THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 2 No. 44
Oct. 29, 1976

Subscription $100 per year

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HSA AUTHORITY OVER CANCER PROGRAMS BECOMES HOT ISSUE; FREDRICKSON OPPOSES EXEMPTION FOR NCI

The question of what to do about the potential problems the Cancer Program could encounter through the new Health Systems agencies is becoming increasingly controversial within the health establishment and perhaps within NCI itself.

HSAs were authorized in legislation designed to put some teeth into local and regional health planning efforts. The goal is to reduce duplicative facilities and services which result in too many empty hospital beds and too much investment in underutilized equipment and personnel.

Local and regional HSAs are the responsible planning bodies and consist of lay and professional members, with the professionals in the minority. The law gives them the authority to review plans for all health-related programs which receive any federal support. NCI con-

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In Brief

CANCER CLAIMS MORRIS KUPCHAN, WHO FOUND PROMISING NEW ANTITUMOR DRUGS IN PLANTS

S. MORRIS KUPCHAN, whose work in isolating antitumor drugs from natural products eventually may save thousands of cancer patients, died of the disease last week. Kupchan was principal investigator for NCI's contract with the Univ. of Virginia under which a host of promising new drugs have been found. Three are now in clinical trials—thalicarpine, which is being prepared for phase II studies; tetrandrine, also nearing the phase II stage; and maytansine, which is approaching the end of its phase I studies. Bruceatin has been approved for phase I. Others include tripdiolide, acernegundo and baccharin. Kupchan received the Ernest Guenther award last year from the American Cancer Society, and last month received an honorary doctor of laws degree from Hokkaido Univ. in Japan for his "new and original approach to the chemistry of cancer control." Kupchan, 53, was the dominant figure on the project. U.Va. will have to recruit a top person to take it over or risk losing the work to another institution. . . . CLINICAL CYTOPATHOLOGY postgraduate course for pathologists at Johns Hopkins Univ. is scheduled for April 11-22. Deadline for applications is Feb. 28. The course will provide an intensive refresher on newer techniques, special problems and recent applications. Write to John Frost, 610 Pathology Bldg, Hopkins Hospital, Baltimore 21205. . . . NEW PUBLICATION: "Cancer—The Behavioral Dimensions" is now available from the Raven Press, $22.50. It is a monograph based on the 1975 conference on cancer control and the behavioral sciences sponsored by NCI's Div. of Cancer Control & Rehabilitation in San Antonio. It was edited by Joseph Cullen, now deputy director of the UCLA Cancer Center, and Ruby Isom and Bernard Fox of NCI.

FREDRICKSON, SOME AT NCI FEEL HSA REVIEW OK FOR CERTAIN CANCER PROJECTS

(Continued from page 1)

struction grants and some cancer control projects may be subject to HSA review. There is concern that other NIH supported research also may be included.

If local and/or regional HSAs disapprove a project, it can be appealed to HEW, where the secretary can overrule the agencies if he is so inclined.

NCI executives have warned that the whole process "could tie us into knots," adding months to the already drawn out process of awarding grants and contracts.

NIH is currently negotiating with the Health Resources Administration, under which HSAs will operate, in an attempt to gain some exclusions from the regulations which HRA is in the process of developing.

The National Cancer Advisory Board is considering another approach, legislative exemption. The Board has a number of proposals for revisions to the National Cancer Act which will be submitted to Congress next year when the Act is up for renewal. Among them is one that would exclude NCI projects from HSA review and approval. The Board will consider the various proposals at its Nov. 15 meeting.

NIH Director Donald Fredrickson does not agree that NCI should receive any special treatment. In a memo to NCI Director Frank Rauscher, Fredrickson said:

"The proposal to exempt projects of the National Cancer Program from HSA review raises complex and sensitive issues. . . . I, too, am gravely concerned about HSA's interference with national research programs. As you know, the question of exempting NIH research activities and control/demonstration is currently being actively considered by a committee working in concert with staff from the Health Resources Administration to develop guidelines for the HSA.

"It would be difficult to support a claim that at least some of the large NCI programs do not have a substantial impact in health resources in a given community," Fredrickson continued. "Specifically, to exempt certain of the large cancer control projects from HSA review would be contrary to the letter and intent of the law. I would suggest that NCI play a vigorous role in the current negotiations with HRA in representing its views. I strongly urge the Board to avoid unilateral action on this matter; it needs to be resolved in the context of all NIH programs."

At least one NCI executive agrees with Fredrickson. "You can't argue that a big new cancer center would not impact a community's health program," he told ***The Cancer Letter***. "Many of the programs we support do tend to put a strain on a community's resources. I think those communities have a right to be heard when those programs are being planned."

The reviews do not have to result in delays, he said. "The program sponsors should have their ducks in line before they come to us with their proposals."

He also agreed with Fredrickson's position that NCI exemption would be "contrary to the letter and intent of the law."

That is exactly the point that the Board is being asked to consider—to get the law changed, so that exemption of the Cancer Program would not be "contrary to the letter and intent."

Those who do not agree with Fredrickson probably are still in the majority at NCI, and certainly among Cancer Program constituents. They feel there are any number of potential situations in which Cancer Program needs would conflict with HSA perceptions of local health requirements. For instance, a principal investigator may find that exclusive use of a piece of equipment, such as an EMI scanner, is absolutely necessary to his project, but other institutions, non-profit or otherwise, may have the same equipment with time available which they would like to rent out. Local jealousies have been known to flare up into bitter confrontations over lesser issues.

The Board does not have to go along with Fredrickson's request, or it could ask Congress to exempt all NIH programs. If the Board declines to recommend any action on the issue, representatives of cancer centers and other Cancer Program participants may want to take their cases to Congress themselves.

There are other Cancer Act revisions the Board is considering, and Fredrickson supports most of them. Robert Schonfeld, chief of NCI's Program Liaison Branch, prepared a statement of those proposed revisions, including the justification for each:

1. (a) Delete the $5 million limit on funding per center; (b) Amend the language to include basic core grant support.

Justification: (a) Section 408(b) of the National Cancer Act is the proper statutory authority for core grants. By using other authorities in the PHS Act for research grants, training grants, cancer control grants, construction grants, and contracts, support for any individual center may exceed $5 million provided that core grants alone do not exceed $5 million. By deleting this ceiling on core grants, reliance can be placed on review groups to recommend the core support level appropriate for each center within the context of an arbitrary ceiling. (The National Heart & Lung Act provides inflationary language to the $5 million limit.)

(b) Technically, under the present statutory language, core awards can only be made for clinical research purposes. By adding the words "basic and" before each use of "clinical research" in this section, we can make it clear that core support is authorized for both types of research.

2. Permit distribution of chemical carcinogens and animals.

Justification: The purpose of this recommenda-

tion is to assure that well characterized reference chemicals and animals a re available to non-NCI supported investigators. Currently, the Act authorizes NCI to distribute biological materials. NCI proposes to distribute reference chemicals for use by non-NCI supported investigators. Many of these chemicals, contained in NCI's chemical repository, are themselves carcinogenic. Demand for these chemicals is limited. However, because of the limited demand and the expenses associated with upgrading facilities to satisfy safety standards established by the Occupational Safety & Health Administration, commercial sources are reluctant to produce these substances. In addition, HEW general counsel has ruled that the Act does not permit distribution of chemicals to any one other than NCI-supported investigators. NCI has taken the position that the National Cancer Program is broader than NCI and its clients, and therefore, to provide these resources to investigators not otherwise receiving NCI support would be an appropriate action within NCI.

3. Increase the number of experts from 100 to 200.

Justification: NCI has reached its ceiling of 100 expert appointments. It is felt after reviewing program requests for experts that an additional 100 positions could be utilized. These appointments have provided a unique and rapid means to utilize on a time-limited basis, individuals with specialized talents and experiences to institute newly mandated programs and to take advantage of newly emerging opportunities. For example, special experts were extensively used to plan and initiate the cancer control program, the cancer diagnosis program, for laboratory research investigators, and to support cancer-related activities in other NIH organizations.

4. Authorize the director of NCI to issue regulations making cancer a reportable disease (such as venereal disease) and authorize him to collect, analyze and report on cancer incidence and mortality.

Justification: A complete epidemiologic base is needed for the National Cancer Program. The SEER Program was established to provide that base. Recent legislation prevents Veterans Administration Hospitals from providing patient data to SEER registries. By making cancer a reportable disease, the NCP would be assured of a full epidemiologic base.

5. Exempt NCI projects from HSA review and approval.

Justification: Construction projects and certain cancer control projects are deemed to fall under the review and approval of Health Systems Agencies. Although construction grants may not cause too much of a time lag, this review and approval would be devastating to the cancer control program. HSA review and approval could cause up to a nine month delay in award time. NCI contends that while many of their programs do have substantial community impact, such impact ma y be secondary rather than primary. These activities may be designed to serve broadly conceived goals in respect to cancer research whether they be field tests, demonstrations, or educations, prevention, treatment, diagnosis, etc., and are not primarily focused on medical care delivery or health resources development in any specific community or region.

The Board at its last meeting approved authorization levels of $1.1 billion for fiscal 1978, $1.2 billion for 1979 and $1.3 billion for 1980. The Board also recommended that the time limit on core grant support be extended from three to five years.

Fredrickson said he has "no reservations" concerning the authorization levels asked by the Board. And he agreed that the recommendations for distribution of chemicals and animals and the increase in number of expert appointments "are positions with which I would be in accord."

He said that the problem involving the $5 million limit on core grants "will obviously require clarification before it can be considered further."

As for making cancer a reportable disease and authorizing collection of data on cancer incidence and mortality, although "worthwhile objectives . . . strikes me as requesting authority the NCI director could not legally have; it also will likely be considered an intrusion on the responsibilities of other agencies, particularly the National Center for Health Statistics. It seems to me that NCI could accomplish the same objective by working with the Center for modification of relevant statutes."

The Board also may be asked to consider the proposal to take the authority for overseeing clinical testing of anticancer drugs away from the Food & Drug Administration, at least for research conducted at nonprofit institutions. Under that plan, NCI would supervise that research, leaving FDA with authority over anticancer drug tests sponsored by the pharmaceutical industry.

TWO WORKSHOPS TO LOOK FOR AREAS OF NEW OR EXPANDED RESEARCH EFFORTS

Two workshops scheduled by NCI, one on immunology and the other on DNA repair and carcinogenesis, are planned to develop plans for future research efforts in those fields.

A review of immunology for application to cancer cause and prevention will be held Nov. 4-5 at the Blair Bldg, Room 110, in Silver Spring, Md. The first session is an evening meeting, 9-11:30 p.m., and the next the following day, starting at 8:30 a.m. This meeting will review and discuss potential applications of immunology to studies of cancer cause and prevention, and to provide program guidance for an expanded effort in this field. This meeting is sponsored by the Div. of Cancer Biology & Diagnosis.

The DNA repair and carcinogenesis workshop is scheduled for Dec. 8-10 at the Old Town Holiday Inn in Alexandria, Va. Meeting times are 8 p.m.–9 p.m.

Dec. 8, 9 a.m.–5 p.m. Dec. 9 and 9 a.m.–noon Dec. 10. The discussion will center on the mechanisms of DNA repair in chemical and radiation carcinogenesis. Associated research areas which may be ready for significant further exploration will be identified. This meeting is sponsored by the Div. of Cancer Research Resources & Centers.

NCI LISTS FDA INSTRUCTIONS ON TESTS INVOLVING THALICARPINE, ANGUIDINE

Interruption of clinical trials with the drugs thalicarpine and anguidine were brought to the attention of the President's Cancer Panel by Emil Freireich during the Panel's meeting in Houston (*The Cancer Letter*, Oct. 15).

John Penta, head of the Drug Liaison and Distribution Section in NCI's Investigational Drug Branch, listed the Food & Drug Administration's contacts with him regarding these interruptions and also the query by FDA regarding M.D. Anderson's maytansine protocol.

Penta's statement follows:

"On June 30, NCI received a telephone call from FDA stating that further clinical trials with thalicarpine and anguidine should not proceed using multi-dose schedules. On July 1, NCI telephoned FDA and was told that all clinical trials with thalicarpine should stop, and that all phase II trials with anguidine at doses greater than 2.4 mg/m^2 daily x 5 must be stopped immediately.

"A letter dated July 7 was sent to NCI by FDA confirming the telephone call regarding thalicarpine. FDA asked for an explanation of mydriasis toxicity, and also for a more detailed analysis of the phase I studies. NCI has already responded to this, as well as to an FDA telephone call to NCI on Sept. 3 requesting more information about EKG changes and phase II protocols, and is now awaiting a response from FDA as to continuation of clinical trials.

"A letter dated July 12 was sent to NCI by FDA confirming the telephone call regarding anguidine. FDA asked for a detailed analysis of toxicity of anguidine when administered in doses of, or greater than, 2.4 mg/m^2, and also asked for further information relating to hematological toxicity. Again, NCI has already responded to this, and is now awaiting a response from FDA as to continuation of clinical trials.

NCI received a letter dated Aug. 24 from FDA in which they asked seven questions regarding a maytansine protocol from M.D. Anderson Hospital & Tumor Institute. M.D. Anderson has since responded to these questions, and NCI has forwarded the response to FDA."

That's how it stands at the moment: All clinical trials with thalicarpine have been stopped, and the limit on anguidine doses remains in effect.

REPORT THAT L-PAM HELPED FIRST LADY STAY FREE OF RECURRENCE CHALLENGED

William Caldwell, director of the Section of Radiation Therapy at the Univ. of Wisconsin Hospitals, objected to the implication that L-PAM may have contributed to First Lady Betty Ford's recovery from breast cancer, as reported in ***The Cancer Letter***, Oct. 15.

The article reported Mrs. Ford's comments at the dedication of M.D. Anderson's new facilities, when she noted that she has now completed two years of adjuvant chemotherapy with no apparent recurrence. Mrs. Ford did not mention L-PAM, but ***The Cancer Letter*** learned (and it has been reported elsewhere) that the drug she received was L-PAM.

"I must express my concern for the quotation of First Lady Betty Ford's comments," Caldwell wrote to ***The Cancer Letter***. "Although this is a pretty well kept secret, the March 15, 1976, progress report of the NSABP (National Surgical Adjuvant Breast Project) shows that there is no benefit for L-PAM for post-menopausal women; this information has not been disseminated and notes such as that in the Oct. 15 issue of ***The Cancer Letter*** do nothing to clarify the issue. In fact, the implication is that Mrs. Ford was probably benefited by the L-PAM regimen. Mrs. Ford is undoubtedly post-menopausal and . . . the probability that she was benefited by L-PAM is zero. The unfortunate aspect of this is that many post-menopausal patients are still being treated with L-PAM–unnecessary morbidity for them and certainly a needless expense.

"Hope you can set the record straight, especially since there were premature announcements of the efficacy of this regimen."

The announcement by NCI two years ago of the apparent success with L-PAM noted that NSABP studies at that time had found the drug significantly less effective with post-menopausal women. A year later (and a year after Mrs. Ford's L-PAM treatment had started) Gianni Bonadonna reported his findings that adjuvant therapy with the drug CMF had achieved a 95% non-recurrence rate, with no difference between pre- and post-menopausal women.

PROPOSED REGULATIONS FOR CORE, PLANNING CENTER GRANTS PUBLISHED

The Aug. 20 issue of the *Federal Register* listed proposed regulations governing award of core support grants and planning grants for cancer centers. Adoption of these regulations will formalize policies and procedures already being carried out by NCI, and therefore will not result in any operational changes.

Those interested in commenting on the proposed regulations, and in suggesting changes, may send their comments to the NCI Director, NIH, Bethesda, Md. 20014, by Dec. 6.

OBEY SAYS NCI CANCER PREVENTION PROGRAM IS "IN A SHAMBLES"

Congressman David Obey, the Wisconsin Democrat whose position as a member of the House HEW Appropriations Subcommittee gives him a certain amount of clout with the Cancer Program, continues to hammer away at NCI. Speaking at a meeting of physicians and other health professionals in Wisconsin in his campaign for reelection, Obey claimed that cancer deaths are increasing at more than three times the rate predicted by federal officials and said that "a key cancer prevention program is in shambles."

"Since 1971 when we first declared 'war' on cancer, the cancer death rate in the United States has steadily increased," Obey said. "During 1975 the National Cancer Institute projected that the number of cancer deaths in the U.S. would increase by 4,500, but the latest figures show that an additional 14,000 deaths actually occurred—more than three times the NCI prediction."

Citing NCI estimates that 80 to 90 percent of all cancer is the result of chemical and environmental factors, Obey said that a key to cancer prevention is to expand and improve the testing of chemicals on animals to determine their cancer-causing potential. "Without such scientific data," he added, "the responsible federal agencies have no way of formulating and enforcing regulations to protect the public from cancer-causing chemicals."

"The major responsibility for those tests rests with NCI and today that program is in shambles," he said. "The program receives less than 6% of the institute's resources and less than 7% of the institute's staff and as a result the number of chemicals on which tests have been initiated has dropped from a 150 per year level the program attained in the early 1970s to a rate today of only 37 per year during the last two years."

Obey said that the program's staff has been so small that studies to determine whether or not particular chemicals used in industry are safe "have been turned over to a complex web of outside research firms who are, for the most part, private businesses that are also contracting with the industries that manufacture these chemicals and in some cases are owned outright by the chemical manufacturing firms."

He added that the quality and efficiency of such contract work "has been appallingly low, in part because of a lack of adequate staff to monitor contract operations."

Although private contractors perform the mechanical aspects of such chemicals tests, Obey said that "the more sensitive and complex job of evaluating and reporting the test results must be done by NCI's own scientists. And because of inadequate staffing, a backlog of more than 200 unevaluated chemical tests have built up." He added that tests were completed on 129 of those chemicals more than a year ago, and on some of them more than five years ago.

Obey noted that many of the top scientists involved in the chemical testing effort "have left in frustration, including the program's director, who resigned from all administrative duties last spring after having predicted the program's demise for more than five years."

Obey, who won adoption of report language in the fiscal year 1977 appropriation providing a 50% staff increase for the chemical testing program, said that this initiative "should help, but there is no chance that this program will succeed without far greater attention and support from the leadership of NCI."

Obey said he hoped that "such support will be forthcoming from the individual who succeeds Dr. Frank Rauscher as NCI Director. The bottleneck in chemical testing is causing serious delays in the entire federal cancer prevention effort, and it must be corrected if we are to have any chance of reducing cancer deaths."

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR NOVEMBER, DECEMBER

Workshop on Review of Immunology for Application to Cancer Cause & Prevention—Nov. 4-5, Blair Bldg, open Nov. 4, 9 p.m.-11:30 p.m., Nov. 5, 8:30 a.m.—adjournment.

Committee on Cancer Immunotherapy—Nov. 4, NIH Bldg 10 Room 4B14, open 1-1:30 p.m.

National Pancreatic Cancer Project Working Cadre—Nov. 6, Continental Plaza Hotel, Chicago, open 8:30-9:30 a.m.

Clearinghouse on Environmental Carcinogens—Nov. 8, Linden Hill Hotel, Bethesda, 8:30 a.m.—5 p.m., open.

Virus Cancer Program Scientific Review Committee B—Nov. 8, Hershey (Pa.) Motor Lodge, open 9—9:30 a.m.

Cancer Control Grant Review Committee—Nov. 8-9, NIH Bldg 31 Room 4, open Nov. 8, 8:30-9 a.m.

Cancer Clinical Investigation Review Committee—Nov. 8-10, NIH Bldg 31 Room 8, open Nov. 8, 8:30—10 a.m., Nov. 9, 9 a.m.—noon.

Cancer Special Programs Advisory Committee—Nov. 8-10, NIH Bldg 31 Room 9, open Nov. 8, 9—10 a.m.

Annual Joint Working Conference of the Virus Cancer Program—Nov. 9-11, Hershey (Pa.) Motor Lodge, open Nov. 9 & 10, 9 a.m.—5:30 p.m., Nov. 11, 9 a.m.—12:30 p.m.

Advances in Head & Neck Cancer Management—Nov. 9, Roswell Park Continuing Education in Oncology, registration required.

Clearinghouse on Environmental Carcinogens Subgroup on Chemical Selection—Nov. 9, Linden Hill Hotel, Bethesda, open 9 a.m.—3 p.m.

National Prostatic Cancer Project Working Cadre—Nov. 11-12, Roswell Park, open Nov. 11, 1-5 p.m., Nov. 12, 8:30 a.m.—adjournment.

Current Concepts in the Management of Primary Bone & Soft Tissue Tumors—Nov. 11-12, M.D. Anderson, registration required.

Cancer Control Supporting Services & Intervention Programs Review Committees Joint Meeting—Nov. 12-13, NIH Bldg 31 Room 5, open Nov. 12, 8:30 a.m.—3 p.m.

National Cancer Advisory Board Subcommittee on Centers & Construction—Nov. 14, NIH Bldg 31 Room 10, open 7—10 p.m.

National Cancer Advisory Board—Nov. 15-16, NIH Bldg 31 Room 6, open both days, 9 a.m.—adjournment.

Conference on Guidelines for Training Programs in Gastrointestinal Oncology—Nov. 18-19, NIH Bldg 31 Room 10, open 8:30 a.m—5 p.m. both days.

Temporary Review Committee for Frederick Cancer Research Center—Nov. 18, NIH Bldg 31 Room 6, 9 a.m., open.

Cancer Center Support Grant Review Committee—Nov. 19-20, NIH Bldg 31 Room 6, open Nov. 19, 8:30—10 a.m.

Breast Cancer Diagnosis Committee—Nov. 21, Landow Bldg Room C418, open 10—10:30 a.m.

White House Conference "Breast Cancer—Report to the Profession 1976"—Nov. 22-23, Washington Hilton Hotel, all open.

Breast Cancer Treatment Committee—Nov. 23, Washington Hilton Hotel, open 6:30—7 p.m.

National Bladder Cancer Conference—Nov. 28—Dec. 1, Miami Beach.

Cancer Control Community Activities & Grant Review Committees Joint Meeting—Nov. 28-29, NIH Bldg 31 Room 7, open Nov. 28, 8:30—9 a.m.

Workshop on Cancer Invasion & Metastasis: Biologic Mechanisms & Therapy—Nov. 29-Dec. 1, Rockefeller Univ., 9 a.m.—5 p.m., all open.

Developmental Therapeutics Committee—Nov. 30, Blair Bldg Room 110, open 8:30—9 a.m.

Workshop on DNA Repair & Carcinogenesis—Dec. 8-10, Old Town Holiday Inn, Alexandria, Va., open Dec. 8, 8—9 p.m., Dec. 9, 9 a.m.—5 p.m., Dec. 10, 9 a.m.—noon.

Chromosomes in Clinical Practice—Dec. 9, Roswell Park continuing education in oncology, registration required.

SELECTED ABSTRACTS OF PAPERS READ AT THERAPEUTIC RADIOLOGISTS MEETING

Following are additional abstracts from papers presented at the 18th annual meeting of the American Society of Therapeutic Radiologists this month in Atlanta. (Other abstracts appeared in ***The Cancer Letter*** Oct. 22). Complete papers from which the abstracts published here were derived are available; write to Charles Honaker, director of public relations, American College of Radiology, 20 N. Wacker Dr., Chicago, Ill. 60606.

DEFINITIVE HIGH DOSE, SMALL VOLUME RADIATION THERAPY IN THE TREATMENT OF CARCINOMA OF THE PANCREAS — R.R. Dobelbower Jr., B.B. Borgelt, N. Suntharingalam, and K.A. Strubler, Thomas Jefferson Univ. Hospital

Eighteen patients with localized or regional adenocarcinoma of the pancreas were treated with high dose, small volume radiation therapy over a 21 month period. All patients had a positive tissue biopsy with placement of radio-opaque clips at laparotomy to define tumor extent. No patients with metastatic disease (exclusive of regional nodal involvement) were treated. External beam irradiation was delivered using the Brown-Boveri Betatron to encompass the clipped tumor volume plus a 1 to 2 cm margin. Thirteen patients were treated by a 3-field technique employing opposed lateral 45 MeV photon fields and an anterior "mixed beam" (50% 45 MeV photons and 50% 15 to 35 MeV electrons) designed to minimize exposure of other vital retroperitoneal organs (Dobelbower et al, Int. J. Rad. Oncol. Biol. Phys., 1:141, 1976). Five patients were treated by a 4-field "box" technique utilizing opposed anterior and lateral 45 MeV photon beams. Minimum dose to the target volume was 6300 to 6700 rads delivered in 180 rad fractions treating 2 or 3 fields per day over a 7 to 9 week period. Post-irradiation follow-up ranges from 4 to 21 months. Ten patients have died, 9 with local and/or metastatic disease and 2 of intercurrent disease. Eight patients are living, 2 with clinical evidence of local disease at 4 and 8 months and 6 with no evidence of disease after 4 to 21 months. Treatment has been generally well-tolerated and there have been no significant radiation complications. Preliminary experience with this therapeutic modality indicates that it is capable of producing improved palliation if not offering definitive radiotherapeutic management of localized unresectable carcinoma of the pancreas.

ON THE HUMAN CLONOGENIC CANCER CELL. II. THE RADIORESISTANT FRACTION AND ITS IMPLICATIONS FOR RADIOTHERAPY — J. Robert Andrews and Kenneth Mossman

The local control of solid cancers by treatment with ionizing radiations is contingent upon the destruction by these radiations of a minimum number of clonogenic cancer cells. Included in this minimum number will be the most radioresistant component of the cancer cell population. It is shown that the slope of a curve developed from clinical radiotherapy cancer control data conforms with the negative slope of the radiation dose, cell survival curve of this most radioresistant component. The reciptrocal of this negative slope, D_Q, is found to have a value of about 400, in terms of Roentgens, rads, or rets. By the application of the Poisson distribution it is shown that, in small human cancers, this minimum number of resistant clonogenic cancer cells is, by absolute standards, small. By relative standards, related to clinically allowable radiation doses and, if the radioresistance is due to the oxygen effect, the potentiality for the local control of large solid cancers by high LET radiations, the number is large.

EMOTIONAL REACTIONS TO RADIATION TREATMENT — Arthur Peck and John Boland

Neither planned programs of public health education about cancer nor the wide coverage given controversies in cancer treatment methods have included radiation treatment. There has been little effort made to assess the cancer patient's concept of this form of treatment.

Fifty patients were interviewed by a psychiatrist before beginning treatment in the Radiotherapy Service of the Mount Sinai Medical Center of New York City. All had cancer. What they were told when they were referred for radiation treatment and how they were affected by the prescription of that treatment was the focus of the interview. These patients were extremely frighted of their treatment and ignorant of the procedures and side effects associated with it. They were afraid radiation would seriously damage them. Yet they did not ask physicians what they very much wanted to know.

Interviews after the completion of the series of treatments revealed an even higher frequency of anxiety and depression than prior to them, indicating that experiencing radiation treatment is in itself stressful. Less than a third of patients described themselves as improved at the end of treatment. Those who felt worse because of treatment did so because of side effects, not because there was a worsening of their disease.

This misunderstanding and a substantial part of patients' other misconceptions about radiation treatment would be minimized by careful, sympathetic, factual explanations by radiotherapists.

CALIFORNIUM-252 FOR INTERSTITIAL IMPLANTATION: A CLINICAL STUDY AT MEMORIAL HOSPITAL — Alvaro Vallejo, Basil Hilaris and Lowell Anderson, Memorial Sloan-Kettering

A Phase I clinical study, using ^{252}Cf sources in temporary implants began in January 1974. The improved ^{252}Cf source design utilized in these implants is patterned after the ^{192}Ir seeds contained in nylon ribbons and is adapted for afterloading. An attempt was made to deliver the same effective dose with ^{252}Cf as that delivered with ^{192}Ir implants (6000 rads in 6 days); the corresponding six-day dose from ^{252}Cf radiation consists of a neutron dose of 840 rads and a beta-gamma dose of 740 rads, using RBE's of 6.4 and 0.86 respectively.

A total of 10 implants have been performed in previously untreated metastatic regional nodes from squamous cell carcinoma. Local control has been obtained in 8 of the 10 patients implanted (80%). No unusual normal tissue effects have been observed up to two years after implantation. Details of the technique and computerized dosimetry will be discussed. Analysis of the results and comparison with our experience with temporary ^{192}Ir implants will be presented.

MEDICAL LIABILITY IN THE PRACTICE OF THERAPEUTIC RADIOLOGY — Bernard Roswit, Francis Bensel

The frequency and the cost of claims and lawsuits for alleged medical malpractice in this country are skyrocketing, as well as the charges for protection. The practice of therapeutic radiology, as in all medical practice, involves the risk of patient injury in return for rescue from a life-threatening disease.

The authors of this communication, a radiation oncologist and a malpractice attorney, believe that the best way to avoid a malpractice suit is "never to deserve one". To this end they have joined forces to offer guidelines in effective prophylaxis against lawsuits charging 1) unauthorized radiation therapy, 2) negligence in the exercise of good clinical judgement and expert treatment technology, 3) failure to gain

an informed consent, which must include a review of possible radiation complication, as well as alterations to radiation treatment, 4) breach of warranty, involving a promise or guarantee of a given result and 5) violation of the radiologist's legal duties to the patient.

A manual or sullabus on malpractice prophylaxis will be made available to all participants.

THE EFFECT OF RADIOTHERAPY IN COMBINATION WITH IMMUNOTHERAPY ON TUMOR CARE AND MACROPHAGE LYMPHOCYTE INFILTRATION — Carleton Stewart, Carlos Perez, and Barbara Hente, Mallinckrodt Institute of Radiology

The potential usefulness of immunotherapy combined with radiation therapy is being tested in animal models. Local tumor radiotherapy was given at subcurative doses, followed twice weekly by doses of BCG, C. Parvum, or levamisole comparable to those used in humans. The regimens were evaluated for curative ability and effects on infiltration of lymphocytes and macrophages into the tumor. Cytotoxicity was observed directly through time-lapse cinemicrography on tumor cells in culture.

In the EMT6 tumor system, which has high immunogenicity, 3000 rads cured 40% of the mice. Addition of BCG raised the rate to 50%, of C. Parvum to 70%, and of levamisole to 80%. Duration of survival in uncured animals was the same with all four regimens. In the $6C_3$-HED lymphosarcoma, 3000 rads cured 30%, and addition of levamisole or C. Parvum had no effect on that rate or on duration of remission. Addition of BCG raised the cure rate to 70% and lengthened clinical remissions markedly. The KHT fibrosarcoma, which has low immunogenicity, was unresponsive to radiation alone or combined with any of the agents.

All tumors were infiltrated with macrophages and lymphocytes. Time lapse movies of the KHT and EMT6 tumors in culture show that tumor cell lysis is caused by macrophages.

PRELIMINARY CLINICAL RESULTS OF 433 MEGAHERTZ MICROWAVE THERAPY AND RADIATION THERAPY ON PATIENTS WITH ADVANCED CANCER — Ned Hornback, Robert Shupe, H. Shidnia, B.T. Joe, and E.M. Sayoc, Indiana Univ. School of Medicine

Because of the recent interest in the literature on enhancing the effect of standard radiation therapy with hyperthermia, several patients with advanced cancer who were refractory to standard medical treatment of surgery, radiation and/or chemotherapy were treated with low-dose radiation, 2000 to 3000 rads supplemented by 433 Megahertz Microwave Irradiation (Hyperthermia). Complete local clinical regression of these previously refractory and aggressive tumors have been promising enough to begin early clinical trials on advanced but previously untreated cancer patients. Techniques, methodology and dose rates of microwave therapy and radiation therapy will be discussed.

FURTHER EXPERIENCE WITH HALF BODY RADIOTHERAPY — Peter Fitzpatrick, Walter Rider, Cyril Danjoux, Princess Margaret Hospital, Toronto

Since 1971, 245 patients with advanced cancer were treated with 355 half body radiation treatments; 99 patients received total body irradiation in two halves. Most patients had failed to respond to conventional treatment. Because of the success in achieving palliation several clinical, radiological, physiological, and pathological parameters have been measured in order to understand the techniques and decide which patients it may benefit.

PRELIMINARY RESULTS USING LOCALIZED CURRENT FIELD HYPERTHERMIA IN ORAL CAVITY CARCINOMAS — Charles Sternhagen, Phillip Day, Morton Kligerman, W. Sterling Edwards, Raymond Doberneck, Fred Herzon, and Terry Powell, Cancer Research & Treatment Center, Albuquerque; James Doss, Los Alamos Scientific Laboratory; Gregory O'Brien, Lovelace Bataan Hospital, Albuquerque.

After extensive preclinical testing since 1973, a preliminary clinical study is underway using localized current field hyperthermia to treat accessible malignancies uncontrolled by conventional methods. Both non-invasive and invasive techniques have been used when control of the primary lesion had failed with conventional treatment. Two post-radiation therapy patients with far advanced persistent squamous cell carcinoma of the base of tongue each received a single non-invasive localized current field hyperthermia treatment. Reduction in tumor size and pain palliation occurred in both cases. A third patient developed a recurrent floor of mouth carcinoma seven years post resection. After a curative course of radiation therapy, the tumor began regrowing and the patient refused surgical resection or chemotherapy. Subsequently the patient received two interstitial hyperthermia treatments two weeks apart achieving tumor control after the second treatment. The basic techniques of applying localized current field hyperthermia to base of tongue and floor of mouth malignancies are presented with followup case reports.

RADIATION THERAPY IN COMBINATION WITH LOCAL HYPERTHERMIA: PRELIMINARY RESULTS — Jae Ho Kim, Eric Hahn, N. Tokita, and Lourdes Nisce, Memorial Hospital, NYC

Radiobiological studies by use and others have shown that hyperthermia selectively enhances the response of tumor cells in vivo and in vitro. One of the aims of this report is to evaluate the response of normal tissues including skin in patients with various cutaneous malignant lesions. Twenty-four patients with multiple malignant cutaneous lesions, (mycosis fungoides, lymphoma cutis and Kaposi's sarcoma) have been studied. They have been treated with radiation alone and radiation immediately followed by hyperthermia. Varying degrees of hyperthermia were achieved by immersing the extremities into the temperature regulated water bath. Various dose fractionation regimens in combination with hyperthermia have been investigated. Rates of tumor regression, maximum improvement obtained, disease-free interval and normal tissue reactions have been used as means of assessment. The normal tissue effects with radiation and hyperthermia following either single or fractionated course of combined treatment do not appear to be greater than those treated with radiation alone. The followup period varies from one month to 15 months. In general, the initial tumor regression rates were faster in patients treated with radiation plus hyperthermia than in radiation alone, particularly in patients with Kaposi's sarcoma.

THE MANAGEMENT OF INFLAMMATORY BREAST CARCINOMA — Robert Kagan, Herman Nussbaum, Harvey Gilbert, and Paul Chan, Southern California Permanente Medical Group

A review of 54 patients with inflammatory breast carcinoma will be presented. Emphasis will be placed on the clinical diagnosis, such as findings of redness of the skin involving more than 1/3 of the breast, enlargement and generalized induration of the breast, with axillary metastases. The findings of subdermal lymphatic invasion on skin biopsy will be evaluated as a prognostic sign.

Inflammatory breast carcinoma is a systemic disease from onset, and patients develop clinical evidence of disseminated disease within one year, and die within two years. In our review of 54 patients, 52 are dead.

All treatment is ineffective and only temporarily suppressive. Mastectomy is contraindicated. With radiotherapy, and a dose of 7000 rads, it is common to see local recurrence within the treated site and tumor extension outside the irradiation portals.

Our conclusion is that initial treatment should consist of multiple chemotherapy agents since the disease is systemic from onset. Radiotherapy should be held in reserve for local failure as needed. Hormonal ablation procedures may be considered as adjuvants. The natural history of the disease is as yet unaffected by present treatment methods.

CARCINOMA OF THE PINNA — Jose Avila, Univ. of Kentucky; Antonio Bosch, Univ. of Wisconsin; Silvio Aristizabal, Univ. of Arizona; Zenaida Frias and Victor Marcial, Puerto Rico Nuclear Center

Over the years the concept that the proximity of a tumor to cartilaginous structures constitutes a contraindication to roentgentherapy has pervaded in the literature. Carcinoma of the pinna is a good example of this clinical situation. The records on 95 consecutive patients with carcinoma of the pinna were reviewed. Fifty-six of the tumors were basal cell and 39 squamous cell carcinoma. Fifty patients were surgically treated and 45 irradiated. Small and/or peripheral lesions were excised and the large and/or centrally located referred for irradiation. Analysis of the results shows that the difference in tumor control rate was not statistically significant, and the complication rate is also comparable with both modalities. Although chondritis is most commonly seen after irradiation, it can also occur after excision. Initial resection would seem preferable in small lesions in which primary closure is possible and in extensive lesions where a good cosmetic result is precluded by the destruction of normal tissue. Roentgentherapy would seem of value in those lesions in which resection would result in objectionable cosmetic defect.

CARCINOMA OF THE MAXILLARY SINUS—A STUDY OF 91 CASES WITH EMPHASIS ON COMBINED THERAPY OF RADICAL SURGERY FOLLOWED BY IRRADIATION — Tah Yee Chen, Roswell Park Memorial Institute

Ninety-one cases of carcinoma of the maxillary sinus treated at the Roswell Park Memorial Institute from 1950 to 1970 were analyzed. Ninety-one percent of the cases had advanced disease and was classified as having T-3 or T-4 lesion according to Sisson's staging. Ten percent of the patients had cervical metastases and five percent had distant metastases. Second primary occurred in four percent of the patients. The treatment methods consisted of radical surgery alone (14 patients), irradiation alone (28 patients) and combined radical surgery and irradiation (49 patients). For the combined treatment, preoperative irradiation was used in all but two patients. The overall five year survival rates (determinate cases) for the group of radical surgery alone was 10%, irradiation alone 23% and combined radical surgery and irradiation 34%. Generally, the patients tolerated the treatment reasonably well including those treated with the combined method. The study suggested that the combined procedure of radical surgery and irradiation is feasible and is the treatment of choice for the advanced cases of carcinoma of the maxillary sinus.

AN ANALYSIS OF DISTANT METASTASIS FROM SQUAMOUS CELL CARCINOMA OF THE UPPER RESPIRATORY AND DIGESTIVE TRACT — Orlando Merino, Robert Lindberg, and Gilbert Fletcher, M.D. Anderson

The charts of 5,168 previously untreated patients with squamous cell carcinoma of the upper respiratory and digestive tract treated for cure from January 1948 through August 1973 were reviewed. These patients had no evidence of distant metastasis when initially treated. Five hundred and fifty-five patients developed clinical evidence of distant metastasis.

The incidence of distant metastasis will be presented according to: 1) the anatomical site of the primary tumor, 2) the treatment of the primary tumor and, 3) the T and N stage of the primary tumor. The time and location of the first clinical evidence of distant metastasis will also be presented.

LOCAL CONTROL OF ORAL CAVITY AND OROPHARYNGEAL SQUAMOUS CARCINOMA WITH 3 VS. 5 TREATMENT FRACTIONS PER WEEK — Roger Byhardt, James Cox, and Maurice Greenberg, Milwaukee County General Hospital

To compare the 18 month local control rates of 3 vs 5 fractions per week, the records of 74 patients at the MCW affiliated hospitals, receiving external beam irradiation alone with curative intent, were selected for retrospective review out of 204 cases of squamous cancer of the oral cavity and oropharynx. Excluded were 130 cases: 45 preoperative irradiation, 29 dead before 18 months of intercurrent or metastatic disease with local control, 26 postoperative irradiation, 18 interstitial implant, and 12 who did not start or failed to complete planned course. With three fractions per week, the total dose was calculated by the Ellis NSD formula, and was taken as that dose associated with the upper limits of connective tissue tolerance (1800-1900 ret), usually 5400-6000 rads in 6-7 weeks given as 300 rads three days per week. Those treated with five fractions per week were taken to 6000-7000 rads in 6-7 weeks (1800-1900 ret). With relatively equal distribution of patients in each fractionation scheme by stage and site of primary, local control of the primary, in those eligible for 18 month followup, was found to be significantly lower (P less than .005) with three fractions per week. While 28/48 (58%) patients achieved local control at five fractions per week, only 5/26 (19%) did so for three fractions per week, all stages and sites combined. A similar trend was observed for each stage and site evaluated separately. The authors emphasize that caution should be used in applying the Ellis formula, which is based on radiation tolerance of normal connective tissue, to predictions of tumor lethal dose, especially when using unusual fractionation schemes.

VOCAL CORD CARCINOMA: THE RELATIONSHIP BETWEEN POST-RADIOTHERAPY AND EDEMA — Carol Milligan, Don Goffinet, Willard Fee, and Malcolm Bagshaw, Stanford Univ. Medical Center

The records of 206 patients with vocal cord carcinomas treated at Stanford with 4.8 & 6 MV linacs between 1957 and 1975 were reviewed specifically for the presence or absence of persistent post-irradiation edema. Moderate to severe laryngeal edema (either requiring the use of corticosteroids, tracheostomy or hospitalization or edema which was rapidly progressive) occurred in 46 or 22% of the 206 patients. The percentage of patients with persistent edema ranged from 18% of those with T_1A vocal cord cancers to 64% in those with T_3 lesions. Over 80% of patients with edema had repeat laryngeal biopsies. A significantly higher incidence of recurrences was noted in patients with persistent laryngeal edema (23 of 46 or 50%) compared to those in whom post-irradiation edema did not occur (20 of 160 or 12.5%), $p < 0.01$. Local control rates at five years, combining patients with state T_1A & T_1B glottic cancers were 92% for 116 patients without edema and 71% for 16 with persistent edema. For the 44 patients with T_2 lesions, the corresponding values were 89% & 21%, respective and 66% and 17% for 30 patients with T_3 carcinomas. Relapse free and actuarial survival at 10 years (88% T_1A, 50% T_{3-4} disease free) and an analysis of time-dose factors and their relationship to the subsequent development of edema will also be presented.

MEGAVOLTAGE IRRADIATION FOR CARCINOMA OF THE PROSTATE — William Neglia and David Hussey, M.D. Anderson

The records of 154 patients with localized prostatic carcinoma treated with external megavoltage irradiation at the Univ. of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, between July 1966 and December 1973 have been retrospectively analyzed. The technique of treatment used at MDAH is illustrated and discussed. The data on survival, local control, complications of treatment, and causes of failure are presented for the entire population and two subgroups: 79 patients treated with irradiation alone, and 75 patients treated with irradiation plus concomitant hormonal manipulation. Results of treatment are also discussed by stage, and a modification of the currently used Whitmore classification is proposed. The results of patients having Stage C disease participating in a national randomized trial between irradiation alone versus irradiation plus estrogens are presented and discussed. Correlations are drawn between dose, field size, tumor volume, local control; and complications and recommendations for treatment are given.

RADIATION THERAPY TECHNIQUES IN THE TREATMENT OF PROSTATIC CARCINOMA; EVALUATION OF CHRONIC SIDE EFFECTS AND AN IMPROVED METHOD FOR TREATMENT — Thomas Roland, Richard Brown, and Henry Plenk, LDS Hospital, Salt Lake City

Numerous radiotherapy techniques have been employed during the past 10 years in an attempt to cure localized prostatic carcinoma. Four most commonly used techniques are analyzed and the morbidity associated with each is compared. Chi-square and independent variable analysis are utilized for statistical comparisons among the treatment groups. A detailed outline of degree of side effects, as well as pictorial representation of treatment techniques, are given. Eighty-six patients treated between 1965 and 1975 are evaluated in terms of chronic bowel and bladder symptoms and symptoma tic subcutaneous fibrosis. Changes in morbidity with alterations in dose-fractionation, volume and field distributions are outlined. Techniques analyzed include: a three-field design with anterior and two posterior obliques; shaped anterior and posterior pelvic fields with prostate boost treated with two separate fractionation schemes; a four-field technique utilizing lateral prostate boosts. Reduction in complications obtained with use of the recently employed four-field technique is shown to be statistically significant. The boost technique employed and time-dose-fractionation schemes appear the most significant factors in overall morbidity.

The Cancer Letter—*Editor* JERRY D. BOYD

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