the pathological history of the mammary gland and (b) the specific need to expand further the study of some of these drugs.

RELATIONS BETWEEN MAMMARY CARCINOMA, ORGANISM AND TISSUES. GROWTH POTENTIAL AND REGRESSION

Role of neuroendocrine stimuli of psychological origin in mammary carcinogenesis—The most desirable type of human study would be a longitudinal one in which women with a high risk for breast cancer and those not at risk would be followed both psychologically and physiologically before breast cancer is suspected. Such a study would of necessity be of long duration, therefore, the cost would be almost prohibitive. The animal studies to date provide good evidence of the effects of stress on mammary tumor incidence, therefore, it seems logical to obtain additional data in well-defined model systems prior to mounting human experimentation. A problem that must be faced in the planning of animal studies is whether to use those with a known incidence of spontaneous mammary tumors or utilize a carcinogen-induced model system. Each of the investigators presenting data at this meeting have submitted their opinions on future studies to the chairman of the task force. Their reports are available to those interested through the office of the Breast Cancer Program Coordinating Branch.

Organotropism of breast cancer metastasis—Biologists working in the area of cell communication should be brought into the breast cancer area. First, because mammary neoplastic cells have not been studied by them and it would be important to know whether data on hepatocarcinomas are transferable to mammary carcinomas. Secondly, because it might be justified to look at the lodging of metastases as a problem of cell to cell communications. The observation that a neoplastic cell in contact with the normal cells reduces their ability to communicate with each

other might be applicable to mammary epithelium and might play a role in "macrophage blocking" or other changes occurring in the microenvironment at the time neoplastic cells lodge in the tissue. Thirdly, because special conditions for communications between mammary neoplastic epithelium and endothelium or fibroblasts of bones, lungs, or liver might account for the organotropism of metastases. Human mammary neoplastic cells are available and a method for collecting and cultivating human endothelium has been described. The BCTF already has an RFP concerned with osteotropism of metastases. Biologists involved in cell communication studies may have submitted proposals. If not, an attempt to involve cell communication biologists in the study of mammary cancer metastases should be seriously considered.

The syllabus included descriptions of three other research areas, including existing contracts and grants, but for which Gullino offered no suggestions for new work. They were:

Isolation, cultivation and recognition of normal and neoplastic mammary cells of epithelial origin.

Genetic, environmental, dietetic and other factors in breast carcinogenesis.

Diagnostic tools in breast cancer detection.

The reorganization includes a BCTF Steering Committee, headed by Gullino and consisting entirely of NCI staff members. Chairmen of the committees are:

William Taylor, Mayo, Diagnosis; Anthony Miller, National Cancer Institute of Canada, Epidemiology; Yale Topper, National Institute of Arthritis, Metabolism and Digestive Diseases, Experimental Biology; and William McGuire, Univ. of Texas, Treatment.

The new meeting schedule, which some members felt might be too ambitious, calls for the committees to meet once every two months. The first day will be in joint session to listen to 10-12 presentations of ongoing work, the second day committees will meet separately for specialized business.

"The joint meeting is necessary to keep everybody informed of the whole program, and the need for six yearly meetings is dictated by the size of the program," Gullino said. "Today the program is too vast and cannot be reviewed in one meeting a year," as was previous custom of BCTF.

BCTF TO HEAR 10-12 PROGRESS REPORTS AT EACH MEETING; SUMMARIES PRESENTED

Among the changes in Breast Cancer Task Force procedure initiated by Gullino will be regular reports from investigators describing progress and problems they are encountering. Gullino said there would be 10-12 of these reports at each of the six general meetings he plans to hold each year.

Summaries of reports presented at last week's meeting follow:

Investigations of Plasma Membranes of Mammary Glands – *Kermit Carraway, Oklahoma State Univ.*

Preparation of purified plasma membranes of mammary tissue is complicated by the difficulties involved in homogenizing the tissue. Partially purified plasma membranes can be prepared by discontinuous gradient centrifugation of a microsomal fraction prepared after homogenization in a Sorvall Omni-mixer. The presence of substantial galactosyltransferase activity suggests that this membrane fraction contains Golgi as well as plama membrane fragments. Treatment of the fraction with digitonin causes a shift in the density of part of the material. The new band has additional enhancements in the 5'-nucleotidase and ATPase specific activities, but essentially no galactosyltransferase. Further characterization of this material is in progress.

Investigations have been performed on the 5'-nucleotidase and Mg^{++} - ATPase of partially purified membranes. At least two forms of nucleotidase (low Km and high Km) are present. Both forms are inhibited by the plant lectin Conconavalin A in a process that shows substantial cooperativity. With the mammary membranes both Km and Vmax are altered by the lectin. Mg^{++}-ATPase is activated by Con A in a cooperative process. In membranes from the 13762 mammary adenocarcinoma only Km is affected by the lectin. The study of plasma membrane enzymes and their perturbation by lectins would appear to offer promise for understanding the role of these enzymes, their association with the membrane and alterations of membrane structure in pathological states.

Metastasis of Mammary Tumors in Perspective – *Untae Kim, Roswell Park*

Immunological and biochemical studies indicated that the spontaneously metastasizing mammary tumor cells shed their surface antigens into the systemic circulation, and seemed to be capable of eluding the host immune surveillance mechanism, while the antigens of nonmetastasizing tumor cells were firmly bound to their plasma membranes. It was also found that the metastasizing capacity of tumor cells was inversely related to the levels of plasma membrane-associated enzymes including cAMP phosphodiesterase. Utilizing these experimental mammary tumor models, the biochemical mechanism of spontaneous antigen-shedding property and the influence of free tumor cell surface antigens on the host immune responses are being studied.

Analyses of glycoprotein turnover in the plasma membranes of mammary tumors indicated that the galactosyltransferase activity was 3-5 times higher in the metastasizing tumors than in the non-metastasizing ones. Furthermore, the number of galactose acceptor sites in the plasma membranes increased with the metastasizing capacity indicating the presence of greater numbers of incomplete glycopeptides on these shedding tumor cell surfaces. Interestingly enough, glycosyltransferase activities including galactosyltransferase, sialyltransferase and fucosyltransferase, in the sera of metastasizing tumor hosts were also markedly elevated as reported by others in cancer patients and tumor bearing animals.

The in vitro lymphocyte migration inhibition (MIF) technique applied to the peripheral lymphocytes, spleen cells and thymocytes from tumor hosts indicated that the migration of lymphocytes from nonmetastasizing tumor hosts was stimulated as compared to normal lymphocytes before an in vitro exposure to their own tumor antigen but it was inhibited after the exposure. On the other hand, the migration of lymphocytes from metastasizing tumor hosts was initially inhibited prior to an incubation with their own tumor antigen but was stimulated after the exposure. The in vitro blastogenesis of lymphocytes from metastasizing tumor hosts, to PHA and Concanavalin A was often irreversibly suppressed, while with the nonmetastasizing, immunogenic tumor hosts the suppressed blastogenic capacity of lymphocytes was not only reversible but often stimulated after surgical excision of the tumor. In the sera of nonmetastasizing tumor hosts, there were tumor specific antibody as demonstrated by the Ouchterlongy immunodiffusion technique, while no tumor specific antibody was found in the sera of metastasizing tumor hosts.

New Probes of Altered Membrane Structure in Malignant Mammary Cells – *Grant Fairbanks, Worcester Foundation*

This project is concerned with the development and exploitation of new technologies for plasma membrane isolation and characterization.

The radiosynthesis of a novel cleavable protein cross-linking reagent, [^{35}S] dithiobis(succinimidyl propionate)("[^{35}S] DTSP"), has been achieved. Because DTSP combines extremely high reactivity with long solution half-life, the radiolabeled cross-linker is a uniquely valuable

probe of polypeptide contact relationships in membranes and other extended biological systems. Other applications of DTSP are the facile assembly of cleavable affinity reagents for cell surface modification and the immobilization of affinity adsorbents through cleavable bonds to inert supports.

DTSP rapidly penetrates 13762 ascites carcinoma cells, and, through cross-linking, makes them highly resistant to disruption by hypotonic shock or shear stress. Programmed reversal of this cell fixation is under study as a convenient approach to plasma membrane purification.

In pilot studies exploring the feasibility of applying ribonucleotide homopolymers as membrane isolation reagents, 13762 and other tumor cells were found to bind [^{3}H] poly (U) rapidly and spontaneously at 0°. Purine and pyrimidine nucleosides effectively compete for this polynucleotide binding site, while bases, ribose and 2'-deoxyribose are without effect; 2'-deoxyribonucleosides give partial inhibition. Treatment of 13762 cells with proteolytic enzymes reduces their capacity to bind [^{3}H] poly(U) and displaces radioactivity previously bound. These and other features of the poly(U) binding phenomenon suggest that proteins on the tumor cell surface bear specific adsorption sites for polyribonucleotides. The physiological role of this receptor apparatus is unknown.

Structure and Function of the Epithelial Basal Lamina — *Merton Bernfield, Stanford*

The basal lamina which separates epithelia from surrounding stroma may be involved in limiting local spread of tumor cells, since an intact lamina is seen associated with pre-invasive carcinomas and the lamina is usually absent or altered at sites of tumor invasion. The lamina consists of Type III collagen and glycoprotetins, and at least in mouse embryonic organs, contains glycosaminoglycans (GAG). In such organs, removal of the lamina is accompanied by loss of organ shape, disorganization of intracellular actin-like filaments and changes in the foci of cell proliferation. Redeposition of the lamina is associated with reversal of these changes, suggesting that the lamina is required for maintenance of normal cellular architecture.

The lamina is derived solely from epithelial cells, contains hyaluronic acid as the predominant GAG and is organized into macroperiodic arrays closely associated with the plasmalemma. The sites of greatest change in epithelial shape and of most rapid cell proliferation are the sites of most rapid deposition and loss of newly synthesized laminar GAG. This pattern of turnover in the lamina is unaltered by inhibition of proliferation or by inhibitors of collagen secretion or cross linking. Studies in progress of post-natal mouse mammary epithelia suggest that prior to pregnancy GAG is present within the lamina and that its pattern of deposition on ducts and end buds is similar to that in branching embryonic epithelia. During pregnancy, however, less laminar GAG is evident. Such studies of the lamina during normal mammary development are a necessary prelude to analogous studies of pre-invasive and invasive lesions.

Immunological Studies of Breast Cancer — *Donald Marcus and Anna Kadish, Albert Einstein*

This contract consists of two projects, an evaluation of ferritin as a tumor-associated antigen, and studies of cell mediated immunity to breast tumor antigens. Ferritins are an isomeric family of iron-containing proteins that are constituents of normal tissues, and ferritin levels are elevated in many tumors and in the sera of tumor-bearing individuals. We have devised a radioimmunoassay (RIA) for measurement of ferritin in human sera. Abnormal ferritin values are found in 30-40% of preoperative patients with breast cancer, and in 60-70% of patients with local recurrences or metastatic disease. We are now carrying out longitudinal studies of patients to determine whether the RIA is useful in evaluating the response of patients to therapy, or in detecting recurrences of breast cancer before they are clinically evident. Some tumors and fetal tissues contain acidic isoferritins that are not detected in adult liver or spleen ferritin. Nothing is known about the isoferritin content of serum and we are now devising methods to determine the isoferritin profile of normal and pathological sera. We have produced absorbed antisera that are specific for acidic isoferritins and we are developing an RIA to selectively measure acific isoferritins in sera. This test might be more sensitive and specific for cancer than the RIA in use at present.

For our studies of cell mediated immunity, we have made 3M KC1 extracts of benign and malignant breast tissues obtained at the time of surgical resection. The extracts are tested by the direct capillary tube leucocyte migration inhibition test (LMI) using heparinized peripheral blood. In our initial studies we found that 14/19 patients with breast cancer showed positive LMI, and there was no difference between autologeous or allogenic extracts. Negative tests were obtained with 6 patients with other types of cancer, 8 normal controls and 4 patients with benign breast disease. One female patient with bladder cancer had a positive response to one extract. Extracts of benign breast tissue failed to elicit LMI in either patients or controls. An extract made from a medullary carcinoma was fractionated by gel filtration on a column of Sephadex G-200. Fraction I (high molecular weight) gave positive LMI tests in 8/15 breast cancer patients but elicited no positive tests in a total of five individuals with benign breast disease, non-mammary cancers and normal controls. Fraction III elicited a positive response in 8/15 breast cancer patients, 3/5 patients with benign breast disease, and 0/5 normal controls or patients with malignancies. An extract of a fibroadenoma was fractionated in a similar manner and is now being tested. These extracts are now being subjected to additional fractionation procedures in order to isolate and characterize the active materials.

Treatment of Minimal Metastatic Breast Cancer — *David Ahmann, Mayo Clinic*

The scope of this discussion will include a brief review of Mayo Clinic's approach to breast cancer, emphasizing research aspects, both clinical and laboratory.

The intent of the Mayo Breast Cancer Program is to improve the care of the breast cancer patient by rapidly bringing to the clinician recent advances to impact on patient care. Clinical trials in both early and advanced breast cancer provide the backbone of Mayo's approach.

Clinical programs involving a biologic base include estrogen binding of tumors, the biologic markers program, and a spectrum of laboratory investigation assessing the hosts immune response with various stages of cancer.

Adjunctive clinical programs to ongoing patient care involve the assessment of clinical-pathologic staging in the operative breast cancer patient, and breast cancer screening to include mammography, thermography, xeroradiography, and shortly EMI scanning. Surgical pathologic correlation is augmented at our Institution by specimen radiography. The assessment of the value of routine preoperative workup, including the isotope bone scan, is currently under way.

Treatment programs at Mayo involve the assessment of the type and extent of surgery, the assessment of radiation therapy as a postoperative adjunctive therapy, the assessment of new biologicals and combinations of biologicals in both early and late breast cancer. The testing of earlier adjunctive therapy is based on an extensive program of clinical trials in patients with advanced breast cancer.

The strength thus far of Mayo's breast cancer program has rested in its clinical trials, particularly in patients with advanced breast cancer. New biologicals are tested in Phase I and later if indicated, in Phase II clinical trials. Agents investigated within the past several years with the reported response rates include: CCNU (10%), TIC mustard (10%), MeCCNU (5%), Ifosphamide (20%), Adriamycin (50%), VP-16 (10%), Cytembena (0%), and currently ICRF and Galactitol. Combinations of agents investigated in patients with advanced breast cancer have included, with their respective response rates, the following: 5-FU/Cytoxan/Prednisone (55%), 5-FU/Cytoxan/Prednisone/Vincristine (45%), 5-FU, Cytoxan/Prednisone/Calusterone (50%), Adriamycin/Methotrexate (38%), Adriamycin/Methotrexate/Vincristine (45%), Adriamycin/Cytoxan (50%), Adriamycin/Cytoxan/5-FU (39%), and Adriamycin/Vincristine (20%), this last group being evaluated in previous polychemotherapeutic failures. Currently, the combination of Adriamycin and Alkeran, and Adriamycin and VP-16 are undergoing clinical trial.

Combined modality studies are also under way at Mayo and include a surgical adjuvant program which entails a randomized treatment program involving multiple drugs (CFP) versus CFP plus radiation therapy versus phenylalanine mustard in patients with operable but prognostically unfavorable breast cancer. An oophorectomy adjuvant program assessing the value of postoperative chemotherapy in patients with pre-menopausally recurrent breast cancer is nearing completion. A program assessing a multiple drug program (CFP) versus CFP plus adrenalectomy in patients with advanced breast cancer, but displaying previous hormonally responsive disease is shortly to be implemented.

Adjuvant Immunotherapy and Chemoimmunotherapy — *Frank Sparks, UCLA*

Adjuvant immunotherapy with BCG given before or after operations can prevent growth of spontaneous metastases from 13762 mammary adenocarcinoma in the Fischer rat.

Chemoimmunotherapy with Cytoxan, Methotrexate, 5-FU and BCG,

with or without an irradiated breast cancer cell vaccine, was administered to 34 patients as an adjuvant to mastectomy in the management of patients with primary breast cancer and positive axillary nodes in a prospective, randomized clinical trial.

None of the patients has recurrence with an average follow-up period of 30 weeks (range 12 to 70) after mastectomy. Toxicity has been acceptable. Immunocompetence, as measured by delayed cutaneous hypersensitivity to PPD and DNCB, has been maintained.

LDH Isoenzyme Patterns in Patients with Advanced Breast Carcinoma – *E.J. Hawrylewicz and W.H. Blair, Mercy Hospital and Medical Center, Chicago*

LDH isoenzyme patterns have been determined for normal human breast tissue and benign breast lesions, fibroadenoma and fibrocystic disease. These patterns are similar with the predominant activity in LDH isoenzymes 1, 2, and 3 (aerobic associated activity). Malignant lesions, infiltrating ductual carcinoma, are characterized by a marked increase in isoenzymes 4 and 5 (anaerobic) and also in total activity. Peritumoral tissue is characterized by a similar distribution pattern. Normal appearing tissue is characterized by a similar distribution pattern. Normal appearing tissue from diseased breast frequently displays atypical LDH isoenzyme activities.

Animal Mammary Tumor Models As Metastatic Test Systems – *Arthur Bogden, Mason Research Institute*

A survey of six transplantable rat mammary tumors, chosen at random from the tumor bank of the Mason Research Institute, revealed not only a spectrum of growth characteristics and of chemotherapy responsiveness but also of incidence of metastases. Percent incidence ranged from 0 in the DMBA No. 1 to almost 100 percent in the 13762 mammary tumors. Metastases from solid subcutaneous grafts of the 13762 mammary tumor occur only after tumors are well established and appear to be via both the blood vascular system and the draining lymphatics. Such metastases from solid subcutaneous growths are more "natural" than those simulated by the injection of cellular suspensions intravenously, and are found in the lungs, liver, kidney, heart and occasionally in the brain.

Studies utilizing combinations of surgery, chemotherapy and immunotherapy revealed that (a) metastases do occur from drug responsive as well as from drug resistant tumors during chemotherapy; (b) metastases from drug responsive tumors are drug responsive and when these tumors become drug resistant the metastases from such tumors are also drug resistant; (c) metastases from drug responsive tumors can become drug resistant during chemotherapy; and (d) once tumors are in maximum remission as a result of chemotherapy they are drug resistant and metastases from these tumors reflect the same resistance. Experimental evidence supported the efficacy of early surgery in preventing metastases from established tumors. Early surgery followed immediately by a regimen of chemotherapy was very effective in the treatment of metastasizing tumors, as was the sequence of a short, non-immunosuppressive regimen of chemotherapy prior to surgery, followed by immunotherapy post-surgery. The transplantable 13762 mammary adenocarcinoma having reproducible metastasizing characteristics lends itself easily to studies of the treatment of drug susceptible as well as drug resistant metastases.

The Effects of Phenylalanine ammonia-Lyase in Vivo on Tumors and Normal Tissues – *C.W. Abell, D.S. Hodgins, R. Shen, and R.R. Fritz, Univ. of Texas (Galveston)*

The therapeutic potential of phenylalanine ammonia-lyase (PAL), an enzyme that deaminates phenylalanine and tyrosine, has been evaluated against mammary tumors (BW10232) in mice. PAL was tested against small, medium and large tumors, both as a single agent and in combination with phenylalanine mustard (PAM). The parameters measured were plasma levels of phenylalanine, tyrosine, and enzyme, tumor growth, and immunological responses. The levels of circulating phenylalanine (or tyrosine) and PAL were found to be inversely proportional. A small but significant inhibition of tumor growth by enzyme alone or in combination with PAM was observed. However, the effectiveness of PAL was dependent on its rate of clearance from the host. The onset of changes in clearance rate and enzyme half-life were influenced significantly by both the dose schedule of PAL and the presence of the tumor.

FDA INVOKES PETTY RULES TO BLOCK TESTS OF PROMISING ANTICANCER DRUGS

The Food & Drug Administration's sudden decision to enforce long-dormant petty regulations has resulted in delaying clinical research with seven anticancer agents, including long-awaited trials with the promising antileukemia drug, maytansine.

Within the past few weeks, FDA has been turning down investigational new drug (IND) applications which do not meet the letter of the agency's regulations. FDA previously approved applications almost automatically which were identical in content to the ones now being blocked.

The result is that four IND applications submitted by NCI have been held up—for maytansine, thiadiazole, hycanthane, and neocarzinostatin. Also delayed are applications from Sloan Kettering, for tetrahydrouradine; from Sidney Farber Center, for amenopterin; and from M.D. Anderson, for peptichemia.

The FDA staff member responsible for the delays, appearing at a meeting of the Board of Scientific Counselors for NCI's Div. of Cancer Treatment, admitted that the delays were based on form rather than substance. R.S.K. Young, group leader for oncologic drug class at FDA, said the decision to enforce previously overlooked details was made following the new wave of criticism of the agency arising out of charges that it had been negligent, or worse, in approving certain drugs. Young mentioned the scandal in which the Army was permitted to test LSD, and referred to criticism aired at the recent hearings conducted by Sen. Edward Kennedy's Health Subcommittee.

Young said the decision was made at the top level of FDA management, presumably including Commissioner Alexander Schmidt. He said Richard Crout, director of the Bureau of Drugs, backed him up in delaying the anticancer drugs.

Young referred to the maytansine application and said NCI had not "provided enough details to permit a scientific review. We looked for the therapeutic rationale, but the only data we got consisted of four tables of different animal studies. We would like to know how the experiments were done, how many animals were used."

DCT Director Vincent DeVita disputed that. "The fact is, we did show therapeutic efficacy," DeVita said. He commented that FDA had five other questions on the application which would require "voluminous" answers.

Members of the Board of Counselors and their consultants were incensed. Emil Freireich, M.D. Anderson, said, "Dr. Young and FDA have created a national crisis. . . . There's no possible way to begin investigation of cancer drugs under FDA's policy. One hundred percent of new drugs go through 12 levels of review (at NCI and institutions). Four hundred people are involved in the reviews. Then Dr.

Young responds, 'Thou shall not.' . . . The question is, who can decide on drug development?"

James Holland, Mt. Sinai, was vehement. "If you tell me the problem is one of form and not of substance, I am appalled," he told Young. "It's shameful. Patients are dying."

Freireich said that M.D. Anderson had responded promptly to FDA's request for more information on its IND application, but more than a month later no further word had come from the agency.

Holland and Freireich, supported by DeVita and other board members, argued that INDs for anticancer drugs should receive special consideration from FDA and be exempted from stringent regulations. Most will be tested in patients with advanced cancer and with very short life expectancy and for which acceptable therapies have failed. "Maytansine is an extraordinary compound, extremely significant for treating advanced leukemia, when mortality is assured," Holland said. "What damage could the drug do that would outweigh the damage to the patient if he dies?"

Henry Kaplan, Stanford, recalled that proposals leading up to the National Cancer Act of 1971 included a provision permitting the NCI director to waive FDA regulations for drugs to be used in patients with advanced cancer. That provision was dropped before the Act was passed. "If this rigidity continues, we should go to Congress and ask that it be put in," Kaplan said.

Harris Busch, Baylor, cautioned against congressional action that "could open doors we may not want opened." He cited FDA's value in blocking "charlatan" drugs such as laetrile and in protecting the U.S. from thalidomide.

DeVita said that he and his deputy, Stephen Carter, had conferred with Crout and had made progress in resolving the problem, at least for the seven INDs currently being delayed. The board approved a resolution calling for the issues to be settled by negotiation, if necessary between NCI Director Frank Rauscher and the FDA commissioner. Failing that, the resolution asked that the problem be presented to the President's Cancer Panel.

THAT'S ONE PROBLEM, NOW FDA OFFERS ANOTHER – CLINICAL TESTING GUIDELINES

FDA's abrupt actions described above are only part of the agency's recent moves which affect clinical cancer investigators. As part of its drawn-out program to develop guidelines for clinical tests in major disease categories, FDA has released a draft of its proposed "Clinical Guidelines for Investigational Antineoplastic Drugs."

The guidelines are intended "to help an investigator formulate his plan of development of a particular substance in conformance with FDA regulations," a preamble states. "They should be construed as general directions, not a set of specific instructions."

Young told the Board of Scientific Counselors, however, that while deviations from the guidelines, when they become final, will be permitted, such deviations must be scientifically justified.

The threat, of course, is illustrated by the examples of FDA's obduration regarding the seven INDs. Although the guidelines may be loosely enforced at first, they offer endless opportunities for capricious actions by nitpicky bureaucrats.

The proposed guidelines will be published in *The Federal Register,* and FDA will solicit comments. Young said the agency hopes to adopt the final guidelines by next spring.

DeVita expressed one major disagreement with the proposals. In Phase I studies, they state, "These studies should define an agent's non-therapeutic effects."

"I would never, never give a drug to a patient with no therapeutic intent," DeVita said. "That's a very serious concern." One more item for DeVita and Crout, or Rauscher and Commissioner Schmidt, to discuss.

The complete proposed guidelines will be published in ***The Cancer Letter*** next week, space permitting, or the next two weeks if necessary.

NCI URGED TO DEVELOP NEW SYSTEM FOR REVIEW, ACTION ON CARCINOGENS

NCI executives and advisors involved with the Carcinogenesis Program, increasingly aware of their potential power to determine the fate of vast numbers of chemicals in the American environment, have been engaged in a struggle with each other to determine how that power should be applied.

Five compounds–four pesticides and one chemical used in food processing–have been taken off the market largely as the result of data derived from the Carcinogenesis Program bioassay segment. Some NCI scientists, and many of their non-government colleagues, now feel that the procedures which brought about their removal were not entirely valid, although acknowledging that the chemicals themselves probably should be out of circulation.

The pesticides–heptachlor, chlordane, aldrin and dieldrin–had their registration suspended in legal proceedings brought before a federal administrative law judge by the Environmental Protection Agency. Data supporting EPA's case against the compounds, as suspected carcinogens, was supplied by Umberto Saffiotti, director of the Carcinogenesis Program and associate director for carcinogenesis of NCI's Div. of Cancer Cause & Prevention.

The case against the food processing chemical, trichloroethylene, resulted in a fiasco. Used primarily to decaffeinate coffee, very low residues remain in the finished product. Animal tests in the screening program indicated it might be carcinogenic, and NCI

issued a "memorandum of alert," a procedure established to warn the public, manufacturers and regulatory agencies of the possible danger. Before EPA or the Food & Drug Administration could take action, however, the coffee processors stopped using trichloroethylene and switched to methylinechloride.

"Trichloroethylene has been around for a long time and used in many ways," an NCI executive told ***The Cancer Letter.*** "Another few months of exposure more or less wasn't going to make that much difference. But methylinechloride is a relatively new compound, and one about which we know almost nothing. The risk could be far greater now."

Saffiotti conducts the screening program with 17 principles as guidelines for determining the carcinogenicity of a substance (Those principles were published in ***The Cancer Letter*** Sept. 26, page 5). After the trichloroethylene affair, considerable doubt developed over the validity of those principles. "If you really wanted to, you could determine that anything —anything, is a carcinogen under those principles," said one NCI staff member. "They're just too broad."

This was the background for NCI Director Frank Rauscher's decision to ask the National Cancer Advisory Board's Subcommittee on Environmental Carcinogenesis to develop a definition of a chemical carcinogen. The subcommittee, chaired by Philippe Shubik, has agonized over that task for two meetings, including a two-day session this week. It finally produced a six-page draft, expanded beyond and abandoning the term "definition" in favor of "criteria for establishing the carcinogenicity of chemicals."

Before developing the draft document, the subcommittee took two related actions which, if backed by Rauscher, would diminish to some extent Saffiotti's role in providing ammunition to the regulatory agencies.

The subcommittee adopted a resolution which called Saffiotti's guidelines for evaluation of carcinogenic hazards "a highly useful background for discussions on the definition of a carcinogen" but that it does not "provide an adequate definition of a carcinogen for use by regulatory agencies or for legislative purposes."

The subcommittee also voted unanimously to support a request by DCC&P Director James Peters to Rauscher that a new advisory committee be chartered to evaluate and interpret data on carcinogenicity on a case by case basis. "This committee will then advise the director as to whatever actions NCI should take in terms of the release of preliminary or nonfinalized carcinogenicity information," Peters said in his request to Rauscher.

If such a committee is chartered, it would have the job of evaluating data provided by Saffiotti and his staff—and by non-NCI sources, too, for that matter. The committee's recommendations would go to Rauscher, and then it would be up to him to present NCI's official position to the public, regulatory agencies, and courts.

"The way it has been," an NCI executive said, "we've attempted to do in a court of law an evaluation of scientific data, instead of in a committee room filled with scientists. We've got to have a sound peer-review system for this evaluation to remain believable. That's what's been missing from the Carcinogenesis Program."

Saffiotti went along with the resolutions and joined in the subcommittee's enthusiastic rewriting, for at least the fourth time, of its guidelines.

Shubik said the draft would be finalized at the subcommittee's meeting in January.

(The complete draft will be published next week in ***The Cancer Letter****)*

RFPs AVAILABLE

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

RFP NO1-CP-65752-69

Title: *The biology of neoplastic liver lesions in mice*
Deadline: *Jan. 17, 1976*

The objective of this project is to perform studies to evaluate the biological characteristics of both spontaneous and induced liver tumors in mice. Biochemical, immunological, morphological, transplantation or other appropriate techniques may be used. The study should be designed to determine the relationship of early lesions to the development of overt hepatocellular carcinomas.

Contract Officer: D.J. Dougherty
Cause & Prevention
301-496-6361

(Radiology abstracts, scheduled to be published here this week, will appear in a subsequent issue.)

The Cancer Newsletter—*Editor* JERRY D. BOYD

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