THE CANCER LETTER
RESEARCH EDUCATION CONTROL

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

Vol. 1 No. 41

Oct. 10, 1975

Subscription $100 per year

"MIND BOGGLING" RESULTS REPORTED IN TRIALS USING 3-DRUG COMBINATION FOR BREAST CANCER

Another startling development in breast cancer treatment was revealed Monday to the National Cancer Advisory Board by Gianni Bonadonna of Milan, Italy, who has been conducting NCI-supported clinical trials using a three-drug combination in adjuvant therapy.

(Continued to page 2)

In Brief

CONTROL GRANT REVIEW COMMITTEE OUT OF GRANTS DIVISION; PROVISIONAL TRAINING ANNOUNCEMENT DUE

CANCER CONTROL Grant Review Committee will be moved Nov. 3 from the Div. of Research Resources & Centers, NCI's grants management division, to the Div. of Cancer Control & Rehabilitation. Following as it did immediately after the move of the Clinical Cooperative Group Program, its review body, the Cancer Clinical Investigation Review Committee and the Clinical Investigation Branch from DRR&C to the Div. of Cancer Treatment, it might seem to some that the program divisions were going to take over management of all NCI grants. That could have broad implications for the future of investigator-initiated cancer research, but it isn't going to happen, NCI executives insist. DRR&C will continue with its grant-supported programs which have counterparts in other divisions—immunology, drug development, carcinogenesis, viral oncology, among them—in the reorganized division. The latest move was initiated by DRR&C Director Thomas King, who felt cancer control grants could and should be better administered by the cancer control division. Unlike many bureaucrats, King has not fought blindly against changes that reduce his staff and budget, has maintained a statesmanlike approach throughout the reorganization. DCC&R Director Diane Fink said the first she heard of the move of the control grant review committee to her division was after the decision had already been made. . . . **RESEARCH TRAINING** programs, still hung up in a bill pending in Congress to renew the National Research Service Act, will be implemented as far as submission and review of grant applications is concerned, under terms of a provisional announcement NIH will make in November. . . . **BENNO SCHMIDT**, chairman of the President's Cancer Panel, feels Cancer Research Emphasis Grant announcements have "jumped right back in to the very thing we were trying to avoid" by being too detailed. "They lapsed into the same error we had with some RFPs for contracts, telling the investigator too much about what we want him to do." Panel member Ray Owen, arguing the point at the Panel's last meeting, said that there are plenty of opportunities for investigators with original ideas to submit applications for traditional grants. "An additional criterion for CREG is that it must have a cancer research emphasis in order to identify areas where good applications weren't coming in."

CMF IMPROVES ON L-PAM ADJUVANT RESULTS, ADDS TO "MOMENTUM"

(Continued from page 1)

Bonadonna reported that, two years after mastectomy, 97% of patients who received the treatment were still disease free. In a control group in which no treatment was administered after mastectomy, only 25% were disease free.

The combination consisted of cychlophosphamide, methotrexate and fluorouracil (CMF). This study was started about a year after the National Surgical Adjuvant Breast Project headed by Bernard Fisher began its clinical trials with L-phenylalanine mustard (L-PAM). Fisher reported a year ago that two-year followup after mastectomy showed that premenopausal patients who had received L-PAM had a five-fold improvement in recurrence over the controls and post-menopausal patients had a two-fold improvement.

Bonadonna's study was designed with the same stratification as Fisher's, with one group 49 and under considered premenopausal and the other from 50 to 75 postmenopausal. Subgroups were formed according to the number of positive lymph nodes; only patients with one or more positive nodes were admitted to the study.

Bonadonna's figure of 97% with no evidence of treatment failure after two years was the average for all groups. There appeared to be no significant difference between the younger and older groups, as there was with L-PAM.

"It's mind-boggling," Vincent DeVita, director of NCI's Div. of Cancer Treatment said after Bonadonna's presentation. DeVita feels the encouraging results of the Fisher and Bonadonna studies and other promising adjuvant trials have generated a momentum "that we've got to keep going." Surgeons who had been skeptical of drug therapy following surgery are coming over, with their patients.

Fisher told the NCAB Monday essentially the same thing he reported to the Breast Cancer Task Force Treatment Committee last month (*The Cancer Letter*, Sept. 12):

- That the promising results with L-PAM were still holding up after another year after treatment, and in fact the gap between the treated and untreated groups had widened somewhat during the year.
- That there was no significant difference in recurrence rates in radical vs. total mastectomy trials.
- That 350 patients had been entered in a new trial which will compare L-PAM alone with a combination of L-PAM and 5-fluorouracil.
- That his group is planning a study which will attempt to compare segmental with total mastectomy if enough patients are found who will enter the segmental protocols.

Fisher said it was fortunate that the L-PAM trial was started before the CMF results came in, since it is unlikely trials would have been undertaken with the less powerful and less toxic L-PAM once the success of CMF was demonstrated. "It could have closed doors that never would be reopened," Fisher said.

There were practically no toxic effects from L-PAM in Fisher's trials, but Bonadonna reported substantial effects from CMF, including leukopenia, thrombocytopenia, oral mucositis, conjunctivitis, loss of hair, cystitis and amenorrhea. However, all were treated as outpatients, none were hospitalized during the treatment and all the working patients continued on their jobs.

DeVita, Fisher and Bonadonna all made a plea for more time before results of these trials are translated into routine practice. "Time is one ingredient that can't be factored out," DeVita said.

NEW SYSTEM DEVISED TO HELP IDENTIFY EMERGING COMPREHENSIVE CENTERS

NCI, with its new associate director for cancer centers Simeon Cantril, has developed a system which attempts to help reviewers in the difficult and, to some in the past, overwhelming job of determining if a cancer center is ready for comprehensive designation.

A 52-page booklet has been prepared for site visitors which Cantril hopes will provide "some yardstick or quantitation device" that will make center reviews comparable. The booklet includes a set of general and specific questions site visitors are asked to consider for each of the 10 characteristics that comprehensive centers are supposed to achieve. Reviewers are to determine which condition applies for each characteristic. The conditions range from the best to worst situation that might exist. For instance:

Characteristic No. 1 is that the center must have a stated purpose that includes carrying out of basic and clinical research, training and demonstration of advanced diagnostic and treatment methods relating to cancer. Reviewers have a choice of seven applicable conditions, starting with, "The institutional support for this cancer center is exceptional, major long-term administrative and leadership commitments have been made, and I believe there is no doubt this center will remain a strong and important component of its parent institution."

The worst of the seven conditions is, "The parent institution's commitment to this cancer center is below the minimum acceptable and it is doubtful if this condition will change in the foreseeable future."

NCI has not insisted that comprehensive designation depends on fulfilling all of the 10 characteristics in optimum fashion. Cantril, in the charge to site visit teams included in the booklet, said, "to the demonstrated accomplishments must be added the institutional intent and potential to develop within a realistic time frame a comprehensive cancer center in

accordance with the mandate of the National Cancer Act as determined by the National Cancer Advisory Board."

Also, reviewers were told that "You should not feel constrained by either the question set or the data base provided; rather, you should draw upon your full knowledge of the cancer field and of the institution under review and its program in reaching a final recommendation."

The booklet was used for the first time when teams, which included NCAB members, visited three of the eight institutions next in line for comprehensive designation—UCLA, New York Univ. and Ohio State. The booklet had been sent to all those who are due for site visits, and Cantril said several asked that the visit be postponed to next year. "Evidently they felt they weren't quite ready to answer those questions," Cantril said.

The NCAB Subcommittee on Centers, chaired by Denman Hammond, Univ. of Southern California, and Cantril are still struggling with the task of developing methods for evaluating the "impact" of existing comprehensive centers. Those centers not progressing satisfactorily in meeting their commitments could lose their comprehensive designation. Cantril told the centers subcommittee this week that he would try to have an evaluation plan ready for discussion at its next meeting.

The subcommittee received a report on a joint meeting in Denver of representatives of the Cancer Special Program Advisory Committee, Cancer Research Center Review Committee and NCI staff. The meeting was convened at the subcommittee's suggestion to enable members of the three cancer center review groups to jointly develop recommendations and guidelines for review of center grant applications and to establish liaison between the review groups.

Excerpts from the report of the Joint Conference Committee (JCC) follow:

"It was recognized that occasional difficulties were encountered in dealing with program project applications where they lacked coherence or where the evidence of interdisciplinary collaboration was inadequate. This was being adequately dealt with by either attaching a rider to the review, recommending a submission of the application in separate subunits for the next review, or by approving only those parts of the program project which form a cohesive program. Administrative requests for reassignment of such applications is an alternative mechanism provided justification is available.

"The JCC considered the 'umbrella' type center grant proposals. It was agreed that this term served no useful prupose. It refers to large institutional cancer programs. As long as such applications presented a cohesive and unified program effort with a common goal, it still represented a program project, irrespective of size. Nevertheless, because of the difficulty of reviewing such large single-instrument applications, the JCC recommended that every attempt should be made by NCI staff to dissuade the applicant from submitting such large conglomerate applications. If advice is ignored, the review groups are obligated to review such applications and be guided by the overriding principle of merit.

"The question of key personnel, shared services and equipment, and seed money or developmental support were discussed. Specific attention in the discussion was paid to the question of the funding of educational outreach programs, rehabilitation and continuing education. It was agreed that these programs should be treated in the review process in the same manner as other components of the core program; that is, that they should be considered eligible for support in the categories of key personnel, shared facilities, etc., as well as for support under the heading of developmental support for periods not exceeding three years. With respect to hospitalization costs, this item should be considered admissible within the terms of the Cancer Centers Program Booklet. It was believed that the wording of this paragraph should more clearly reflect the intent of giving the center director access to and availability of clinical facilities to allow for development of new programs of clinical research when these are not funded through program projects or other means.

"It was also agreed that applications for additional planning support from institutions already in receipt of core funding should be submitted as a supplement to the core grant, since planning can be viewed as a legitimate developmental function of a cancer center.

"With respect to construction grants, it was agreed that in general the review of the scientific merit of construction applications was functioning satisfactorily. Unlike program project and core mechanisms, in the case of construction grants, many additional factors enter into the decision-making process. The JCC reviewed the document prepared by the Chief of the Research Facilities and Construction Branch, NCI, and concurred that most of the "non-scientific" components of the application, in fact, also enter into the evaluation of applications by review groups. It was recognized that, in the past, recommendations for construction grants were often inadequately related to the program considerations, and it was agreed that site visiting teams and review groups should in future examine more explicitly the relationship between programs and construction requests.

"With respect to the request by the Subcommittee on Cancer Centers for the development of review guidelines, the JCC has examined the existing guidelines used for instruction of site visitors and committees and found these satisfactory and adequate for the purpose. As mentioned above, the document relating to core grants was reviewed and appropriately revised. The JCC agreed that difficulties are being experienced by NCI staff because of personnel shortages by executive secretaries and the Grants Administration

CCIRC NOTES PROBLEMS IN EXPANDING TO INCLUDE MULTIMODALITY STUDIES

Members of the Cancer Clinical Investigation Review Committee, following a Potomac Conference recommendation, have started planning for expansion of the Cooperative Group Program into multiple modality studies. At CCIRC's recent meeting (*The Cancer Letter,* Oct. 3), a subcommittee which included Nell Sedransk, Amherst; Cornelia Dettmer, Christ Hospital of Cincinnati; and Theodore Grage, Univ. of Minnesota, reported on anticipated problems and suggestions for handling them:

"1. The chairman's grant, the chairman's own participant's grant and the statistics office grant should be three separate grants because the time frames for these activities may not (as experience shows) always coincide—whether or not the individual who is the group chairman is PI for all three grants.

"2. Rotating positions such as modality committee chairmanships (in some groups) where the activity is a continuing one although the personnel may change should be funded under the chairman's grant (because the appointment of these individuals is usually the prerogative of the chairman). The particular mechanism (subgrant, etc.) should be selected on the basis of type and level of activity.

"3. Travel funds for all individuals (representing all modalities) from one institution to regular group meetings should be funded locally, through the participants' grants.

"4. Individuals in another specialty than the primary modality of therapy who participate in group activities by treating or providing regular follow-up examinations should be funded as appropriate through the participating institution grant. 'As appropriate' is intended to include defraying the cost of data collection and management plus any unusual demands for personnel required by the protocol. Frequency and type of activity should dictate the mechanism as well as the amount of funding.

"5. Problem without definitive solution—funding the individual who provides one part of therapy in multiple modality studies for several different groups (at a low level for each particular group but at a substantial level—requiring additional personnel—in sum). Per unit dispersal will not provide for his personnel requirements although for each group singly this would be the mechanism of choice.

"Possibilities: Minute fractions of personnel from each participant's grant. Request for stable funding from a modality-associated non-group or intergroup grant—either as a separate grant or as a subgrant from a major modality grant."

The reorganization which resulted in stripping CCIRC of most of its policy-making authority has not yet impinged on another of its activities, that of sponsoring symposia designed to update practicing MDs on advances in cancer therapy and cancer research in general.

A symposium on "Cancer Epidemiology and the Clinician" is scheduled for the Sheraton-Boston Hotel in Boston Oct. 23-25. Its purpose is to review current epidemiologic risk factors related to cancer and to summarize significant investigative efforts now under way. The continuing awareness of such data and the importance of a close interface between clinician and epidemiologist will be emphasized. Topics include, the meaning of epidemiology to the clinician, occupational cancer, diet and cancer, cancer clusters and viruses, genetic and familial cancer, iatrogenic cancer, and new developments in cancer epidemiology.

Howard Lessner, Univ. of Miami, is program chairman.

A symposium on "Modern Concepts in Brain Tumor Therapy, Laboratory and Clinical Investigation" is scheduled for the Sheraton-Biltmore Hotel in Atlanta Feb. 26-28. The preliminary program includes therapy research—animal models in screening, and drug considerations; neuropathology, diagnostic techniques, biochemical markers, data accumulation and a report on current therapeutic trials; and a session on therapy to include discussions on biopsy vs. resection in glioma surgery, therapy for metastatic tumors, use of corticosteroids, hyperbaric O_2 and radiation therapy, and intrathecal therapy for meningeal tumors.

Audrey Evans, Children's Hospital of Philadelphia, is program chairman.

Symposium sessions are open to all medical and health related professions. There are no registration fees.

CONTRACT AWARDS

Title: Award of 15 additional tasks involving construction, alteration and renovation, expansion of effort for project 4, and incrementally fund the contract as necessary for the performance of the cancer research program being conducted at the Frederick Cancer Research Center.
Contractor: Litton Bionetics, $3,308,523.

Title: Biomedical engineering research services
Contractor: Arthur D. Little, $899,300.

Title: Development and implementation of an at-home rehabilitation program
Contractor: Univ. of Utah, $193,876.

Title: Activation of C-particles and induction of cancer by immunologic and non-immunological methods
Contractor: Massachusetts General Hospital, $143,915.

Title: Continue operation of a central micoplasma diagnostic laboratory
Contractor: Stanford Univ., $49,676.

Title: Biologic studies of solubilized tumor antigens
Contractor: Litton Bionetics, Inc., $215,542.

Title: Continue studies on the viral etiology of a malignant lymphoma outbreak in Rhesus monkeys
Contractor: Univ. of California (Davis), $105,590.

Title: Measurement of aryl hydrocarbon hydroxylase in cultured human lymphocytes
Contractor: New York State Dept. of Health, $144,660.

Title: Continuation of study of the oncogenic potential of defective human viruses
Contractor: Pennsylvania State Univ., Hershey Medical Center, $458,743.

Title: Studies of tumor viruses in nonhuman primates
Contractor: Rush-Presbyterian-St. Luke's Medical Center, $600,000.

Title: Continue production of sarcoma and leukemia viruses
Contractor: University Laboratories, Inc., Highland Park, N.J., $329,800.

Title: Preparation and characterization of antisera to oncogenic viral antigens
Contractor: Huntingdon Research Center, Brooklandville, Md., $354,959.

RFPs AVAILABLE

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

RFP NCI-CB-64015

Title: *Vaginal-cervical cell sample sources for cytology automation*
Deadline: *Nov. 24*

Obtain gynecologic cytopathology specimens for flow system analysis. The contractor should have available large numbers of gynecologic patients, including normals, patients with cancerous and precancerous lesions of the uterus, cervix and vagina and patients with other type of abnormalities of the gynecologic tract such as cervicitis and infections which are diagnosible by cytopathologic methods.
Contracting Officer: Harold Simpson
Biology & Diagnosis
301-496-5565

SOLE SOURCE NEGOTIATIONS

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

Title: Preparation and characterization of antisera to oncogenic viral antigens
Contractor: Huntingdon Research Center, Brooklandville, Md.

Title: Production of oncogenic or potentially oncogenic viruses
Contractor: Electro-Nucleonics Laboratories

Title: Prototype clinical chemotherapy program in cancer control
Contractor: Mt. Sinai School of Medicine

Title: Prototype network demonstration project in breast cancer
Contractor: Univ. of Vermont School of Medicine

Title: Fibrinolysis as a parameter of in vitro transformation
Contractor: Children's Hospital of Los Angeles

ABSTRACTS OF PAPERS FROM ACS CONFERENCE ON GYNECOLOGIC CANCER

The National Conference on Gynecologic Cancer, sponsored by the American Cancer Society, included during the three-day meeting sessions on new concepts in gynecologic oncology, advances in diagnostic techniques, research in gynecologic oncology, advances in therapeutic techniques, and current status of the treatment of the sites of gynecologic cancer.

Abstracts of papers presented in those sessions follow (contact ACS, 219 E. 42nd St., NYC 10017 for information on availability of complete papers):

THE ESTROGEN–CANCER HYPOTHESIS – *Roy Hertz, George Washington Univ. Medical Center*

The estrogen-cancer hypothesis postulates that endogenous and exogenous estrogens play a highly significant role in the pathogenesis, clinical course and treatment of cancer in the estrogen-sensitive tissues of man and animals.

A comprehensive review of the epidemiologic, experimental and clinical evidence bearing out this hypothesis will be documented. Special emphasis will be given to cancer of the breast, endometrial cancer, and vaginal cancer. The significance of the apparent estrogen-independence of cancer in such equally estrogen-dependent sites as the Fallopian tube and the cervix will be developed.

A series of studies for the further testing and validation of the estrogen-cancer hypothesis will be proposed aong experimental and epidemiological lines.

RADIATION THERAPY AND GYNECOLOGIC CANCER – FUTURE PROSPECTS – *Luther Brady, Hahnemann Medical College*

Much progress has been made in the utilization of radiation therapy techniques in the management of

gynecologic malignancies. However, new techniques will continue to emerge for the management of these disease processes. Hi LET radiation is particularly exciting as are the potential possibilities for combined modality therapy. It is the expressed hope that these techniques will lead to improved results in terms of management. The appropriate management for carcinoma of the uterus is excellent for the early stages, but treatment for later stages of the disease are not settled at this time.

The high probability of involvement of periaortic lymph nodes in carcinoma of the cervix warrant a more appropriate look at the treatment techniques to be employed in the management of the disease, if the maximum potential for cure is expected.

In carcinoma of the ovary, various factors influencing the ultimate prognosis have now been identified and these must be taken into consideration when planning treatment. If carcinoma is known or thought to have been left in the pelvis only, vigorous postoperative pelvic irradiation is mandatory. There is evidence to suggest, however, that equally good results can be obtained in those series by the utilization of chemotherapy. In view of the frequency of seeding to the peritoneum, whole abdominal irradiation should be considered for Stage IB through Stage III carcinoma of the ovary.

OVERVIEW OF TUMOR IMMUNOLOGY IN GYNECOLOGIC ONCOLOGY – ***Philip DiSaia, Univ. of Southern California***

Highlights of recent advances in the field of gynecological tumor immunology will be presented in an effort to demonstrate that at least some cancers of the female genitalia evoke an immune response which can be quantitated in the laboratory. The overview will touch on in vitro assays of cell-mediated immunity as well as the clinical testing of delayed hypersensitivity reactions with clinical correlations.

The effect of therapeutic modalities on cell-mediated immunity will be described utilizing monitoring devices such as migratory inhibiting factor (MIF) and T-cell rosette determinations. Finally, some discussion will be given to the status of isolation of tumor associated antigens as well as the prevalence of carcinoembryonic antigens in the plasma of patients with gynecological malignancies.

CURRENT STATUS OF THE TREATMENT OF ENDOMETRIAL CANCER – ***S.B. Gusberg, Mount Sinai***

The treatment of endometrial cancer has been surgical traditionally with preoperative radiation gaining favor in the past three decades.

This surgical treatment has been confined to simple total hysterectomy and bilateral salpingo-oophorectomy in most clinics because of the pattern of spread of corpus cancer and the alleged benignity of this disease. Even now, the role of radical surgery, the timing of radiation therapy and its mode and the place of hormonal treatment for primary disease are still the subject of discussion and clinical investigation.

The definition of virulence factors and an appropriate staging dependent upon these factors has helped clarify some of these problems and will help the analysis of cure rates when we can understand the selection of the material. With such a prospect for quality control and establishment of a protocol of individualization of treatment, we have a right to expect that appropriate surgical and radiotherapeutic measures will gain their proper priority and adjuvant hormonal therapy and chemotherapy may be incorporated.

CURRENT STATUS OF THE TREATMENT OF GYNECOLOGIC CANCER BY SITE – OVARY – ***Hugh Barber, Lenox Hill Hospital, NYC***

Cancer of the ovary is the leading cause of death from gynecologic cancer. The constant challenge presented by ovarian cancer is that about 11,000 women die from ovarian cancer each year and the results in 1973 are no better than have been achieved in the previous two decades.

Standard practice with truly invasive common epithelial ovarian cancer includes total hyterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy and postsurgical insertion of tubes and administration of P^{32} (if the disease is limited in its extent).

Although it is occasionally necessary to resect isolated segments of bowel, exenterative or ultraradical surgery in the management of ovarian cancer is not usually chosen because of the natural history of the disease. However, aggressive surgery is indicated not so much because it is curative, but it potentiates other forms of treatment.

All stages I through IV are treated surgically, removing as much tumor as possible without running a risk of a gastrointestinal or genitourinary fistula. Radiation therapy has been utilized in addition to the surgical therapy in stage II cancers and selectively in stage IV to control supraclavicular and/or inguinal node involvement.

Single agent alkylating chemotherapy is chosen for the treatment of common epithelial ovarian cancers. Combination chemotherapy does not produce better results at this time, except in the treatment of embryonal tumors.

The treatment of the common epithelial tumors by stage will be outlined in the manuscript. The treatment of germ cell tumors, gonadal stromal tumors, ovarian tumors in childhood, ovarian tumors in pregnancy as well as tumors not specific for the ovary will be discussed.

PERSISTENT AND RECURRENT DISEASE – ***George Morley, Univ. of Michigan***

During the 10-year period from July 1, 1965 to July 1, 1975, 74 patients were treated with some type of pelvic exenteration at the Univ. of Michigan Medi-

cal Center with over 75% being treated for persistent or recurrent pelvic malignancy. Total pelvic exenteration was performed in over 75% of the cases. The most recent figures suggest an approximate three year and five year survival rate of 60%. The surgical mortality is 1.3%. The hospital mortality is 1.3%. The patients with squamous cell disease have a better prognosis than do others and those patients with regional lymph node involvement have a bad prognosis.

Advances in therapeutic techniques during this 10 year period include: 1. use of prophylactic antibiotics; 2. transverse lower abdominal incision; 3. so-called "ski-position" on the operating table; 4. prophylactic compartmentalization of the inferior vena cava; 5. uretero-sigmoid conduit for urinary diversion; 6. peritoneal graft as a "lid" over the pelvic vault; and 7. split thickness skin graft vaginoplasty as part of the rehabilitation program will be discussed in detail.

THE EFFECT OF ENZYMES UPON METABOLISM, STORAGE, AND RELEASE OF CARBOHYDRATES IN NORMAL AND ABNORMAL ENDOMETRIA – ***Edward Hughes, SUNY (Syracuse)***

This paper presents preliminary data concerning the relationship of various components of glandular epithelium and effect of enzymes upon metabolism, storage, and release of certain substances in normal and abnormal endometria. Activity of these endometrial enzymes has been compared between two groups—252 patients with normal menstrual histories and 156 patients, all over the age of 40, with abnormal uterine bleeding. Material was obtained by endometrial biopsy or curettage. Pathologic classification of the group of 156: 30 patients had secretory endometria; 88 patients had endometria classified as proliferative; 24 were classified as endometrial hyperplasia, and 14 were classified as adenocarcinoma.

All tissue was studied by histologic, histochemical, and biochemical methods. Glycogen synthetase activity caused syntheis of glucose to glycogen increasing in amount until mid cycle when glycogen phosphorylase activity caused the breakdown to glucose during the regressive stage of endometrial activity. This normal cyclic activity did not occur in the abnormal endometria with activity of both ensymes continuing at low contact tempo. Only the 1 form of glycogen synthetase increased as the tissue became more hyperplastic. With the constant glycogen content and the increased activity of both the TPN isocitric dehydrogenase and glucose-6-phosphate dehydrogenase occurring in the hyperplastic and cancerous endometria, tissue energy was created resulting in abnormal cell proliferation. These altered biochemical and cellular activities may be the basis for amlignant cell growth.

MORPHOLOGY AND ULTRASTRUCTURE – ***Alex Ferenczy, McGill Univ.***

Our knowledge of the morphology and pathogenesis of malignant neoplasms of the female genital tract has traditionally depended heavily on their light microscopic characteristics. The introduction of transmission, and most recently, scanning electron microscopy into the field of gynecologic pathology has resulted in a considerable improvement in the diagnosis of difficult to classify genital cancers and provided valuable information for a better understanding of their subcellular dynamics and pathogenetic development. This paper describes and illustrates the ultrastructural alterations which are considered specific for the most common cancers of the genital system in this context. The value of electron microscopy in the morphologic study of genital cancers warrants its increased use in routine diagnostic pathology as well as further evaluation in basic research in this challenging area of investigation.

HORMONE RESEARCH IN GYNECOLOGIC ONCOLOGY – ***Erlio Gurpide, Mount Sinai***

The discovery, characterization and measurement of levels of hormone receptors have provided an experimental approach to study the variable responsiveness of tumors of the female genital tract and mammary gland. Receptors can be blocked by hormone competitors and receptor levels are susceptible to modification by other hormones. These concepts serve to rationalize therapeutic regimens.

Measurements of hormonal levels by radioimmunoassay have contributed to a proper evaluation of the hormonal environment in high risk patients and to the interpretation of epidemiologic findings. Further understanding of the relations between hormones, hyperplasia and neoplasia resulted from the application of tracer methods to estimate rates of production and clearance of the hormones, to identify the sources of circulating estrogens, and to study hormonal metabolism in tumors.

Advantage has been taken of the availability of human tumor cell lines to determine specific effects of individual hormones, eliminating some of the complexities of in vivo experiments. Current research on hormonal effects on gene transcription is most relevant to the cancer problem.

VIRAL INFECTION AND CANCER OF THE LOWER GENITAL TRACT – ***William Josey, Andre Nahmias, and Zuher Naib, Emory Univ.***

The importance of viruses as oncogenic agents in animals is well established. Recent work has suggested that viruses may also be etiologically related to some human cancers. Herpes simplex virus type 2 (HSV-2) and genital wart virus are prime suspects in carcinomas involving the female lower genital tract. In particular, a close association has been found between HSV-2 infection and neoplasia of the cervix. This association was first noted cytohistopathologically and subsequently demonstrated more specifically by seroepidemiologic methods.

Preliminary results of prospective studies show that women with herpetic infection have an increased

risk of developing cervical neoplasia. In progress also are additional studies on animal models, including subhuman primates, and continuing efforts to confirm the presence of viral genetic material or its expression in human cervical tumor cells. The possibility that genital wart virus infection is a precancerous condition has been suspected primarily on the basis of clinicopathologic observations. Further research will be necessary to determine the precise role of each of these two viral agents in genital cancer.

PRE-TREATMENT STAGING – ***James Nelson, SUNY (Downstate)***

Since January 1970 when a preliminary report was made by the Gynecologic Oncology Service of Downstate Medical Center, great interest in surgical staging has been seen. The initial report concerned stages IIB and II carcinoma of the cervix. Since then reports have appeared in which all cases of cervical carcinoma have been subjected to laparotomy prior to institution of any therapy. In 1975 many additional reports appeared. Most of these confirmed the earlier findings, namely, that 35 to 48% of patients with stage II carcinoma of the cervix had metastases either to para aortic lymph nodes or to other sites above the pelvis and beyond the usual field of radiotherapy.

These findings, plus the recent reports indicating a surprisingly high incidence of lymph node involvement in ovarian carcinoma, have created a move toward routine surgical staging in all cases of gynecologic malignancy.

In 1975 the reports also indicated serious complications resulting when patients with advanced cervical carcinoma had a laparotomy, followed by radiation to the pelvic and para aortic areas.

This paper will recount the experiences to date on surgical staging in cervical, ovarian and endometrial malignancies.

COLPOSCOPY – ***Adolf Stafl, Medical College of Wisconsin***

Colposcopy provides the clinician with additional dimensions in the evaluation of the physiology and pathology of the uterine cervix. Although colposcopy was developed almost 50 years ago, only recently has it gained wide interest in the United States. The acceptance of colposcopy in this country has been stimulated by new concepts in the natural history of cervical neoplasia, the change in priorities in the clinical application of colposcopy, and the improvement of colposcopic training. The main clinical value of colposcopy is in the clinical diagnosis of patients with abnormal cytology. Colposcopy can improve the diagnostic accuracy and decrease the cost of cancer detection. In a colposcopically directed biopsy it is possible for an experienced colposcopist to sample with a high degree of accuracy the most advanced histopathologic changes which allows significantly a decrease in the frequency of diagnostic conizations.

Contemporary colposcopy is based on the concept of the transformation zone. The transformation zone is an area on the cervix originally covered with columnar epithelium which by the process of squamous metaplasia is partially or totally replaced by metaplastic epithelium. A clear understanding of the transformation zone is important not only for colposcopic diagnosis but also in comprehending the origin and development of cervical neoplasia which originates in the transformation zone.

ADENOSQUAMOUS CARCINOMA OF THE ENDOMETRIUM – ***James Reagan, Case Western Reserve Univ.***

Mixed adenosquamous cancer is composed of a squamous and a glandular component the cells of which resemble their neoplastic counterparts. In the female genital tract this type of carcinoma occurs in the vagina, the uterine cervix, the endometrium and the ovary. Mixed adenosquamous cancer of the endometrium, unlike its cervical counterpart, is being detected with increasing frequency both in the United States and elsewhere. At the University Hospitals of Cleveland the neoplasm has been detected with significant frequency in the past decade and accounts for more than one-third of the endometrial cancers detected in the five-year period ending in 1974.

A total of 112 mixed adenosquamous cancers of the endometrium has been observed. The squamous component resembled large cell cancer in 82.1% of the cases, keratinizing cancer in 15.2% of the cases, and small cell cancer in 2.7% of the cases. Ultrastructural changes confirmed the squamous nature of the epithelium. The glandular component was classified as Grade I in 15.2% of the cases, as Grade II in 58%, as Grade III in 25.0%, and as Grade IV in 1.8% of the cases.

As compared with other types of endometrial cancer, mixed adenosquamous cancer is being encountered more frequently, is detected at an older age, has a shorter symptomatic period, is more advanced at time of detection, is more readily demonstrated by means of cellular studies, is more varied in its routes of spread and has a poorer five-year survival (20%). On the basis of studies covering aperiod of 35 years, there is evidence to indicate that this is a newly emerging neoplasm.

(Additional abstracts from the conference will be published next week.)

The Cancer Newsletter—*Editor* JERRY D. BOYD

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