CARCINOGENESIS
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NEW BREAST CANCER THERAPIES MOVE INTO GENERAL PRACTICE; FISHER, MIAMI PLAN SEGMENTAL TRIALS

When should a promising new anticancer therapy, still considered by investigators as experimental but with the potential for saving thousands of lives, be made available to the patient population at large?

That question has been haunting many who are aware of the remarkable results obtained in breast cancer adjuvant therapy research using L-phenylalanine mustard (L-PAM) and the three-drug combination of cychlophosphamide, methotrexate and fluorouracil (CMF). More than

(Continued to page 2)

In Brief

WHITTAKER CORP. TRYING TO HIRE NCI DIRECTOR; ENVIRONMENTAL CARCINOGENESIS ON NCAB AGENDA

FRANK RAUSCHER confirmed that it is the Whittaker Corp. which has made him an offer he almost can't refuse, but insists he still hasn't decided he'll take it. Whittaker is the parent company of Microbiological Associates, which has about $6 million a year in NCI contracts and does about $12 million a year total. Whittaker grossed $778 million in 1975, which makes Micro's contribution seem small. "Nevertheless, if I take the job, I'll keep hands off Micro completely," Rauscher said. Whittaker products include industrial metals and structures, recreation products, textile chemicals and transportation products. The firm is headquartered in Los Angeles. . . . "PREVENTIVE MEDICINE," published by the American Health Foundation, recently reported a study on relationship of alcohol and tobacco to head and neck cancer by Joseph Feldman, Marc Hazan, Menna Nagarajan and Benjamin Kissin at SUNY Downstate. They found that nonsmoking drinkers were at only slightly higher risk to head and neck cancer, whereas nondrinking smokers had two to four times the risk of abstainers of both products. The risk for a heavy drinker who smoked, however, was from six to 15 times as great as the nondrinker-nonsmoker. . . . ENVIRONMENTAL carcinogenesis discussions will take up most of the March 22-24 meeting of the National Cancer Advisory Board. Louise Strong, director of the medical genetics clinic at the Texas Medical Center, will talk on cancer from interaction of the environment and genetics in man; Bernard Weinstein, Columbia, will discuss opportunity for cancer control based on molecular mechanisms; David Rall, director of the National Institute of Environmental Health Sciences, will talk on carcinogenesis and environmental health research; and NCI staff members James Peters, Thomas King, Umberto Saffioti, and Leonard Chiazze will discuss the various programs under way or planned, investigator initiated research in the field, analysis of cancer mortality statistics, and the bioassay program. Edward Scolnick of the Virus Cancer Program also is on the agenda to discuss transforming genes of mammalian RNA tumor viruses as probes for the metabolic pathways involved in human cancer.

COMMUNITY CENTERS ASKED TO HELP WITH BREAST CANCER, OTHER TRIALS

(Continued from page 1)

90% of patients on one or the other of those protocols have had no recurrence of disease after three years, in the L-PAM trial, and two years with CMF. Breast cancer patients treated only with surgery and with evidence of metastatic disease (one or more positive axillary nodes) recur 70-75% after two to three years.

Those involved in the trials—NCI executives as well as clinical researchers working in the cooperative groups and the Breast Cancer Task Force at the participating institutions—have been reluctant to push the L-PAM and CMF therapies into general practice. They plead for more time, to accumulate five-year data at least. The possibility exists that the drugs only delay recurrence which will show up in the fourth and fifth years. Promoting the new treatment now only for it to fail would be a shattering blow to the cancer program and to their own credibility.

They also still have some concern about the long term toxic effects of the drugs, although most are convinced that those risks are not nearly so great as leaving the patient untreated after surgery.

In the meantime, 90,000 women will be diagnosed with breast cancer this year, and 33,000 of them eventually will die from it unless they receive improved treatment. If the new treatment does turn out to be successful, most of those 33,000—66,000 if the delay is two years—will have died needlessly.

So when should a new therapy be moved into general practice? The answer, at least regarding the new breast cancer therapies, appears to be: Whenever alert and aggressive clinicians hear about it and decide that it can help their patients.

The Cancer Letter learned at the annual meeting of the Assn. of Community Cancer Centers last week that L-PAM and CMF are being administered regularly to an increasing number of patients at many of the major cancer centers; a growing number of physicians at community cancer centers and smaller hospitals are using them; and at least one comprehensive center —Miami—is actively engaged in encouraging postoperative chemotherapy in hospitals throughout Florida.

Charles Vogel, who heads the breast cancer team at Miami, told ACCC members that CMF "is an accepted form of therapy" and should be considered standard practice despite not yet having been proven out as a "cure."

Gordon Zubrod, director of the Miami center, led a presentation on principles of clinical trials which outgoing ACCC President James Donovan said "is really a course in clinical research for community physicians."

Zubrod told ***The Cancer Letter*** that the task of encouraging use of new therapy such as the breast cancer developments is "what our program with Jacksonville and ACCC is all about"—the effort supported by an NCI cancer control grant to foster cooperative clinical research between community and comprehensive centers.

Informed of the comments by Vogel and Zubrod, Fisher insisted that "the final answer is not in. What we have found is exciting, encouraging, but the danger is that we'll be locked into them (L-PAM, CMF) with no more clinical trials. We'll wind up waiting another 100 years for more improvements."

Fisher said he prefers to see community breast cancer treatment programs used as mechanisms for evaluating the new therapies. "We're still in the position of refining them, improving them. It's unfair to say that we have conquered breast cancer. It's still in a state of flux, with a whole bunch of clinical trials going on."

Vogel was not in disagreement with Fisher and was careful to point out that although he felt CMF is an accepted form of therapy, "it certainly can not be considered curative at this point. It's still too soon for that."

Vogel said Miami is preparing a "second line" of chemotherapy defense to follow relapse after CMF treatment. These will include adriamycin with L-PAM and BCNU, and hexamethylmelamine with L-PAM and BCNU.

Fisher now has 550 patients enrolled in a study comparing L-PAM vs. L-PAM plus 5FU.

"The greatest service the community centers can do is to line up with us in clinical trials," Fisher said. That's exactly what Vogel proposed, and described Miami's plan to cooperate with Fisher's effort to find out if segmental surgery can replace total and radical mastectomies.

Fisher has received approval from NCI and cooperating institutions in the Breast Cancer Task Force to proceed with the segmental study. This study will compare segmental surgery plus axillary dissection, with and without radiotherapy, with modified radical mastectomy. All patients with positive nodes will receive L-PAM under the present plan, although Fisher has indicated other drugs might be used later.

Vogel said Miami has not yet decided to follow Fisher's protocols in detail. Vogel suggested one variation—patients with negative nodes would be divided into two groups, one receiving L-PAM after segmental surgery and one not receiving any chemotherapy.

"We now cure 85% of those with negative nodes by surgery alone," Vogel said. "We want to make that 100%." L-PAM, least toxic of the breast cancer drugs so far, would be the vehicle with which to reach 100%. Patients with positive nodes would receive the more potent drugs, Vogel said.

Fisher previously had expressed some doubts that physicians and surgeons would encourage their patients to enter segmental studies. But he said last

week that there was a lot of interest developing around the country and internationally. "It's very exciting. I don't think we'll have any trouble getting the patients," he said.

Vogel said that expanded clinical research, with breast cancer and other sites as well, depends on the cooperation of community physicians. "Where are the patients? They're with you," he told ACCC members. "If your patients don't get into the protocols, we're going to be set back years . . . More patients must be entered into the protocols. That's where ACCC can be a tremendous resource."

Zubrod discussed the use of controls in clinical trials. "Any new treatment must be compared with the best existing treatment," he said. "If there is no existing treatment, then we have to wrestle with the problem of untreated controls."

Use of historical controls is complicated by a number of factors, Zubrod pointed out—the disease itself may have changed; earlier diagnosis now results in comparisons that are not always valid; various techniques can improve survival without affecting the disease itself. "So historical retrospective controls are deficient, although they sometimes are useful," Zubrod said.

Randomized trials with concurrent controls are often the only way to demonstrate small changes, "as we did with childhood leukemia," Zubrod said. This resulted in a series of small changes, "which when we put it together," brought about ability now to cure 50% of patients in a disease which had been 100% fatal.

Zubrod said he believes that comprehensive and community centers "can work together comfortably, if we develop mutual respect for each other's competencies." He encouraged phase IV treatment of patients in community hospitals, following protocols, in cooperation with comprehensive centers. "Let's get on with the new treatment, as long as it's well defined, safe and accepted."

Francisco Tejada, of Zubrod's staff, discussed general protocol compliance, what he called "the nuts and bolts of clinical research." He explained the necessary record keeping and the need for trained personnel to relieve the physician of that burden.

"You have the responsibility to look at the data and to respond to it, throughout the trial," Tejada said. "You have to make sure the data are proper, reproducible and readable."

ACCC CONSIDERS ROLE OF ALLIED PERSONNEL, COMPONENTS, FUNDING

The expanding role of cancer care personnel was described to ACCC members by four specialists who work entirely with cancer patients.

Beatrice Reister, Wilmington, Del., Medical Center, discussed the clinical nurse specialist who she said "is between the nurse and the physician—she's not a doctor, not a nurse. The definition is not clear." Examples of tasks she performs include routine functions involved in admissions, including histories and physicals. "My physicals are usually more complete than those by physicians."

Her job includes relationships with families, "to help the family help the patient; to help the hospital staff see the meaning of a patient's actions. Patient demands frequently upset the hospital routine, and it infuriates the other nurses. When I support the patient, that anger is directed at me. They ask, 'Who runs this hospital, the patients or the staff?' "

Reister insisted that nurse oncologists are "non-doctor professionals, not paraprofessionals."

Saundra Lang, nursing coordinator for the Michigan Cancer Foundation, explained the role of the home assistance nurse. The program is aimed at "enhancing the quality of life of the cancer patient during a catastrophic period" by enabling him to live at home as long as possible. She helps families deal with the patients and "draw on the personal strengths of the family and the patient."

Patricia Porcher, of the Northeast Florida Cancer Program, described the work of the enterostomal specialist. "We're a new specialist, and we're not always greeted joyously" by other health professionals, she said. Her primary job is to teach the patient proper and total self care, to return to the community as a normal person, she said. Half her time is spent teaching others how to teach patients, she commented.

Nurses are trained as enterostomal specialists with the help of grants by the American Cancer Society at one of eight training centers. Porcher said ACS limits grants to nurses who will work full time in the specialty. This would require a 700-bed hospital or one in which there are at least eight ostomy patients on any given day. The institution has to guarantee that the specialist will work at it full time.

Gale Katterhagen, Tacoma General Hospital, challenged that restriction. "If we're willing to pay a nurse's salary I don't see why we shouldn't have a part-time enterostomal specialist. A 200-300 bed hospital can't use one full time, and there is no reason why a nurse trained for other duties can't spend part of the time in that area, part with ostomy patients."

Sharon Klein, director of patient services and rehabilitation with the Michigan Cancer Foundation, described the multiple roles of the social worker in a cancer program. These include:

—Detection, as an outreach worker, to help identify individuals, families and groups at high risk.

—Linkage, steering patients to existing services.

—Advocacy, fighting for the rights of individuals in need of help.

—Evaluation, helping to determine priorities.

—Mobilization, of existing institutions and resources. "No single institution has all the resources, money, and manpower."

—Instruction, of patients.

—Behavior change, working to bring about behavior change in individuals and groups.

—Community planning, consultation, information processing, administration, and continuing care.

The components of a community cancer program were discussed by representatives of a metropolitan and a rural hospital, a comprehensive cancer center and the ACS.

Karl Jonas, Doctors Hospital, Washington, D.C., said that a metropolitan hospital should have a tumor registry, multidisciplinary cancer committee, regular education cancer conference, consulting service, and a system for quality control.

Alan Schroeder, Northern California Radiation Therapists and Oncologists Medical Group, described the difficult task of organizing the widely scattered rural facilities, resources and patients into an effective cancer program in his area. Problems include the need for a feasibility study; lack of acceptance by local MDs, especially surgeons and other specialists, although "we work hard at keeping communications open;" data retrieval; difficulty in maintaining tumor boards; loss of interest in teaching oncology; understaffing. "We had a great idea, we made some giant steps forward, encountered many problems, solved some, but failed in many aspects," Schroeder said.

Alan Davis, ACS vice president for governmental relations, said ACCC members must recognize the need for "coordination, cooperation, and dovetailing" their efforts with those of the local ACS chapters. "It's important that we use the strengths we have to help build each other," Davis said.

Jack Hartmann, Hutchinson Comprehensive Cancer Center, described his center's efforts to work with community programs in its region, Northwestern U.S. The center has established an extramural council to work with the communities.

The problem of how to fund community cancer programs was the subject of a discussion which included H.G. Pearce, representing the Blue Cross Assn.; Manuel Levine, of the Social Security Administration's Bureau of Health Insurance; and Jonathan Rinehart, professional fund raiser. The consensus: Money is getting harder to find.

Pearce explained Blue Cross and Blue Shield coverage, that services related to cancer care not previously covered are being included in many new policies but that costs involved inevitably drive premiums up. An example is the contract with General Motors, in which the increase in premiums paid by the company wiped out the company's entire profit for one quarter and resulted in dropping some benefits.

"We've reached the point where there is no choice," Pearce said. "We will work to help you improve cancer coverage, but we must go for the best care, not for all the care there is."

Levine described the limits placed on Medicare coverage by law. An example is that the law does not reflect the existence of free-standing cancer clinics or centers, and unless they are associated with hospitals or can otherwise meet the definition of hospital, Medicare reimbursement frequently cannot be made. Limits are also placed on services of allied personnel, and on reimbursement for drugs prescribed for outpatients.

Rinehart described the sources of private fund raising, presented figures on how much of it is drying up, and suggested that despite difficulties individual giving still offers the biggest payoff in raising funds for worthwhile causes.

JOHN NELSON ELECTED ACCC VP; YARBRO HEADS SCIENTIFIC BOARD

John Nelson, director of the Northeast Cancer Program in Jacksonville, Fla., was elected ACCC vice president at the annual meeting. He filled the position vacated by Gale Katterhagen, who was elected president (*The Cancer Letter*, Feb. 6).

Other officers remain—David Johnson, Deaconess Hospital, Evansville, Ind., secretary; and James Hochstadt, West Coast Cancer Foundation, treasurer.

ACCC has established its own scientific advisory board, chaired by John Yarbro, formerly head of the NCI centers program and now director of the Missouri Cancer Center. Other members are Michael Brennan, Michigan Cancer Foundation; John Durant, director of the Univ. of Alabama Comprehensive Cancer Center; John Hartmann, associate director of the Hutchinson Comprehensive Cancer Center; Harold Rusch, director of the Univ. of Wisconsin Comprehensive Cancer Center; and Gilbert Friedell, St. Vincent's Hospital, Worcester, Mass.

SHUBIK SUBCOMMITTEE FAILS AGAIN TO AGREE ON CARCINOGENESIS DRAFT

The National Cancer Advisory Board's Subcommittee on Environmental Carcinogenesis wrestled mightily last week with still another draft of its attempt to establish "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances." But the effort resulted only in the decision to come back for another meeting, March 4, and give it another try with another draft to be written in the interval.

The committee and its consultants, as they did at previous meetings, disagreed on major and minor items throughout the document, resulting in so much rewriting that it was almost impossible to follow the original draft.

Among the most difficult areas to resolve, and one that sparked the most disagreement, was the definition of a malignant as opposed to a benign neoplasm. Chairman Philippe Shubik assigned several members to write that definition during the lunch break, which they did. But the rest of the committee promptly ripped it apart.

The proposed definitions for malignant and benign

neoplasms were:

"A malignant neoplasm is one composed of a relatively autonomous population of cells displaying progressive growth and anaplasia with invasion of normal tissues and the potential of causing death to the host. The biologic behavior of malignant neoplasms includes the actual or potential for metastatic growth by one means or another. Benign neoplasms are defined as neoplasms which contain a relatively autonomous growth of cells exhibiting little or no anaplasia and invasion of normal tissues and which do not metastasize successfully. While in most instances the differences between benign and malignant behavior of neoplams are relative, i.e. growth rate, invasion, anaplasia, etc., the critical distinction between the two is that benign neoplasms do not metastasize whereas malignant neoplasms have this capability. In particular cases however benign neoplasms may endanger the life of the host by a variety of mechanisms including hemorrhage, encroachment on a vital organ or unregulated hormone production.

"It is recognized that the cytologic and histologic criteria utilized in determining whether a lesion is benign or malignant differ depending upon the tissue in which the neoplasm arises. Evaluation of whether a specific lesion is benign or malignant should, therefore, follow standard criteria used by experimental oncologists and pathologists with the emphasis on the correlation of the histopathologic pattern with the biologic behavior of the lesion or type of lesion under investigation. It is recognized that in some equivocal cases the precise diagnosis of a specific lesion may require a panel of experts."

That section was to be added to the 10-page draft, but the committee worked it over word by word, cutting out phrases and entire sentences, and adding sentences. The general thrust of the malignant-benign definitions as described above remained intact, however, and apparently will be included in the new revised draft of the entire document.

The subcommittee has a deadline, the March 22-24 meeting of NCAB, when the final draft is scheduled for presentation to NCI Director Frank Rauscher. Rauscher had asked for the guidelines, or criteria, or as it was first envisioned, a simple definition of a chemical carcinogen. He needed one to offer to the regulatory agencies to help them make decisions on whether or not to order the ban of suspected carcinogens. Those agencies have turned to NCI for scientific support, and the effort has become increasingly more complicated. (***The Cancer Letter,*** Nov. 14).

Until recently, Shubik's subcommittee worked in relative anonymity, with only ***The Cancer Letter*** and one or two other health publications reporting on its deliberations. After the subcommittee's November meeting, however, a copy of one of the earlier drafts of the "Criteria" fell into alien hands and was used in a court proceeding. This led to an attack on Shubik by Samuel Epstein, Case Western Reserve, and awoke government regulators and those they regulate to the significance of the subcommittee's work. At last week's meeting, representatives of government agencies, the food and chemical industry overflowed the committee meeting room and forced a move into larger quarters.

Shubik opened the meeting by reading a statement deploring the premature and unauthorized use of the draft and explaining how it came about:

"As I am sure many of you must know the proceedings of this committee have aroused considerable attention since our last meeting. I find in reading through the transcripts somehow I must have had a prescience of things to come when I said to Dr. Weinstein 'Let me warn you in advance, Doctor, that things said at this meeting have a tendency to get wide distribution from time to time and drafts are taken reasonably seriously.'

"It is unfortunate that our deliberations have resulted in the rousing of considerable emotion and have possibly been misused. For certain, our procedures have been misunderstood and I believe that both a careful reading of our transcript and of the Freedom of Information Act would have obviated certain problems that have arisen.

"Dr. Sam Epstein has been kind enough to send me a copy of his remarks made on Jan. 12 to the Environmental Study Conference held at the Rayburn House Office Building. In this draft Dr. Epstein states, 'The chairman of the NCAB subcommittee issued in public a draft document which had not been seen, let alone approved by the subcommittee members and which contained major scientific distortions and inaccuracies. The draft was then introduced by Velsicol Chemical Co. into the EPA suspension hearing on chlordane and heptachlor. Subsequently the chairman and subcommittee members stated to the EPA that this draft was preliminary and should not be used for regulatory purposes. Nevertheless, this draft appears to have influenced the administrative law judge in his decision, 12/12/75, not to recommend the suspension of these pesticides.'

"It would not, I believe, be necessary to provide detailed evidence for members of the subcommittee to clarify the number of gross inaccuracies contained in this statement. However in view of the considerable publicity accorded to these remarks and the inferences drawn from them I believe that it is quite essential that, at the outset of this meeting these matters be clarified. In the first instance the chairman of this subcommittee did not, as alleged, 'issue in public a draft document which . . . '. The executive secretary of this subcommittee, in accordance with the Freedom of Information Act, was duty bound to provide all and sundry with copies of the preliminary draft document. Indeed some of the most vociferous critics of our procedure were prominent amongst those demanding copies of this draft. In the minutes of the meeting I stated, following considerable discussion

of a draft produced initially by Dr. Weinstein and modified by the committee, '. . . well, in that case, what we will do with your document is have it retyped, incorporating your various suggestions and have it sent out to everybody and reconvene the group within the time limits imposed upon us.' The 'time limits imposed' refer to the Committee Management Act.

"There are some other references at the end of the meeting to this matter but the remainder of the meeting was devoted to the other business of the committee. It was made amply clear throughout and on the headings of the draft that this was a preliminary draft. As Dr. Epstein has pointed out in his talk the chairman of the subcommittee and subcommittee members did inform the EPA of the preliminary nature of the document. In view of the seriousness of the implied allegations made, I should like to correct this statement.

"I responded to calls from both attorneys in the chlordane and heptachlor suspension hearings and asked the attorney representing Velsicol not to use the document and sent Mr. Howard, the associate general counsel to the EPA, a telegram which I have with me. I further volunteered to appear athe hearing on behalf of Judge Perlman to clarify the matter and informed the counsels that I could, under no circumstances, take sides in this case. The EPA counsel informed me that it would be unnecessary for me to have to travel to Washington and that my telegram had satisfactorily resolved the matter. It is my understanding that contrary to the suggestion in Dr. Epstein's manuscript the deliberations of the subcommittee did not play a role in Judge Perlman's decision.

"I must apologize to the group for presenting this matter in such detail but feel that this is the only manner in which the air can be cleared. Apparently Dr. Epstein cannot have had access to the complete transcript of our proceedings at the time he prepared his remarks and has not understood the constraints under which we are forced to operate under the Freedom of Information Act. I, for one, would much prefer to have been able to wait until a final document had been prepared and approved prior to its release; this is just not possible. I may say finally that Dr. Epstein's remark that the document that was released was not finally approved by the committee is correct—it was, as stated, a working draft and how this could have been made more clear to all concerned I do not know. . . .

"We have received a gratifying response from many prominent members of the scientific community to our preliminary draft; there is a general agreement to the bulk of the draft; the particularly controversial issues, namely the interpretation of the significance of benign neoplasms, the importance of experiments being reproducible and the induction of 'unphysiological conditions' in experiment are repeatedly discussed with the predictable split of opinion."

The draft presented at the November meeting was published, with changes made at that meeting, in ***The Cancer Letter,*** Nov. 21. Additional changes were made in the draft brought to the meeting last week, refining sections dealing with criteria in human studies, criteria in experimental animal studies, short term or in vitro tests for carcinogens, and extrapolation of experimental data to man and the evaluation of human risks.

The most extensive change was the addition of an introduction and a section on definitions. Those additions follow (the definitions of malignant and benign neoplasms were added to this section):

NCI is increasingly asked to advise governmental regulatory agencies on the possible carcinogenic hazards of substances that might be introduced into, or already exist in, the human environment. National Cancer Program Director Frank Rauscher, therefore, asked the NCAB Subcommittee on Environmental Carcinogenesis to develop general criteria for use in the assessment of whether environmental substances are or are not carcinogenic. The remainder of this document represents this subcommittee's current formulation of these criteria. In assembling these criteria, the subcommittee clearly recognized that at the present time there is no simple and universal definition of either carcinogenesis or neoplasia. The criteria which are listed below should, therefore, be considered as general guidelines and not rigid and universal criteria. The complexity of the problem dictates that in the final analysis, the evaluation of the potential human hazards of a given substance must be individualized in terms of the chemical and metabolic aspects of that substance, its intended use, the data available at the time that the decision must be made, and other factors pertinent to the case under consideration.

For purposes of clarity, the general criteria have been classified into three groups in terms of the sources of the data: 1) criteria from human studies, 2) criteria from animal bioassays, 3) criteria from in vitro or short-term tests. This does not imply that human carcinogens are distinct from animal carcinogens. Nor does it imply that carcinogens can be defined absolutely by any of the currently available in vitro or short term tests.

The major source of our data on carcinogenicity comes from bioassays done in experimental animals. Experience has indicated that, with few exceptions, compounds that are carcinogenic in humans are also carcinogenic in one or more experimental animal bioassays. In addition, several compounds first detected as carcinogens in experimental animals were later found to cause human cancer. The clear demonstration that a compound is carcinogenic in experimental animals must, therefore, be taken as evidence that it is likely to be carcinogenic in humans unless there is strong evidence to the contrary.

We must stress that the general criteria listed in this

document reflect the judgment of this subcommittee based on its assessment of the current "state of the art". These general criteria should be reviewed on a continuing basis and revised as necessary in the light of new knowledge.

For other discussions of principles of carcinogenicity and carcinogen assessment, the reader is referred to separate references on this subject.

1. In this document the term *carcinogen* is used in its broad sense with no attempt to distinguish precarcinogens, proximate-carcinogens, ultimate carcinogens, initiating agents or promoting agents. This has been done because most of the current human epidemiologic and animal bioassay data do not permit such distinctions. This is obviously a serious limitation and there is a need to develop new assay procedures which will permit such distinctions.

This document is concerned only with the causation of cancer by chemical agents, and not with the assessment of radiation or viruses as causative agents, simply because two groups of agents require their own set of criteria. In the evaluation of carcinogenesis data attention must, of course, be paid to the composition and identity of the chemical agents tested and their stability under conditions of storage and administration.

2. This subcommittee has found it useful to state generalized definitions of malignant and benign neoplasms, recognizing that such definitions are not all encompassing and that in practice the diagnosis of a particular neoplastic lesion is an operational one based on convention and experience.

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-65758-69

Title: *Development and validation of an in vitro mammalian cell mutagenesis system for carcinogenesis screening*

Deadline: *March 23*

Since the numbers of chemicals impacting upon man and the environment far exceeds the capacity of existing long-term animal carcinogenesis test systems, NCI is interested in developing a matrix of rapid short-term in vitro tests for use in initial evaluation of chemicals for possible carcinogenic potential and to provide the tools to investigate basic mechanisms of action of chemical carcinogens.

An objective of the in vitro carcinogenesis program is to develop detailed methods and protocols for carcinogen screening using cell culture assays. The specific aim of this proposed project is to evaluate and determine the usefulness and reliability of an in vitro cell mutagenesis system using L5178Y mouse lymphoma cells for routine use as an assay for initial determination of the carcinogenic potential of chemical compounds.

In the initial phase, the contractor will establish the L5178Y mouse lymphoma mutagenesis assay according to the methodology described in the following reference:

Clive, D. and Spector, J.F.S.: Laboratory Procedure for Assessing Specific Locus Mutations at the TK Locus in Cultured L5178Y Mouse Lymphoma Cells. Mutation Res. 31: 17-29, 1975.

The following modifications are to be considered in development of the system: 1) An alternate procedure for toxicity testing of compounds to be used, and 2) Increasing the exposure of the cells to the chemicals to 24 hours. The initial group of compounds to be used in evaluating the system will include 3-methylcholanthrene, 7, 12-dimethylbenz-(a)anthracene, benzo(a)pyrene, N-methyl-N-nitro-N-nitrosoguanidine, N-acetoxy-N-2-fluorenylacetamide, 2-acetylaminofluorene, ethyl methanesulfonate, 3[1] methyl-4-dimethylaminoazobenzene, phenanthrene, pyrene, diphenylnitrosamine, benzidine, hycanthone, β-naphthylamine, p-rosaniline, and methyl methanesulfonate.

When there is sufficient confidence with the system using the initial group of 16 substances, and in consultation with the project officer an additional group of approximately 100 preselected reference chemicals, consisting of both carcinogens and non-carcinogenic analogues, will be assayed double-blind, to determine the response of the assay system. All chemicals will be supplied by NCI.

It is recognized that the immediate value of the system will be for direct acting chemical carcinogens. It will not be adequate for those compounds requiring more complex metabolic activation. Therefore, effort will also be directed to defining activation methodology which can be used with this system.

The government estimates that performance of the above described services will entail approximately 1½ professional man years of effort per year.

Contract Specialist: Linda Waring
Cause & Prevention
301-496-6361

RFP NO1-CP-65757-69

Title: *Validation and utilization of microbial mutagenesis systems as prescreens for chemical carcinogens*
Deadline: *March 23*

The objective of this proposed project is to validate the microbial mutagenicity assay for identification of carcinogens and to demonstrate its predictive ability using known carcinogens and substances under test for carcinogenicity.

Approximately 100 substances, to be supplied by NCI, will be tested for mutagenicity in a double-blind study. The substances will be tested using Salmonella typhimurium strains TA-98, TA-100, TA-1535, TA-1537 and TA-1538 (1,2,4), Escherichia coli strains WP-2/uvrA$^-$ (3), and W3110/polA$^+$ and p3478/polA$^-$(5).

All substances will be tested both with and without metabolic activation. The metabolic activation systems will be derived from the livers of uninduced and Arochlor 1254-induced male Fischer rats, C57B16 x c3H[He]/F$_1$ mice, and Syrian hamsters. The C57B16 x C3H[He]/F$_1$ mice will be supplied by NCI. Other animals must be obtained by the offeror. Tests will be performed in triplicate using 5 dose levels. Appropriate positive and solvent controls will be run at all times.

The Salmonella strains and E. coli WP-2 will be tested using the quantitative plate test of Ames (1,2, 4); E. coli W3110 and p3478 will be tested in a spot test.

Therefore, the following will be required:

1. There will be a start-up time at the beginning, using 5 known substances prior to testing the 100 blind substances.
2. Protocols will be standardized among the different laboratories.
3. All laboratories will use the same dose ranges; additional doses may be used at the discretion of the individual lab.
4. The assay results will be entered into a data base. The data format and system to be used for such entries will be provided by NCI.
5. All unknown compounds will be supplied in groups of 20-25.

The government estimates that performance of the above described services will entail approximately 1½ professional man years of effort per year.

Contract Specialist: Linda Waring
Cause & Prevention
301-496-6361

RFP CDC-99-OSH-100(6)

Title: *Effect of elevated temperature on carcinogenesis*
Deadline: *Approximately April 1*

Organizations interested in determining the possible differential effect of heat exposure on carcinogenesis by examining the interaction of temperature and a known chemical carcinogen on the incidence and development of skin carcinomas in male mice are solicited.

Contact: Contracting Officer
National Institute for Occupational Safety & Health
Room 1-58
5600 Fishers Lane
Rockville, Md. 20852

CONTRACT AWARDS

Title: Study of genetic and immunologic factors in viral leukemogenesis
Contractor: Albert Einstein College of Medicine, $170,000.

Title: Research on oncogenic and potentially oncogenic viruses
Contractor: Merck, $734,960.

Title: Immunoprevention of spontaneously occurring neoplasma
Contractor: Microbiological Associates, $655,000.

Title: Immunotherapy of cancer in man
Contractor: Univ. of Minnesota, $90,000.

Title: Pre-clinical studies on tumor protective activity of MER
Contractor: Hebrew University, Jerusalem, $122,212.

Title: Developmental planning for cancer control pathology reference centers
Contractor: American Society of Clinical Pathologists, $229,785.

Title: Programming services in support of contract management system
Contractor: Sigma Data Computing Corp., Bethesda, Md. $14,311.

SOLE SOURCE NEGOTIATIONS

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

Title: Metropolitan Atlanta SEER
Contractor: Emory Univ.

Title: Breast cancer detection demonstration project
Contractor: Guttman Breast Diagnostic Institute.

The Cancer Letter—*Editor* JERRY D. BOYD

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