THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 1 No. 15
April 11, 1975

Subscription $100 per year

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"EXCITING" DEVELOPMENTS IN DIAGNOSIS, SCREENING METHODS REPORTED BY BERLIN AS HE LEAVES NCI POST

Diagnosis and screening techniques for the major cancer killers now being tested or in various stages of development were called "exciting" and "encouraging" by Nathaniel Berlin in his final presentation to the National Cancer Advisory Board as director of NCI's Div. of Cancer Biology & Diagnosis.

Berlin left NCI to become director of the Northwestern Univ. cancer center. Alan Rabson is the new director of the division.

"Our research goal is diagnosis before metastasis," Berlin said, and in fact offered a definition for early diagnosis as diagnosis before metastases occur.

From 65-70% of cancer patients (excluding those with skin cancer) have metastatic disease at the time they first present themselves to a

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In Brief

GALLO LISTS FOLLOWUP PROJECTS FOR HUMAN CANCER VIRUS; ZUBROD RESPONDS TO CANCER PROGRAM CRITICS

"**WHERE DO** we go next?" Mary Lasker, National Cancer Advisory Board member, asked that question of Robert Gallo after his report to the Board on the isolation of a human cancer virus by NCI. Gallo listed four immediate followup projects: development of a larger supply of the virus, both for use by NCI scientists and to supply other labs; seriological epidemiological studies; hybrid experiments; and development of virus proteins in greater quantities "to make antibodies and to see if there is a cytotoxicological effect on leukemia cells" . . . . **NEW MEMBER** of the House Ways & Means Committee is California two-term Republican William Ketchum, a former rancher. Ketchum fills the vacancy on the committee, which heavily influences much health legislation, created by the death of Jerry Pettis. . . . **GORDON ZUBROD**, director of the Comprehensive Cancer Center of Greater Miami and former head of NCI's Div. of Cancer Treatment, challenged critics who claim there has been no progress in the cancer program. In an address to the Woman's Cancer Assn. of the Univ. of Miami, Zubrod pointed to the drastic improvement in survival rates for victims of acute lymphocytic leukemia and Hodgkin's disease. "More importantly, basic research has found why it is that drugs and surgery and radiation can be used together in attacking some common tumors . . . and have been able to apply these principles to such diseases as breast cancer," Zubrod said. . . . **EARLIER DIAGNOSIS** and treatment would save 110,000 cancer patients a year in addition to the one out of three who will not die, ACS President George Rosemond and Chairman W. Armin Willig pointed out in the American Cancer Society annual report. "This is a challenge that makes us move into 1975 with renewed energy," they said.

MAJOR PROBLEM: HOW TO GET HIGH RISK GROUPS INTO SCREENING PROGRAMS

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physician. The probability of metastases at time of diagnosis for the most common and lethal cancers: pancreas, 99%; lung, 90%; prostate, 70%; bowel, 60%; breast, 55-75%; cervix, 45-50%; and uterine corpus, 32%.

Given those figures and the fact that surgical or x-ray eradication of localized or regional lymph noded tumors offer the best chances for cure, developing systems for early diagnosis is critical to improvement of survival rates.

Berlin discussed current screening methods and those in development for:

Lung—current, cytology and x-ray; in development, AHH (arylhydrocarbon hydroxylase).

Breast—Physical examination, x-ray, thermography; cytology and ultrasound.

Bowel—rectal examination, sigmoidioscopy, fecal occult blood; cytology (in conjunction with barium enema).

Uterus cervix—cytology; do-it-yourself kits.

Prostate—rectal examination.

Serological and immunological screens in development include:

Hormonal (HCG, pituitary polypeptide B-chains); enzymatic (regan esoenzyme-placental lactic dehydrogenase); protein (alpha fetoprotein); skin tests (DCNB, recall antigens not tumor specific, and tumor associated antigens); T cells and %T cells (low values in cancer patients); cytotoxicity (lymphocyte vs. tumor cells); and migration inhibition (lymphocyte factor inhibits migration).

Even with the ultimate in screening techniques available, the problem of determining what population should be screened, and convincing those persons to undergo the tests, will remain. "We must convince apparently healthy people that they should be screened," Berlin said.

Those who should be screened for the various cancers include—uterine cervix, females over 20 years old; breast, females over 40; lung, male cigarette smokers over 45 and women over 55; bowel, everyone over 50; uterine corpus, females over 50; and bladder, smokers and others over 55.

Robert Fontana, principal investigator for a lung cancer project at Mayo funded by NCI, pointed out that 85% of heavy smokers do not develop lung cancer, and "we need to identify the 15% who do." Mayo is cooperating with Johns Hopkins and Memorial Sloan-Kettering on an NCI project to determine whether a battery of tests—sputum cytology and chest x-ray—applied clinically every four months can significantly reduce death rates.

"Lung cancer can be detected and localized," Fontana said.

The problem is more difficult with cancer of the pancreas, the fourth largest cancer killer in the United States.

William Pomerance, chief of the diagnosis branch who heads a pancreatic cancer project with Mayo, Memorial Sloan-Kettering and Univ. of Chicago as contractors, said "we are starting from scratch" in the study to find high risk groups and identify possible screening tools.

William Go, principal investigator for the project at Mayo, reported that a pancreas scanner, cytology, retrograde pancreatography and ultrasound techniques all hold promise.

Pomerance said that the most encouraging development so far was the determination that tests can find the asymptomatic pancreatic cancer patient.

NORRIS COTTON, NEW NCAB MEMBER, SAYS YOUTH EXPECT CANCER "CURE"

Norris Cotton, who during his years as the senior Republican on the Se nate Appropriations Committee played a key role in securing increased funds for NCI and all biomedical research, was recently named by President Ford to the National Cancer Advisory Board. He replaced Clarke Wescoe, who resigned with three years remaining on his term.

Cotton was asked by NCAB Chairman Jonathan Rhoads to comment on criticism of the cancer program.

"You're ignoring public psychology," Cotton said. "In two months, I'll be 75, and I'm very interested if someone tells me I'll live five more years, or three more years. But young people aren't impressed by five-year survival rates. They live in hope that a big, crashing breakthrough will come, the cure for cancer."

Congress frequently generates false hopes, Cotton said, "although they don't entertain it themselves."

EXCERPTS PUBLISHED FROM PAPERS PRESENTED AT ACS WRITERS SEMINAR

Excerpts from presentations made to science writers at a seminar sponsored by the American Cancer Society appear on the following pages. Some of the material has been previously published, some of it includes preliminary data from ongoing studies.

ACS has a limited number of copies of most of these papers and will send them upon written request, as long as they last. Write to ACS, Alan Davis, vice president—science editor, 219 E. 42nd St., NYC, 10017.

PENETRATION OF MAMMALIAN SOMATIC CELLS BY SPERMATOZOA AND ITS POSSIBLE IMPLICATION IN CANCER — *Ellen Borenfreund, Sloan Kettering*

Incubation of mixtures of mammalian somatic cells with spermatozoa resulted in the penetration of these cells by the sperm. Transfer of nucleic acid from the sperm heads into the nuclei of the target

cells could be observed. Abnormalities which developed in the morphology and growth patterns of the recipient cells resembled changes which occurred when such cells were treated with carcinogens. An additional alteration, suggesting the induction of early stages of malignant transformation, was the appearance of embryonic antigens in these cells, a characteristic which frequently accompanies a state of dedifferentiation and malignant change. We believe that these laboratory findings merit serious considerations in view of the high incidence of prostatic and cervical cancer. Spermatozoa might play a role in such as these.

DNA SYNTHESIS AND THE GENERATION OF DIVERSITY AMONG NORMAL AND ABNORMAL CELLS – ***Howard Holtzer, Univ. of Pennsylvania***

The transition from a normal mammary cell, or a normal colon cell to its neoplastic daughter cells involves further differentiation within the mammary and colon lineages, respectively. This view of tumorgenesis rests on two basic assumptions: (1) the emergence of the neoplastic cell involves the same regulatory mechanisms that are responsible for normal differentiation, and (2) the cell-specific molecules that must be altered to produce and perpetuate the neoplastic mammary cell will be different from those molecules which must be altered to produce and perpetuate the neoplastic colon cell.

CANCER MORTALITY AMONG MORMONS – ***James Enstrom, UCLA***

Preliminary results indicate that the cancer mortality rate of California Mormons is roughly one-half that of the general California population. These results are based on Mormon church records and have been largely confirmed by other data on the predominantly Mormon state of Utah.

Mormons are a conservative religious group and their "word of wisdom" proscribes the use of tobacco, alcohol, coffee, and tea. Deaths are less than expected for all sites of cancer, including many sites not predominantly associated with smoking or drinking. The total cancer mortality rate and total mortality rate for California Mormons as a whole are among the lowest of any substantial United States population group.

CONTROL OF GROWTH OF MAMMALIAN CELLS – ***Robert Holley, Salk Institute***

Recent studies in various laboratories suggest that the growth of normal cells in controlled by polypeptide hormones and other hormone-like materials present in the blood. Certain of these hormones have been identified. Many other, unidentified hormones are probably also involved in the control of growth. Different hormones appear to be active with different types of cells. Combinations of hormones are often more effective than any individual hormone.

Evidence from various laboratories suggests that the polypeptide hormones act at the cell surface membrane. The hormones appear to affect the permeability of the cell membrane and also the intracellular levels of cyclic nucleotides, perhaps by way of the prostaglandins. Changes in intracellular levels of cyclic nucleotides seem to be associated with the initiation of growth of quiescent normal cells.

GENETIC VARIATION IN CARCINOGEN METABOLISM: IMPLICATIONS FOR INDUSTRIAL MEDICINE – ***Charles Shaw, M.D. Anderson***

The fact of genetic variation among animals in susceptibility to chemical carcinogens suggests another approach to the problem of human industrial carcinogenesis. If animals vary in susceptibility, so also may man. Evidence is accumulating that this is true. Why then not attempt to develop tests in human subjects to determine their relative susceptibility to a particular chemical? This would provide the capability for matching the genotype to the job, an altogether new form of genetic screening.

Most of the known chemical carcinogens do undergo metabolism after entering the organism. The several structural forms of the molecule, occurring during the course of its metabolism, vary widely in their carcinogenicity, from zero to very high. The highly active form, called the proximate carcinogen, is thought to bind to the cell DNA and effect some structural modification, perhaps a form of mutation which leads to malignant change. Most of the steps in carcinogen metabolism are under enzymatic control. Certain of these controlling enzymes have been shown to vary within different organisms, including at least one in man. The latter study, from our laboratories, relates the amount of the hydrocarbon metabolizing enzyme, aryl hydrocarbon hydroxylase (AHH) to susceptibility to lung cancer. The AHH is thought to act in conversion of hydrocarbon pollutants to an active carcinogen. Other enzymes which detoxify the active carcinogen would, theoretically, if present in high levels, be protective against malignancy.

The capability for such screening for susceptibility or resistance to chemical carcinogens in man, while not presently available, appears to be within the grasp of our growing technology.

PROGRESS IN THERAPEUTIC RESEARCH – ***Vincent DeVita Jr., NCI***

Several important events have changed the therapeutic climate. (1) The importance of the immunologic system in controlling cancer has been rediscovered. Experimental work suggests, when used by itself, immunotherapy will benefit only patients with a small volume of tumor and here is where it is being applied clinically. (2) Drugs, single or in combination, have become accepted as safe and effective enough for use in patients with early disease and are being used in this fashion. In patients in Group I even greater success in patients with early stages of highly

responsive tumors should be assured with a combination of modalities. In Group II the low volume of tumor cells present post-operatively may make drugs with marginal activity against advanced cancer more impressive. Two important trials in the past several years promise much success for this approach. The results of the use of high dose methotrexate and citrovorum factor rescue and/or adriamycin in osteogenic sarcoma, postoperatively, and the adjuvant treatment of breast cancer with L-PAM and drug combinations (CMF, cytoxan, methotrexate and Fluorouracil) have been dramatic. Ovarian cancer is a leading candidate for such studies and with the recent development of more effective systemic treatment of advanced colon cancer by Moertel at Mayo Clinic adjuvant studies have been initiated in this very common cancer.

The pace is quickening. Recent data from UCLA suggest that immunotherapy is making inroads as an adjuvant treatment in patients with Stage II malignant melanoma and combinations of immunotherapy and chemotherapy have finally changed the survival curves in acute myelocytic leukemia of adults here and abroad. With the addition of Adriamycin and DTIC (an imidazole carboxamide derivative) to the therapeutic armamentarium, tumors previously considered unresponsive to treatment now appear responsive (bladder cancer, other sarcomas, melanoma, heptomas and thyroid cancer) and offer new opportunities to test adjuvant systemic treatment.

Medical treatment with drugs and immunotherapy has an established place in cancer treatment, and they are now taking their place along side of surgery and radiotherapy in the treatment of the cancer patient *at diagnosis.* The combined use of regional and systemic treatment of early disease, based on results in advanced cancer, appears to be the key approach for the next decade.

NEW APPROACHES TO PARENTERAL DRUG ADMINISTRATION – ***Emil Freireich, M.D. Anderson***

The treatment of cancer with drugs (chemotherapy) requires, in addition to the selection of the appropriate drugs and an appropriate dose, an important choice of schedule of drug administration. The drug methotrexate was amongst the first treatments where the enhanced effectiveness of high dose intermittent treatment as compared to low dose continuous treatment, was appreciated. More recently, the introduction of the drug cytosine arabinoside for the treatment of adult acute leukemia has restimulated interest in the problem of schedule of drug administration.

. . . In the Southwest Oncology Group, we studied comparatively two schedules of drug administration: continuous infusion for 48 hours compared to continuous infusion of 120 hours. The theoretical basis for this study derived from studies of patients with normal bone marrow function. When the drug was given by injection, at any dose, there was little depression of bone marrow function. In contrast, if the drug was given by continuous infusion for 48 hours, there was a continuous dose response, that is, with an increase in dose, there was progressively more severe depression of bone marrow function. This was the shortest duration of continuous exposure which had this property and therefore, it (48 hours) was compared to 120 hours. We found that the frequency of complete remission was almost twice as high by the 5 day infusion as it was by the 2 day infusion (38% vs. 20%).

We have just completed a study where the infusion period was prolonged by 10 days of continuous infusion, and found that the complete remission rate was over 50% of patients treated by this schedule (cooperative group study of the Southwest Oncology Group, chairman, James Hewlett of Cleveland Clinic).

Once a patient is in remission, if the treatment is continued on an ambulatory basis, these prolonged periods of infusion require hospitalization in order to technically accomplish such infusions. In addition to the financial cost of such a period of hospitalization, there is the loss of functionally effective time that the patient could have enjoyed otherwise were he not required to be in the hospital for such treatment. Therefore, we have been investigating new approaches to parenteral drug administration which would allow not only precise scheduling, but would also have the advantages of being portable and permitting infusions of long duration.

For these investigations, we are utilizing a new liquid infusion system and evaluating the pharmacology of the drug ara-C utilizing this liquid infusion system. We have been successful in administering continuous infusions of ara–C over 5 day periods on an ambulatory basis in a small number of patients. In addition, we have initiated investigation of unique routes of administration, such as continous subcutaneous administration of drugs.

In addition to the drug cytosine arabinoside, other drugs have their effectiveness and their limiting toxicological effects significantly affected by the schedule of administration. The drug methotrexate has recently come of great interest with the description by Frei and Djerassi of the methotrexate-citrovorum rescue, which requires accurate control of the amount of drug being delivered and the amount of antidote. Recently, bleomycin has been shown to have a better effect when delivered by continuous infusion and the drug fluorouracil has significantly different limiting side effects when given by continuous infusion as opposed to daily injection. . . .

A number of supportive aspects of treatment could be improved by the capability of delivering continuous blood levels of drugs. There are a number of antibiotics where continuous blood levels will give better therapeutic results than intermittent injections. With the drug heparin, which has a short half life, management of complications of cancer, such as the dissemi-

nated intravascular coagulation syndrome, would be potentially better managed by continuous drug administration. Parenteral alimentation or the delivery of sufficient calories and other nutrients, could be improved by this technology. Finally, the control of the hormonal environment for those malignancies responsive to hormonal manipulation is another potential application.

CHEMOTHERAPY BY WAY OF LYSOSOMES – *Christian de Duve, International Institute of Cellular and Molecular Pathology, Brussels, and Rockefeller Univ.*

With a group of Belgian investigators headed by Professor Andre Trouet, I have initiated a new form of chemotherapy, termed "lysosomotropic," which takes advantage of differences in what may be called the "feeding habits" of cells. Clinical trials performed in Belgium and a few other European countries over the last 2½ years have given encouraging results in various kinds of leukemia and some solid tumors.

Most chemotherapeutic drugs enter cells freely. Therefore, when administered to cancer patients, they poison many normal cells in addition to tumor cells. This is the main stubling block in the chemical treatment of cancer. Owing to the indiscriminate effect of the drugs, it is very difficult to eradicate cancer cells completely without causing irreparable harm to the patient.

In order to achieve better selectivity, we attach the drug to a carrier that does not penetrate readily through cell membranes, but can be taken up by the special engulfing process called pinocytosis. Materials taken up by this process are directed towards lysosomes, which are miniature stomachs present in all cells. They are then digested in the lysosomes. When this happens to an appropriately designed carrier drug complex, the carrier is broken down by lysosomal digestion and the drug is released in free form, whereupon it diffuses out of the lysosomes and attacks the cell that took up the complex. What we are doing, therefore, at the cellular level, is to put poison in the food rather than giving it as such.

The main advantage of this new form of therapy is that there are big differences, both quantitative and qualitative, in the pinocytic properties of different cell types. Some cells are "greedier" than others, and will for this reason be more sensitive to poisoned "food." Furthermore, different cells have different tastes, which means that selectivity may possibly be enhanced by appropriate choice of the "food" to be poisoned, i.e. of carrier for the drug.

Nothing is know so far of the preferences of cancer cells, but it is obvious that information on this topic is urgently needed. For once we know of materials that are "eaten" selectively or preferentially by cancer cells, we may have the means of conveying poison to these cells with the same degree of selectivity.

NIPPLE ASPIRATION OF BREAST FLUID IN STUDIES OF THE CYTOLOGY, BIOCHEMISTRY AND EPIDEMIOLOGY OF HUMAN BREAST CANCER – *Nicholas Petrakis, Univ. of California (San Francisco)*

These studies are based on a long known but seemingly forgotten fact that the mature nonlactating breast continuously secretes and reabsorbs fluid from the alveoli and ducts. . . . We have used this technique for cytological screening for early breast cancer and for biochemical, virological, nutritional and epidemiological studies of breast cancer. . . . The following areas of research have been of great interest to us:

Association of race, age, menopausal status and cerumen (earwax) type with breast fluid secretion in nonlactating women; studies of lipid peroxidation of breast secretions–we have developed a working hypothesis that continued exposure of the breast duct epithelium to peroxidated lipids may be a precursor factor in malignant transformation, alone or in combination with secreted chemical carcinogens (or viruses?); and studies of mammary virus markers.

NEW VIEWS ON CONTROL OF THE CELL SURFACE – *Gerald Edelman, Rockefeller Univ.*

The properties of a new system for controlling the motion and distribution of molecules at the cell surface have been revealed. From experiments on its function, we suggest that this system probably consists of an assembly of proteins lying under the cell membrane. These protein structures, called microtubules and microfilaments, form part of the skeleton of the cell and also regulate its movement. There is evidence to suggest that the microtubular portion of this sytem is also involved in committing cells such as lymphycytes to divide. Thus, there are strong grounds for suspecting that a general submembranous structure exists relating cell surface activity, cell motion, and cell division.

STRUCTURE AND DYNAMICS OF MEMBRANE ANTIGENS – *Harden McConnell, Stanford Univ.*

Many investigators in the field of cancer research will agree that one of the fundamental questions is how the immune system responds to abnormal cells. Some of this response is doubtless at the interface between the abnormal cell and various molecular and cellular components of the immune system. Critical questions concerning these interactions are beclouded by a multitude of uncertainties. There are questions such as: What is the structure of a normal cell membrane? What molecular events are involved in the triggering of an immune response? Which of the innumerable differences that must exist between normal cells and tumor cells are significant for the immune system, either for triggering the immune system, or for escaping from immune attack?

Gillian Humphries and I have approached this problem from the combined points of view of an immuno-

logist, and a physical chemist. Our first step has been to prepare model membranes of precisely defined chemical and antigenic composition, in which the lateral mobilities and lateral distributions of the membrane antigens can be measured using various physical techniques. The second step has been to study the interaction of cytotoxic antibodies, and cytotoxic antibodies plus complement, on these model membranes. In this way we have discovered that membrane "fluidity" is significant for this mode of cytotoxic attack on cell membranes. In future work we hope to investigate the interaction of other components of the immune system with model membranes.

At the present time we have no reason to believe that membrane "fluidity" (as measured, for example, by antigen mobility) could not play a significant role in the interaction of abnormal cells with the immune system, and in the possible escape of some cells from cytotoxic attack.

FREEZE-FRACTURE AND ELECTRON MICROSCOPIC STUDIES OF MACROMOLECULAR INTERACTIONS IN MEMBRANE STRUCTURE – ***Daniel Branton, Harvard Univ.***

New methods of electron microscopy using rapidly frozen specimens allow one to visualize structure within biological membranes. This structure is maintained by molecular interactions which appear to be altered in abnormal or cancerous conditions. We have studied membranes such as that of the red blood cell which serve as models in which the molecular basis of normal, structurally important interactions can be investigated by combining electron microscopy and biochemistry.

Normal tissues of our body are composed of cells which interact. When the interactions break down or fail to elicit normal cellular responses, abnormal tissues and cancerous growths may develop. Because these interactions are transmitted by or through the membranes which surround each of the cells in every tissue of our body, we have focussed our attention on those molecular interactions which maintain and stabilize the normal structure and topography of cellular membranes.

While investigating the structure of the common onion root cell, I discovered that biological membranes can be split so that their internal structural organization can be explored with an electron microscope. The technique that produces this remarkable split in biological membranes is known today as freeze-fracturing. In recent years, freeze-fracturing has been used in many laboratories to explore structure in a wide variety of natural and model membranes.

CELL MEMBRANE RECEPTORS AS TRANSDUCERS IN CELLULAR COMMUNICATION – ***Martin Raff, University College London***

All immune responses directly involve antigen binding to the surface of a small number of lymphocytes which have surface receptors that fit the antigen. This interaction stimulates these lymphocytes to divide and make a specific response. In addition a variety of non-specific mitogens, which bind to all lymphocytes, irrespective of the antigen specificity of their receptors, can stimulate a large proportion of lymphocytes to divide. Only in the case of these non-specific mitogens do enough lymphocytes respond to enable one to study the early stages of activation.

Unfortunately, most of these non-specific mitogens bind to a variety of different cell surface proteins, only one of which may be the relevant receptor for the activation of the cell; thus, unlike the mast cell, one cannot study the change in the receptor following ligand binding. On the other hand, following the work of others who have shown that some lymphocytes take up Ca^{2+} soon after mitogen activation, we have developed a reliable and simple method for studying Ca^{2+} uptake by mouse lymphocytes stimulated by the mitogenic plant lectin, Concanavalin A (ConA).

ConA is known to bind to all lymphocytes (and all cells) but only to induce thymus-derived T lymphocytes to divide. We have been able to show that the binding of ConA to T, but not B, mouse lymphocytes opens 'Ca^{2+}-gates' in the surface membrane within 30 seconds, following which the gates rapidly close. In addition, we have found that cyclic AMP inhibits this opening of the 'Ca^{2+}-gates' by ConA while cyclic GMP enhances it. Thus we have a simple method for studying these gated Ca^{2+}-channels and have evidence that they may be regulated by cyclic nucleotides. The relationship between ConA-induced Ca^{2+} influx seen within seconds, and the cell division seen two or three days later is still unclear.

CHOLERA TOXIN, MEMBRANE GLYCOLIPIDS, ADENYLATE CYCLASE AND HORMONE RECEPTORS – ***Pedro Cuatrecasas, Johns Hopkins***

The protein which is produced by certain bacteria, and which is responsible for the diarrhea of clinical cholera, has proven to be a very useful tool for probing special hormone-like effects in numerous cells. This toxin ubiquitously stimulates adenylate cyclase by first interacting with very specialized glycolipids (gangliosides) on the surface of the cell. The detailed mechanisms give important insights into the normal mechanisms by which natural hormones may modify cell functions. Transformed or cancerous cells which have deficiencies in surface glycolipids have decreased quantities of receptors as well as impaired responses to the toxin. . . .

These studies may have important implications in our understanding of the normal mechanisms by which a variety of physiological hormones (e.g., adrenal stimulating hormones, glucagon, insulin, various gastric hormones and protaglandins) stimulate adenylate cyclase. In addition, the toxin is a useful tool for measuring and probing the content and dynamics of certain glycolipids in normal as well as malignant

cells. Furthermore, because this protein can stimulate ubipquitously adenylate cyclase, and thus increase the levels of cyclic AMP, it may help our understanding of the role that this cyclic nucleotide may have in governing cell growth and differentiation.

THE CONDUCTOR OF THE IMMUNOLOGICAL ORCHESTRA – ***Richard Gershon, Yale***

Most, if not all, tumor cells have sufficiently altered membranes to be recognized as foreign material by the lymphoid cells of the host in which the tumors arise. Under ordinary circumstances, such recognition by the lymphocytes would lead to rejection of the foreign material. Clearly, this rejection mechanism fails in cases of clinical cancer. Our research is directed toward determining why.

We have discovered a subpopulation of thymus processed lymphocytes whose function is to turn off the immune response. These cells which have been called suppressor T cells are responsible for most forms of immunoregulation and evidence is accumulating that they are responsible for self-tolerance; they teach the body not to reject itself. Tumor cells are particularly good activators of these cells for several reasons. One which we find most intriguing is that tumor cells share membrane properties with fetal cells. It is in the fetal period that suppressor T cells are most active.

A good deal of our work has been concerned with how the suppressor T cell interacts with other subpopulations of immunologically competent cells. These multiple interactions can best be summarized by likening the interactions between the various components of the system to that of an orchestra. Using this metaphor one can consider the precursor of the suppressor T cell as the conductor of the immunological orchestra in that it calls the immunological tune.

IMMUNOTHERAPY OF HUMAN CANCER: RECENT ADVANCES IN THE MANAGEMENT OF HUMAN MELANOMA, LEUKEMIA, AND CANCER OF THE LARGE BOWEL – ***Giora Mavligit, M.D. Anderson***

Immunotherapy has been recently introduced as an additive therapeutic tool for human cancer, mainly in conjunction with the more conventional therapeutic modalities such as surgery, radiotherapy, and chemotherapy. . . . A great deal of experience with immunotherapy has been accumulated at M.D. Anderson Hospital of the Univ. of Texas System Cancer Center during the past three and one-half years. Starting with a group of melanoma patients who had regionally advanced cancer in lymph glands draining the site of the primary melanoma, we were able to demonstrate a prolongation of survival by using BCG immunotherapy following surgical resection of the involved lymph glands compared to patients who had surgery alone for this condition. Unfortunately, if the melanoma was primarily located in the head or neck areas, BCG was ineffective. It was effective if the tumor was primarily located on the trunk or on one of the extremities.

By extending the use of BCG to the management of patients with adult acute leukemia we were able to achieve a prolongation in the duration of remission among these patients. These patients were first treated with massive chemotherapy intended to reduce the tumor burden to a minimum and to achieve a complete clinical remission. At this point, remission is usually maintained and supported by periodic administration of chemotherapy which will suppress any regrowth of the leukemic process. The addition of BCG to this maintenance chemotherapy appears to confer an additional protective effect, against the neoplastic process, which is manifest by the prolongation in the duration of remission as compared to patients whose remission is maintained by chemotherapy alone. . . .

With the encouraging preliminary results in melanoma and acute leukemia, we decided to employ BCG immunotherapy in a more commonly diagnosed neoplastic disease, cancer of the large bowel. In this clinical experiment a special group of patients was selected according to the degree of tumor penetration and invasion through the bowel wall as found at the time of primary surgery. This particular group with cancer of the large bowel had tumor invasion of the regional lymph glands draining the primary tumor site. Although surgical resection in this condition is potentially curative, the overall prognosis is rather poor and the need for additional therapy cannot be overemphasized in order to prevent tumor recurrence or prolong survival. In such an attempt, we gave BCG immunotherapy either alone or in combination with chemotherapy. The results are still preliminary and final conclusions cannot be drawn yet. However, there is already a strong indication that following surgical resection of the tumor, immunotherapy with BCG alone and even more so when it is combined with chemotherapy, has a protective effect against tumor recurrence in this group of patients as compared to patients who had surgery alone for this condition. If these preliminary results will continue to hold on as expected, they would provide, in addition to the improved prognosis among certain patients with cancer of the large bowel, a further support for a wider utilization of immunotherapy in other patients with commonly occurring neoplasia.

PREMALIGNANT CHANGES IN THE METABOLISM OF CORTISOL – ***Charles Nabors Jr., Univ. of Utah***

Studies in our laboratory have shown that the metabolism of cortisol in peripheral tissue of dogs is altered prior to the onset of any clinically detectable malignancy in animals bearing carcinogenic doses of radiation. The radiation produces bone cancers in these animals. Cortisol metabolism is increased both in skin and in the osteogenic sarcoma. Skin is, of

course, distant from the primary tumors. However, osteosarcomas in bone have been shown to contain C type viruses which may be the agent that propagates metabolic changes in skin. These data suggest the possibility that the onset of a malignancy may be detected at a time when it can be more effectively treated.

SARCOMA OF SOFT TISSUE: SUCCESS WITH A NON-ABLATIVE APPROACH – *Herman Suit, Harvard*

Definitive treatment of 200 patients with sarcoma of soft tissue sarcoma at MDAH by precision and high dose radiation therapy, usually combined with limited surgery, has demonstrated that a very high success rate in destroying the primary tumor *and* retaining near normal function of the affected part can be achieved by this non-ablative approach.

This is illustrated by these data: 89 patients with sarcoma on an extremity who have been followed for 2-12 years following this type of treatment 12 or 13% have had regrowths of the primary tumor. All 89 patients had had amputation recommended as the surgical procedure of choice. By use of modern and sophisticated radiation therapy techniques, about 75% of such patients retain normal or near normal function of the affected limb.

Our results have been better than are generally reckoned likely for this group of tumors because: 1) tumors accepted for treatment are small or moderate size; 2) simple surgery removes the bulk of tumor; 3) the amount of tumor tissue which must be destroyed by the radiation is small; 4) radiation dose is high; 5) full use of modern techniques and equipment of radiation therapy; 6) treatment portals are designed so that the distribution of radiation dose conforms to the known and likely distribution of tumor cells *viz* an intensive effort is made to exclude from the treatment volume normal tissues.

Additional papers presented at the American Cancer Society science writers seminar will be excerpted in future issues of ***The Cancer Letter.***

SOLE SOURCE NEGOTIATIONS

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

Title: Breast Cancer Detection Demonstration Project
Contractor: University City Science Center, Philadelphia.

Title: Biomedical computing software services in support of the clinical and diagnostic trials program
Contractor: EG&G/Mason Research Institute

Title: Standardization of aryl hydrocarbon hydroxylase assay as a screening method to determine smoking hazards in man
Contractor: Microbiological Associates.

Title: Metabolic studies on tobacco smoke constituent
Contractor: Huntingdon Research Center, Brooklandville, Md.

Title: Continuation of pharmacology study of antileukemic and other anti-cancer drugs
Contractor: Southern Research Institute.

Title: Continuation of programming services in support of the contract management system
Contractor: Sigma Data Computing Corp., Bethesda, Md.

Title: Housing and maintenance of a chimpanzee breeding colony
Contractor: Southwest Foundation for Research & Education.

Title: Immunological studies on the relationship of embryonic antigens to virus-induced tumor antigens
Contractor: Univ. of Tennessee.

Title: Preparation and purification of viral components
Contractor: Pfizer, Inc.

CONTRACT AWARDS

Title: Continuation of metabolism of antineoplastic agents study
Contractor: Stanford Research Institute, $93,923.

Title: Planning for a cervical cancer screening program
Contractor: Hawaii Dept. of Health, $50,000.

Title: Cancer public information publication
Contractor: Information Services, Inc., Bethesda, Md., $64,200.

Title: Chemical carcinogenesis and immunology
Contractors: Ohio State Univ. Research Foundation, $187,833; NYC Public Health Research Institute, $72,940.

Title: Therapy of patients with gastric carcinoma
Contractors: Children's Cancer Research Foundation, Boston, $105,390; New York State Dept. of Health & Health Research, Inc., $103,962; Mayo Foundation, $100,550; Mt. Sinai School of Medicine, NYC, $150,782; Univ. of Southern California, $143,500, and Yale Univ., $102,200.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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