THE CANCER LETTER
RESEARCH
EDUCATION
CONTROL

Vol. 2 No. 30

July 23, 1976

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

Subscription $100 per year

STUDY FINDS PHYSICIAN REFERRAL BY CENTERS FRAUGHT WITH PROBLEMS, POTENTIAL DANGERS

A study commissioned by NCI's Div. of Cancer Control & Rehabilitation to examine the ramifications of physician referrals by NCI-supported Cancer Information Service offices at comprehensive cancer centers developed a list of 12 recommendations in dealing with the touchy and potentially controversial subject.

DCCR has followed some of the recommendations; the report of the ad hoc committee on physician referrals and the recommendations were discussed last March in Miami at a meeting of CIS coordinators; and they were aired at the recent meeting of the American Assn. of Cancer

(Continued to page 2)

MAMMOGRAPHY FOR WOMEN UNDER 50 DEBATED; CUT OF 3-4% OFFERED AS BUDGET TRIMMER

A REPORT released this week at a hastily convened joint NCI-ACS meeting recommends immediate cessation of routine mammography for breast cancer screening of women under age 50. The report of Dr. Lester Breslow, dean of UCLA's school of public health, sparked sometimes heated debate among professionals, seven of whom spoke in favor of the technique from their vantage point as directors of NCI-ACS breast cancer detection demonstration projects. Among the most outspoken was Dr. Philip Strax, director of Guttman Institute's BCDDP, who said, "The real risk may be of not doing mammography. It is our only means of detecting non-palpable (breast) cancer." Breslow's report is one of three commissioned by NCI in October, 1975; his was to assess the risk/benefit ratio of mammography in the HIP breast cancer screening project (N.Y.).Dr. Louis B. Thomas, chief of NCI's laboratory of pathology, and Dr. Arthur Upton, dean of the school of basic health sciences, SUNY, Stony Brook, N.Y., who are completing the other two NCI-requested assessments on mammography, gave status reports. NCI director Dr. Frank J. Rauscher Jr. said he wants to see their final reports before releasing NCI recommendations on mammography; he hopes for a time frame of two-three weeks . . . HERE's HOW cuts might be made in the fiscal 1977 budget from the $845 million "mid-level" figure NCI had hoped to get to the $805-815 million it is likely to get: Cut every program across the board 3-4%, which would save about $25 million. Director Frank Rauscher said he would prefer that over cutting out some entire programs, with a couple of exceptions. "If the budget is real tight, I would be hard put to buy interferon," he told the National Cancer Advisory Board. NCI plans to spend about $1 million on interferon development and testing. Rauscher also has indicated the construction budget might be chopped somewhat more than 3-4% if necessary. And he has been eyeing the $6 million going into the effort to develop less hazardous cigarettes (See article inside).

AD HOC GROUP OFFERS RECOMMENDATIONS FOR HANDLING PHYSICIAN REFERRALS

Continued from page 1)

Institutes. But at least one committee member was disappointed with NCI's reaction and says the report was "buried."

The study was requested by Elaine Bratic and Warren Dunn, project officers for the DCCR contract with comprehensive centers for development of the Cancer Information Service network.

"We felt the centers should address the problem of what to say when asked for names of doctors who treat cancer," Dunn told ***The Cancer Letter.*** "We did not advocate any particular response. We were not trying to develop an NCI or DCCR policy. We were under no direction from NCI or DCCR to take on this problem. It was only a concern of the project officers."

Dunn denied that the report was "buried." It was forwarded to his superiors at DCCR, he said, but "We did not intend that DCCR or NCI should take any action on it."

The general thrust of the recommendations was that NCI should not establish any hard and fast national policy or national referral list, Dunn pointed out. "In essence, the report said we should not establish an NCI policy, and we're going along with that."

DCCR Director Diane Fink said that some of the recommendations were incorporated into the CIS guidelines which were completed and distributed in May. "The report was discussed with the centers people and will be again," she said. "It definitely was not buried."

Serving on the committee were Allen Chandler of Missouri and William Lees of Illinois, heads of the medical societies in their respective states; John Durant, director of the Univ. of Alabama Comprehensive Cancer Center; Gale Katterhagen, president of the Assn. of Community Cancer Centers; Lorraine Hannah of Illinois, Dave Bennett of Fox Chase Cancer Center, and Bob Deniston, Mayo, CIS officers; and Lee Mortenson, communications director for the Johns Hopkins Comprehensive Center, who was chairman.

The committee report listed as its objective, "To improve access to physicians interested in treating cancer for members of the patient population with a legitimate need, in a way that will improve relationships between centers and the physician community."

The committee reported it had found that:

- A review of current referrals by NCI shows that physician referrals can be misperceived. The caller frequently hears what he or she desires to hear, adding his/her own interpretation. This means that even calls handled in an appropriate manner may not be perceived as such. Possible interpretions—if his/her doctor's name is not given then that doctor is not "qualified"; current care is not the best—other, better care is available (even when this is not the case); the physicians names given are the only qualified cancer doctors in the area.
- Information from the American Medical Assn. shows that a current "system" of cancer referrals does not exist through their component organizations. Most medical society referral is currently done by local, county societies. Some is done by state societies. However, only 300 of the 2,900 county societies in the US have staff, so there are many areas without any referral source. Additionally, few referral systems managed by medical societies currently have data on cancer specialists.
- The American Cancer Society is currently doing physician referral, usually at the organization level closest to the community (i.e., the unit level). A survey of all divisions showed that 25% of current ACS calls deal with physician referral questions.
- ACS information indicated that the key to successful screening of physician referral calls is in the professional capability and training of telephone interviewers. Individuals with a professional background, or well trained paraprofessionals are needed to deal with patient and patient family dynamics.
- Attempts to get formalized (written) agreements from organizations involved in physician referral (ACS, medical societies, etc.) can be counterproductive. Informal agreements are more useful to the development of needed cooperation.
- The screening process prior to the provision of a physician name should be extensive to insure that all other alternatives (such as discussion with the current physician) have been attempted.
- Physicians are aware that at some times during care, patients will be anxious for additional opinions, different treatment, new hope, and will not indicate those needs to the managing physician. The CIS offices might undertake to act as an intermediary to the physician prior to referral, and thus, serve both patient and physician.
- Physicians concerned with malpractice are likely to encourage second opinions and other CIS intermediary activities if the physician is kept informed and involved in this process from the outset.
- Community physicians, already wary of medical school institutions (the town-gown split), may perceive a center-controlled referral service as an attempt by the center to "acquire" patients.
- Community physicians are concerned about government attempts to "certify" the competency of physicians. If the center, as a federal contractor, is perceived as "certifying" competent cancer physicians in its area, physicians will not cooperate and may act politically to stop this NCI activity.

While improvements in cancer referral are needed, the report said, some changes can lead to new problems, including:

—A patient overload on those physicians taking referrals through CIS offices.

—A patient overload on institutions taking referrals through CIS offices.

—Patients may be directed away from appropriate treatment.

Because of the small relative funding of the CIS offices, many center directors have not given the effort great attention, the report said. Many are not aware of the implications this effort might have on community relationships.

The committee concluded that:

- CIS offices are likely to get a high percent of physician referral calls. Increased awareness of a source of cancer information coupled with existing patient and patient family dissonance is likely to increase demand for this service. Individuals not usually "in the market" for a physician change may decide to seek it out. Screening will become an essential requirement to determine those individuals not really needing this advice.
- Whatever agreements are developed on physician referral must be developed in conjunction with those organizations currently acting as physician referral sources. The CIS offices should avoid attempting unilateral changes in the existing referrral system.
- Policy decisions on the relationships between comprehensive centers and other community organizations must precede technical or mechanical decisions. These policy decisions must be made in conjunction with center leadership.
- A voluntary system of physician agreement to participate in receiving referrals is necessary. The CIS offices should consider areawide surveys to develop these agreements.
- A set timetable or a specific referral system cannot be developed. Since agreements with organizations outside the control of contractors are necessary, these cannot be ascertained in advance. However, a method for handling physician referral inquiries will be needed by each CIS office prior to its public opening.
- Community physicians are more likely to accept referral if they perceive that the referral is being given by a part or agency without a vested interest in seeing patients. Those centers that have established consortium or co-sponsored efforts have had the most success in developing a workable physician referral service. This minimizes the community's perception that the center is seeking additional patients.
- Local, informal systems of referral currently used by centers and ACS offices often deliver useful, needed information. However, the volume of calls expected probably could not be handled by this informal system. Nonetheless, every attempt should be made to keep physician referral as close as possible to the local level.
- CIS offices must make every attempt in formulating promotional strategies to minimize exaggerated expectations by callers. If callers believe that they will get access to better care (especially when there may not be better care available) the community will react negatively to the CIS service.
- It is clear that medical society cooperation on the local, state and national levels needs to be solicited at an early date.
- Money for community participation by other organizations may be necessary to compensate them for additional work loads caused by their participation in CIS referrals.
- Referrals of callers to a single individual may not be the best alternative. Team care is a major emphasis of current cancer efforts. One alternative following this approach would be to refer callers to a hospital team. By recommending a specific physician, we may be participating in telephone triage.
- In many cases, better methods of care are simply not available. The prevailing care system is doing the best job. Promotional efforts to the profession might emphasize this recognition.
- Criteria for physician selection is a key problem. Legal and community relations problems stemming from non-selection could damage center-community and NCI-community relations. Without cosponsoring organizations, the center should not do any type of referral that could be perceived as certifying physicians.
- Terminology may need to be changed—"referral" may be the wrong term, legally and medically; "oncologist" is too exclusive a term—we are interested in those physicians who are in the cancer treatment area.
- Overloading participating physicians may be a serious problem. Small scale pilot testing and frequent, informal surveys of these physicians will be necessary to insure that this does not take place.

The committee's recommendations:

1. NCI should allow each CIS office, in conjunction with its center leadership, to develop whatever improvement in the physician referral system that can be accomplished given the time, dollars available and the prevailing political climate.
2. There should be no national list of physicians for referrals. NCI should refer callers to local entities for this service. Existing local lists will change too quickly and local circumstnaces will affect referral choices.
3. Indepth examination of the consequences of new physician referral systems on the existing institutions, organizations and treatment systems must be made at a pilot level prior to widespread use of a new system. This should be the case with each new system at each comprehensive center.
4. Current information of the legal liabilities involved in this system is negligible. NIH and NCI should provide a greater depth of research on the potential legal problems of physician referral.
5. NCI should create a permanent advisory board with members from the existing health care community to provide NCI with input on potential commun-

ity reactions to proposed community-oriented efforts.

6. A joint meeting of center directors and their communications office staff to discuss the policy implications of this service is needed and needed soon.

7. Network office staff may find some additional resource information by using the directory of the Federated Oncology Societies.

8. The crossing of a center's state boundaries into a new state should be postponed until additional policies are formulated. The political implications of this action are great and will necessitate national level activity to secure cooperation from a totally new set of organizations.

9. The draft policies for network operation should be referred to the center directors as a group for their input prior to final policy formulation.

10. Regional meetings of involved health care organizations might assist in developing joint policy agreements between centers and other referral groups.

11. The number of CIS offices might be increased to keep this service as close to the local level as possible (to specialized centers, etc.).

12. Phones should be answered by the highest level of competent assistance available—if possible by professionals.

SMOKING PROGRAM MAY HAVE SUCCEEDED, RAUSCHER SAYS, LOOKING AT ITS BUDGET

In casting about for ways to cope with the leveling off of NCI appropriations at a time when demands on those funds are soaring, Director Frank Rauscher has looked for projects at the lower end of the priority scale that could be cut back or dropped entirely.

Inevitably, the $6 million a year Smoking & Health Program has become the No. 1 candidate for the chopping block.

The major thrust of that program has been to encourage the development of a less hazardous cigarette. With the new low tar and nicotine cigarettes which came into the market during the past year apparently finding a considerable degree of smoker acceptance, "we should consider ending that program now—we may have already succeeded," Rauscher said.

To some, that sounds somewhat like the statement by a U.S. Senator at the height of the Vietnam War—that "we should declare victory and withdraw."

Rauscher's "declaration of victory" may be a little premature, according to Gio Gori, director of the Smoking & Health Program. And it assumes more credit for the development of the new cigarettes than the tobacco industry is willing to give NCI.

Gori agrees that the new cigarettes present considerably less hazard to health, although he would like to see them cut the tar content just a little more. "But there is still a lot we don't know, particularly about nicotine. We don't know what the health hazard is from nicotine."

Nicotine is a prime suspect in tobacco-related cardiovascular disease, and its role in cancer is yet to be determined one way or another. The nicotine content of cigarettes has accompanied the downward trend of tar—some brands have only .2 mg of nicotine per cigarette, compared with the average of 1.5 to 2 mg.

Gori and others feel that it is crucial to continue the large animal inhalation studies started this year which have as their primary goal determination of nicotine's effects.

Nicotine is the addictive agent in cigarettes which keeps sending smokers back to the store for more. Is it possible that as their nicotine consumption goes down, smokers' ability to kick the habit will go up? That if smokers all use the less hazardous brands, most of them eventually will be able to quit and perhaps put the cigarette industry out of business?

"That would be a happy result of all this," said a representative of the American Cancer Society, which holds to the position that the only safe cigarette is an unlit one. "And you can be sure that the tobacco industry will resist with all its might pressures to further reduce nicotine content, just for that reason. The point is, no one knows what the addictive level is—probably different for different people. Just as no one really knows the safe levels of tar content."

Gori may suffer some cuts in his program, but it isn't likely it will be wiped out. The inhalation studies probably will be permitted to continue to their completion. "We are committed to those studies, which will require four years to complete," Gori said. He has planned on phasing down to a level of about $2 million a year within five years, primarily to support epidemiology studies following trends, with one important role being to assess the impact of the less hazardous brands.

The techniques that enabled cigarette manufacturers to develop the new cigarettes had received considerable attention in Gori's program. Not even Gori, however, claims credit for them. Gori says only that "It was our effort that stimulated the industry to proceed with the development and marketing of less hazardous cigarettes."

Industry spokesmen won't even acknowledge that. "It's ridiculous to say that the little bit of money Dr. Gori's program put into cigarette design had any effect," a spokesman for one cigarette manufacturer told ***The Cancer Letter.*** "My company alone spent millions."

But Gori, Rauscher and others are convinced that it was the Smoking & Health Program's determination, and ability, to support development of a less hazardous cigarette that impelled the industry to go ahead on its own. NCI was in the process of demonstrating that low tar and nicotine cigarettes could be made that would be acceptable to smokers. Eventually someone in the industry would pick it up and could grab a big share of the market with a less hazardous brand while the rest of them were still hawking their more dangerous wares.

The industry insists that marketing opportunities were the primary motive. "Our surveys showed that 90% of smokers had tried the existing low tar brands, but only 1% continued them," one industry spokesman said. "The obvious consumer desire for low tar delivery was there."

The most visible of the new cigarettes are *Merit,* by Philip Morris, and *Now,* by R.J. Reynolds. They are the most visible because they are spending the most money on advertising and promoting their products—$29 million a year for *Merit,* $20-25 million for *Now.* According to the companies, both are smashing successes.

Philip Morris sold 1.45 billion *Merits* in the first quarter of this year, after introducing them in the last few weeks of 1975. The company considered that phenomenal, at least on par with their other top sellers, *Marlboro* and *Benson & Hedges* at similar stages. The company's total sales for the quarter were 37.27 billion cigarettes, 25.3% of the entire U.S. cigarette market.

During the same period, Reynolds—which introduced *Now* at the same time *Merit* came out—captured .8 to 1% of the entire market for its new brand. However, Reynolds said *Now* was not available throughout the nation until May. Reynolds feels that *Now* sales are comparable to its top brands at similar stages—Winston had 2% of the market after one year, and presently has 15%.

The advertising budgets for *Merit* and *Now* are as much as or more than either company has ever spent introducing new brands.

The Cancer Letter, Jan. 9, reporting introduction of the new cigarettes and the implications for the Cancer Program, made two observations which were challenged by industry representatives. These included:

—That nicotine was a suspected carcinogen.

—That cigarettes have been blamed for as many as 500,000 deaths a year in the U.S.

At that time, industry spokesmen were correct in claiming there was no evidence associating nicotine with cancer. However, Fred Bock, Roswell Park, reported in May at the meeting of the American Assn. for Cancer Research that his studies implicated nicotine as a modifying factor which triggers the carcinogenic effect of other substances in tobacco.

As for the 500,000 deaths attributed to cigarettes, that figure was high, according to two sources, at least for deaths reported in 1966 and 1967. The American Cancer Society attributed 301,560 deaths to tobacco in 1967—41,012 to lung cancer, 28,045 to other cancers, 145,956 to coronary disease, 42,821 to other vascular diseases, 43,726 to other diseases including emphysema and bronchitis. The National Science Foundation credited 299,614 deaths to cancer in 1967, with approximately the same distribution.

TEXAS INSTITUTIONS COMBINE EFFORTS TO FORM JOINT DENTAL ONCOLOGY DEPT.

The Univ. of Texas System Cancer Center and the university's Health Sciences Center have established a Dept. of Dental Oncology to encompass both the Dental Branch of the Health Science Center and the Cancer Center's M.D. Anderson Hospital.

The two institutions have conducted joint dental oral cancer programs since 1948. They feel now that further planning and development is required to add new programs in patient care, education, research and cancer control and rehabilitation and to expand the staff to accommodate the increased patient load those activities will generate.

The new department is organized so that the institutions are coequal in its management, with two cochairmen. Joe Drane is cochairman for the Cancer Center and Samuel Dreizen is cochairman for the Dental Branch. Each functions as head of the department for his institution and reports to the director of his institution. R. Lee Clark, president of the Cancer Center, appointed Drane, with the concurrence of Charles Berry, president of the Health Sciences Center. Berry appointed Dreizen, with Clark's concurrence.

Robert Hickey, director of M.D. Anderson, and John Olson, dean of the dental branch, are also involved in the chain of command.

Although the Univ. of Texas is the parent institution for the Health Sciences and Cancer Centers, both are autonomous in most respects. The organization of the Dept. of Dental Oncology demonstrates one approach that might be considered by other institutions with independent units planning a joint oncology program. Clark said that this new department is the first of its kind in the country.

Any professional assigned to work in both institutions has dual responsibilities. A professional assigned by a cochairman to the other institution is responsible to the cochairman in his institution for the quality of his professional performance. He is also responsible and reports to the cochairman to whom he is assigned for day-to-day compliance with that institution's rules and procedures and for professional performance.

Any administrative and support personnel assigned to work in both institutions are directly responsible and report to the cochairman of the institution in which they are working for day-to-day direction of their activities.

Each staff member is responsible to the cochairman in his institution for the quality of his professional performance.

The functions of the department reflect the activities commensurate with the overall mission of M.D. Anderson and the Dental Branch. Those ordinary activities of laboratory research and education are well understood but, clinically, activities of the

department will be confined to the clinical responsibilities now recognized as dental procedures.

The clinical care of patients will be under the direction of the department administering treatment (radiation therapy, medicine, developmental therapeutics, pediatrics and surgery, especially head and neck) with the Dept. of Dental Oncology performing a supportive role.

Clinical investigative programs involving patients shall require the prior approval of the head of the appropriate clinical department and such approvals as required by institutional policy for research involving human subjects.

The Dept. of Dental Oncology will participate in the surgical, radiologic, or chemotherapeutic treatment of the patient with cancer through dental and diagnostic evaluation, treatment planning, infection (oral) control, treatment prostheses, rehabilitation, and similar services.

The professional staff may be assigned to work in both institutions. Individuals assigned to work more than 50% of their time at M.D. Anderson will be appointed by the president of the Cancer Center upon the recommendation of the cochairman for M.D. Anderson. And those assigned to more than 50% of their time at the Dental Branch will be appointed by the president of the Health Science Center upon recommendation of the cochairman of the Dental Branch.

Staff members should receive joint appointments to each institution. In such cases, tenure or term appointment status, whichever is applicable, is the responsibility of the parent institution.

AMERICAN RADIUM SOCIETY MEETING ABSTRACTS; COMPLETE PAPERS AVAILABLE

Abstracts from selected papers presented at the 58th annual meeting of the American Radium Society follow below. Copies of these papers, and of other papers presented at the meeting, may be obtained from Charles Honaker, American College of Radiology, 20 N. Wacker Dr., Chicago, Ill. 60606.

COMBINED THERAPY FOR ENDOMETRIAL CANCER: PREOPERATIVE INTRACAVITARY IRRADIATION FOLLOWED PROMPTLY BY HYSTERECTOMY – Joel Ohlsen, G.H. Johnson, J.R. Stewart, James Eltringham and M.A. Stenchever, Univ. of Utah Medical Center

In an attempt to provide the potential benefits of adjunctive radiation for prevention of vaginal recurrence while limiting the risk of whole pelvis irradiation to only those patients most likely to have occult node metastases or pelvic implants, the Div. of Radiation Therapy and the Dept. of Obstetrics & Gynecology at the Univ. of Utah Medical Center in June, 1971, jointly developed a new treatment protocol for endometrial carcinoma.

This treatment plan includes preoperative intracavitary irradiation followed by immediate TAH & BSO (with 72 hours of removal of the applicators) for apparent Stage I tumors. External beam irradiation of the pelvis is added post-operatively if deep myometrial invasion is present histologically, if the tumor is poorly differentiated or anaplastic, if cervical extension is documented in the specimen, or if pelvic metastases are present. All clinical Stage II patients are treated with combined intracavitary and external beam irradiation prior to TAH & BSO. From June 1, 1971 to Jan. 1, 1975, 112 patients were considered for treatment in this manner. One hundred patients had preoperative intracavitary irradiation. Of these 100 patients, 16 have had whole pelvis irradiation. Complications have been noted in seven patients. Eight deaths have occurred, six of these due to cancer, one due to pulmonary embolus, and one unrelated death. One patient is alive with known lung and bone metastases. There have been no isolated vaginal recurrences.

Pathologic evaluation of the operative specimen obtained within 72 hours of intracavitary irradiation allows selection of patients for whole pelvis external irradiation based on precise pathologically confirmed determination of risk factors.

PROSPECTS FOR IMPROVEMENT IN THE TREATMENT OF CANCER – Robert Young

Ovarian carcinoma is now the most common fatal gynecologic malignancy in the United States. Approximately 10,000 women per year die of ovarian cancer and in spite of the extensive use of surgery, radiotherapy and/or chemotherapy, the death rate from this disease has not been appreciably altered over the past 30 years. These grim statistics emphasize a need for a detailed re-examination of the present techniques of diagnosis, staging and therapy. Survival rates for localized ovarian cancer (Stage I 65% - 5 yr. and Stage II 30% - 5 yr.) suggest that significant understaging has occurred. Data generated from several studies employing lymphangiography and peritoneoscopy have revealed large numbers of patients with disease actually spread outside the true pelvis although apparently localized at initial surgery. The frequent requirement of total abdominal radiotherapy and the general dissatisfaction with the results has led to an intense investigation of chemotherapy in the treatment of this malignancy. Alkylating agents remain the drugs of choice at present but for the first time non-alkylating a gents and combinations are now being prospectively investigated in well designed randomized trials. As better forms of chemotherapy are defined for advanced disease (FICO Stage III and IV) they will be tested in earlier stages as adjuvants to existing optimal therapy. Such prospective well designed clinical trials should define optimal therapy for all stages of ovarian carcinoma and lead to improved survival.

DEFINITIVE RADIATION THERAPY IN CARCINOMA OF THE PROSTATE CLINICALLY LOCALIZED TO THE PELVIS – Carlos Perez, Robert Royce, and Walter Bauer, Washington Univ. School of Medicine

Approximately 120 patients with carcinoma of the prostate localized to the pelvis have been treated with radical irradiation in the past eight years and are available for follow-up longer than one year after treatment. All patients had a histological diagnosis of carcinoma of the prostate and were evaluated by blood determination of alkaline and acid phosphatases, a bone scan, in most instances pedal lymphangiogram and in about 30% of the patients, bone marrow acid phosphatase determinations.

Approximately 50% of the patients have received prior or concomitant hormonal manipulation. About 20% had their tumor diagnosed some time before the institution of radiation therapy. The basic treatment involves the delivery of 7000 rads T.D. to the prostate, 6000 rads to the hypogastric and external iliac and 5000 rads to the common iliac nodes with progressively decreasing fields using 23 MeV betatron x-rays.

STAGING AND LOCALIZATION OF TUMORS BY GALLIUM^{67} –SUBTRACTION SCANNING – Yosh Maruyama, Frank Deland, J.R. van Nagell Jr., and Robert Beihn, Univ. of Kentucky and VAH Medical Center

Recently, we have described a new method by which ^{67}Gallium scanning can be extended in its application to clinical diagnostic problems. This method, the ^{67}Gallium-subtraction scanning method, utilizes ^{67}Gallium which is known to accumulate in neoplastic and inflammatory tissue as an agent for total body labeling. A second radioisotopic material ^{99m}Tc attached to appropriate agents which localize selectively in lung, bone, liver, and spleen can then be injected as a second label which selectively permits the activity and contribution to the image of lung, bone, liver or spleen to then be SUBTRACTED leaving as a residual image, the abnormal isotope accumulations in e.g. neoplastic or inflammatory tissue. This method has been applied in this study to the evaluation of patients with ovarian tumors, Hodgkin's disease and other tumors in this clinic.

The method improves detection of cervical, mediastinal, and paraaortic disease when applied to lymphoma staging and localization. The method is being applied to the study of advanced ovarian tumors in an

effort to determine its efficacy in the detection of fluid and masses for ovarian tumors. Preliminary results will be described as well as the principals on which the method is based. One of the major problems in the therapy of ovarian tumors is the inaccuracy of currently available staging methods. This report describes results with a new and promising method of evaluating intraabdominal disease and a preliminary assessment of its effectiveness.

CURRENT TRENDS IN THE RADIOTHERAPY OF OVARIAN CARCINOMA – Zvi Fuks

Although megavoltage radiotherapy has significantly improved the prognosis of patients with ovarian carcinoma, many patients with apparently curable disease treated with aggressive postoperative radiotherapy still die of their malignancy. Despite maximal therapeutic efforts, nearly 20% of treated patients with initial Stage I disease, 60% of Stage II patients and 90% of the patients in Stage III disease succumb to their ovarian neoplasm. Recent clinical studies using lymphangiography, peritoneoscopy and radioisotopic scans of peritoneal drainage have suggested that retroperitoneal lymph node involvement as well as diaphragmatic involvement may occur relatively early in the course of ovarian carcinoma and with a much greater frequency than has been appreciated.

Occult para-aortic lymph node and/or diaphragmatic involvement, if untreated, may account for a significant proportion of treatment failures that have made these patients such a difficult therapeutic challenge to the radiotherapist. A new radiotherapeutic technique for treatment of these diseases, directed toward these frequent sites of occult involvement, is being tested.

TREATMENT OF OSTEOGENIC SARCOMA WITH VINCRISTINE, HIGH-DOSE METHOTREXATE AND CITROVORUM FACTOR ("CITROVORUM FACTOR RESCUE") – Norman Jaffe

The high-dose methotrexate program (VCR-MTX-CF) involves the administration of vincristine (2 mg/m^2 followed one-half hour later by a 6-hour infusion of methotrexate (3 gm/m^2, 6 gm/m^2 and 7.5 gm/m^2 at 2 to 3-weekly intervals). Two hours after the completion of the methotrexate infusion, citrovorum factor "rescue" is administered over 72 hours. Utilizing the program as "adjuvant" treatment at 3-weekly intervals to eradicate pulmonary microscopic disease, 7 of 12 patients in whom local control was achieved remain free of pulmonary metastases for 18+ to 40+ months. One additional patient with pulmonary metastases was rendered free of disease by surgical resection of tumor. When compared to an historical control group, the incidence of pulmonary metastases is highly significant (p 0.01).

In 1974, a new "adjuvant" program incorporating adriamycin into the high-dose methotrexate regimen (VCR-MTX-CF-ADR) was initiated. Among 20 patients in whom local control was achieved, 16 remain free of pulmonary metastases for 6+ to 18+ months.

During the past year, a weekly schedule of VCR-MTX-CF was investigated for the treatment of pulmonary metastases and as pretreatment of the primary tumor in preparation for surgical removal short of amputation. Three of four patients with pulmonary metastases achieved responses including 2 with complete disappearance of tumor. Complete responses were also achieved in 3 of 4 patients with primary tumors. In one patient with an extremity lesion, a local en bloc resection was performed with insertion of a Bucholz total shoulder prosthesis permitting preservation and useful function of the limb.

Weekly high-dose methotrexate has also been employed in combination with radiation therapy for the treatment of residual disease following relapse to "conventional" modes of chemotherapy. Recurrent tumor has not been observed following this combined therapeutic approach in 3 patients after resection of pulmonary metastases and in one following resection of inguinal node disease. The duration of response has varied from 2+ to 14+ months. Partial regression of an unresectable pelvic lesion in one patient with this combined approach was also achieved.

These results demonstrate that VCR-MTX-CF alone, and in combination with other therapeutic modalities, has had a major impact on the biological behavior of osteogenic sarcoma.

IMMUNOSUPPRESSION ASSOCIATED WITH RADIATION THERAPY – William Wara

Many reports have demonstrated immunosuppression of cell mediated immunity following radiation therapy. Several hypotheses have been proposed to explain this phenomenon, including irradiation to the thymus, irradiation of large volumes of blood within the treatment field, or production of a serum factor which depresses immunity.

Suppression of cell mediated immunity following radiation therapy probably results from the irradiation of large volumes of blood within the treatment fields. This effect can be measured by T-cell rosette formation and phytohemagglutinin (PHA) lymphocyte stimulation in patients who have received parasternal irradiation for breast carcinoma. Impaired lymphocyte response to PHA has been reported in patients previously irradiated for Hodgkin's disease, usually treated with large fields which encompass the thymus. In treatment of nasopharyngeal carcinoma (with even minimal thymic irradiation), a profound post radiation immunosuppressive effect can be measured by PHA stimulation and T-cell rosette formation, lasting for periods of six months to two years. A rapid decrease of B and T circulating lymphocytes in patients receiving irradiation to the mediastinum and pelvis has been measured by EAC and E-rosette formation, acute depression lasting about three weeks, with modest chronic depression remaining, especially in T-cells.

To determine the effect of this decrease in cell mediated immunity on prognosis and survival is the subject of ongoing clinical trials, involving surgery and radiation, which may correlate immunosuppression with the growth of primary tumors and/or occult metastatic disease.

RETROPUBIC IMPLANTATION OF IODINE 125 IN THE TREATMENT OF PROSTATIC CANCER – Willet F. Whitmore

Bilateral pelvic lymph node dissection and simultaneous retropubic implantation of I-125 containing seeds in the prostate has been under clinical study in the treatment of selected patients with clinically Stage B or Stage C prostatic cancer (exclusive of lymphangiographic findings) for approximately 6 years at the MSKCC. Almost 200 patients have been so treated. The physical impact of the procedure has generally been mild, the postoperative hospitalization averaging 8 days. There has been a single operative mortality. Wound infection, generally mild, has been the most common surgical complication. Transient irritative urinary symptoms have been common, but immediate or delayed complications attributable to irradiation have been rare. The effects of the treatment on the cancer have been judged from local symptoms, digital rectal findings and survival without metastasis. Symptomatic evidence of local tumor growth has been uncommon. More than half of patients demonstrate palpable evidence of regression within one year of operation and more than three-fourths within 2 years. About one quarter of patients with Stage C lesions have demonstrable regional lymph node metastasis at operation. Approximately 60 percent of those with positive nodes will have demonstrable bone metastases at two years. Available data indicate that survival rates with this method of treatment are as good as those of alternative methods of treatment of corresponding stages of the disease and the quality of life post treatment seems as good or better than that achieved with any other active therapeutic program for comparable tumor stages.

STAGES I - III HODGKIN'S DISEASE IN CHILDREN: RESULTS OF STAGING AND TREATMENT – Leslie Botnick, Robert Goodman, Norman Jaffe, B. Chem, Robert Filler, and Robert Cassady

Fifty children with clinical stages I-III Hodgkin's disease were evaluated for disease extent and treatment at the Joint Center for Radiation Therapy between 1969-1974. All underwent laparotomy and splenectomy. Two had liver involvement and are excluded from this analysis. There were 31 males and 17 females with a median age of 11 (5-15). Pathologic staging revealed 5 stage IA, 27 IIA, 4 stage IIB, 5 stage IIIA, and 7 stage IIIB. Eleven patients (21%) had a change from initial stage and subsequent treatment because of the laparotomy. Median follow-up is 29 months (7-72) since initiation of treatment. The 32 patients with stages I and IIA were treated with irradiation alone, 3600-4000 rad to the mantle and para-aortic fields. One stage IIA patient has relapsed nodally, but not in the untreated pelvis; he is alive without disease after retreatment with chemotherapy (MOPP). The eleven stage IIB and IIIB patients were treated with total nodal irradiation (TNI) (3600-4000 rad) and subsequent prophylactic MOPP. Ten out of 11 are continuously free of disease. One patient died of viral pneumonitis while on chemotherapy. Three of five patients with stage IIIA disease developed nodal relapse after TNI; all are alive without evidence of disease after irradiation (3) and MOPP (1).

Thus, 43 of 48 patients (90%) have remained continuously free of disease after completion of the planned treatment, and overall, 47 of 48 (98%) are alive without evidence of disease. There were no serious sequelae associated with laparotomy and splenectomy.

We feel that such results justify continuation of our staging and treatment philosophy in children with Hodgkin's disease.

USE OF THE PIG AS AN EXPERIMENTAL MODEL FOR LONG TERM STUDIES OF RADIATION EFFECTS ON NORMAL TISSUES — J.C. Probert, C.M. Siu, H.S. Saben, and C.J. Gregory

John Hunter, in the 18th Century, declared the pig to be the most useful of all animals for physiological research. More recent work has revealed a long list of similarities between the pig and man both in organ structure and physiological response. In spite of this the pig has not been widely used for medical research.

The present paper deals with the first stage of a larger study to exploit these advantages in an investigation of the relative long-term effects of π^- mesons and ^{60}Co γ-rays on the functional and structural integrity of critical organs in the pelvis and abdomen. These initial studies have concentrated on the development of a number of procedures prerequisite to the definition and follow-up of radiation induced changes. Experimentation with methods of handling, anaesthesia, and various radiologic and dosimetric techniques indicate that the pig is well suited to this type of study and may constitute the experimental animal of choice for future radiotherapy research.

FOLLOW-UP EXPERIENCE IN EXTENDED COMBINATION THERAPY OF RHABDOSARCOMA — Charlene Holt

Historically, rhabdomyosarcoma, the most common soft tissue tumor of childhood, has had a dismal survival rate of 10-12% for five years when treated with surgery and radiation therapy. Since 1969, at the Denver Children's Hospital Oncology Center, and the Presbyterian Medical Center, an aggressive approach including surgery, radiation therapy with mega voltage techniques concurrent with combination chemotherapy with Vincristine, Dactinomycin and cytoxan for 1-2 years has resulted in remarkable improvement. To date, 13/21 patients are surviving with no evidence of disease for 19-54 months. Toxicity has been tolerable and no toxic deaths have occurred.

CONTRACT AWARDS

Title: SEER and Third National Cancer Survey data processing
Contractor: GEOMET Inc., $269,629.

Title: Study of high risk breast cancer families
Contractor: Michigan Cancer Foundation, $347,356.

Title: Sequencing studies of nucleotides and avian myeloblastosis virus
Contractor: Massachusetts General Hospital, $35,100.

Title: Support for Cancer Surveillance System
Contractor: Fred Hutchinson Cancer Research Center, $40,768.

Title: Studies on role of hormonal factors on induction of mammary tumors
Contractor: Mason Research Institute, $260,964.

Title: Perform curatorial and development of reference grade tumor viruses
Contractor: American Type Culture Collection, Rockville, Md., $78,150.

Title: Epidemiological investigation of cancer in Utah
Contractor: Univ. of Utah, $505,917.

Title: Breast cancer demonstration project
Contractors: Good Samaritan Hospital and Medical Center, Portland, Ore., $238,796, and Cancer Research Center, Columbia, Mo., $335,000.

Title: Repository for storage and distribution of reagents, sera and tumor specimens
Contractor: Flow Laboratories.

Title: Development of immunodiagnostic tests for cancer
Contractor: Robert B. Brigham Hospital, Boston, $59,424.

Title: Biochemical and physiological investigations based on familial genetic patterns
Contractor: Montefiore Hospital, $186,400.

Title: Investigations of possible correlations be- morphological and epidemiological characteristics of breast cancer
Contractor: University Hospital, Uppsala, Sweden, $119,900.

Title: Conduct a combined study of the possible association of dietary factors and non-contraceptive exogenous estrogens with breast cancer
Contractor: Univ. of Hawaii, $110,000.

Title: Evaluation of surgical adjuvant chemotherapy utilizing 5-FU, cytoxan and prednisone
Contractor: Mayo Foundation, $81,570.

Title: Support services for immunological and biochemical studies of mammalian viral oncology
Contractor: Meloy Laboratories Inc., $37,350.

Title: Immunological studies of human breast cancer
Contractor: Albert Einstein College of Medicine, $104,000.

Title: Operation of a registry of tumors in lower animals
Contractor: Smithsonian Institution, $119,500.

Title: Analysis of breast secretions
Contractor: Univ. of California (San Francisco), $87,600.

Title: Breast cancer family resources
Contractor: Creighton Univ., $59,500.

Title: Studies based on familial genetic patterns
Contractor: Creighton Univ., $118,900.

Title: Study of mammary gland responsiveness to multiple hormones
Contractor: Univ. of California (Berkeley), $60,000.

Title: Perform a study on familiality of breast cancer to be conducted in Iceland
Contractor: International Agency for Research on Cancer, Lyon, $32,000.

The Cancer Letter—*Editor* JERRY D. BOYD

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