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MSK INVESTIGATORS REPORT SIALIC ACID TEST 95% ACCURATE; NEGATIVE IMMUNOTHERAPY RESULTS TOLD

The lipid bound sialic acid test is 95 percent accurate in distinguishing cancer patients with a wide variety of malignancies from normal

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In Brief

HOUSE, SENATE AUTHORIZATION MEASURES WAITING FLOOR ACTION; MONEY BILL MARKUPS PENDING

KEY LEGISLATION is still on hold in Congress, but action could come soon on authorization bills renewing the National Cancer Act. Sen. Kennedy's S. 988 is ready to go to the floor but is not yet on the calendar. H.R. 7036, Congressman Waxman's bill, is waiting for clearance by the Rules Committee before it can go to the House floor. Neither the House nor Senate HHS Appropriations Subcommittees have scheduled markups on their bills. . . . **EDWARD SCOLNICK**, chief of the Laboratory of Tumor Virus Genetics in NCI's Div. of Cancer Cause & Prevention, has received the 1980 Eli Lilly Award for sustained high quality research in microbiology and immunology. . . . **FOURTH ANNUAL** Cancer Symposium sponsored by Scripps Memorial Hospital Cancer Center is scheduled for Oct. 27-29 in San Diego. The program will include sessions on breast cancer, urologic cancer, management of the cancer patient, controversies in lymphoma, and lung cancer, plus updates on a variety of other malignancies. Contact Nomi Feldman, Cancer Symposium Coordinator, 2321 Morena Blvd., San Diego 92110, phone 714-275-0650. . . . **THIRD INTERNATIONAL** Conference on the Adjuvant Therapy of Cancer will be held in Tucson March 18-21, 1981. It is sponsored by the Cancer Center Div. of the Univ. of Arizona, with Sydney Salmon and Stephen Jones as cochairmen. Abstract forms are now available; the deadline for their submission (prepared in the AACR/ASCO format) is Nov. 1. Contact Mary Humphrey, Conference Coordinator, Cancer Center Div., Univ. of Arizona, Tucson 85724. . . . **SUBCELLULAR METHODOLOGY** Forum on cancer organelles will be held Aug. 27-30 in Guildford, UK. Sponsored by NCI and the Univ. of Surrey, the forum will emphasize molecular and biochemical approaches to isolation and characterization of membrane and organelle fractions from solid tumors and tumor cell lines. Abstracts will be accepted to Aug. 1. Send to D. James Morré, Purdue Cancer Center, Lafayette, Ind. 47907. . . . **AACI HANDBOOK** on organization and management of cancer centers is available at $10 per copy from H.D. Putney, Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia 19111. Three new sections have been added, on capital plant and moveable equipment, management information, and fundamentals of fund raising and evaluation of its costs. For those who already have the handbook, the new sections are available for $3.

BLOOD TEST FOR CANCER TO RECEIVE LARGE SCALE EVALUATION WITHIN YEAR

(Continued from page 1)

controls, Memorial Sloan-Kettering Cancer Center scientists reported at the American Assn. for Cancer Research annual meeting last month.

The inexpensive blood test will be made available to investigators for large scale evaluation within a year. It will be tested on additional cancer patients, on persons who have positive results on the hemoccult test, and on high risk populations such as workers exposed to carcinogens and persons with familial polyposis.

C. Chester Stock, MSK vice president; Yashar Hirshaut, associate attending physician at Memorial Hospital, and biochemist Nonda Katopodis participated in the study. Katopodis presented the data at the AACR meeting.

In tests of more than 1,000 samples of whole blood, plasma, and frozen blood serum from cancer patients and healthy individuals over the past three years, Katopodis said, virtually all the cancer patients had sialic acid levels higher than those of the controls.

Tests of frozen blood sera of 400 cancer patients and normal controls found that levels of total lipid bound sialic acid was greater than 20 mg/100 ml for the patients; normal controls had levels below 20 mg, with a few exceptions. The test proved to be about 90 percent accurate in this group of samples.

When the test was performed on 250 fresh plasma samples instead of frozen blood sera, accuracy was increased to about 95 percent, Katopodis said. Sialic acid levels are rarely elevated above 20 mg/100 ml in patients with other types of medical conditions, with the exception of some patients with chronic heart congestion.

"Though additional studies must be performed before we know if the lipid bound sialic acid test can detect the presence of cancer in its earliest stages, so far it appears to be one of the more promising tests that I have seen in many years," Stock commented.

The test requires so little blood that the sample can be taken from the finger. Results can be obtained within hours, and the test involves no special equipment beyond what is standard in most clinical biochemistry laboratories.

The sialic acid test for cancer is an outgrowth of earlier work by Sloan-Kettering researchers, including Marion Barclay, who noted in the early 1960s that cancer patients had smaller amounts of a fraction of lipoproteins (HDL_2) in their blood than did healthy persons, and Vladimir Skipski, who found in 1966 that some of these HDL_2) lipoproteins from cancer patients contained a complex of carbohydrates, proteins and lipids not found in healthy individuals. He found the same difference when he looked at extracts made from cancers and normal tissues from laboratory animals.

In 1975 Skipski showed that lipid-bound sialic acid compounds were present in higher than normal quantities in the blood of rats with hepatoma than in the blood of healthy animals. He and Ann Dnistrian also demonstrated that these compounds are more abundant in the cell membrane of malignant hepatic cells than in the membrane of normal liver cells. This suggests that cancer cells liberate lipid-bound sialic acid compounds into the blood.

Studies in mice by Stock and Katopodis have supported this finding. When they implanted malignant tumors into normal healthy mice, the blood levels of lipid-bound sialic acid in the mice rose significantly within one day.

In addition to its potential future use as a screening device, the lipid-bound sialic acid test could be used to monitor the effectiveness of cancer treatments and adjuvant or maintenance chemotheray, the investigators suggested.

Not all reports at the ASCO/AACR meetings were positive: Immunotherapy was found ineffective in one study, and levamisole treatment in another was blamed for an increase in tumor recurrence.

Robert Cooper, reporting on a Cancer & Leukemia Group B study, said the test was designed to determine if remission rates for a specific category of patients with Hodgkin's disease could be prolonged with immunotherapy using MER/BCG.

"The category consisted of those patients who initially had advanced Hodgkin's disease but who had little remaining evidence of their cancer following six months of therapy to induce a remission and two years of therapy to maintain a remission. This category of patients was thought to be the one most likely to benefit from immunotherapy," Cooper reported.

The clinical study using MER/BCG refutes the original idea of prolonging remission. No effectiveness of MER/BCG could be measured when administered by the techniques of this study, Cooper said.

The study also showed:

1. That immunotherapy with MER/BCG is characterized by significant side effects, while patient and/or physician compliance is difficult.
2. That the factors which are significant in predicting whether the remission period for the immunotherapy patients will be prolonged consist of a patient's age, whether the patient has had prior radiation therapy and whether the patient has had prior exposure to chemotherapy.

A significantly better prognosis was found among patients less than 50 years of age and among those with prior radiation therapy than among those older than 50 and those who received no prior radiation therapy. The study also showed that an immunotherapy patient's prior exposure to chemotherapy re-

sulted in a significantly poorer prognosis.

3. That the frequency of relapse in patients with advanced Hodgkin's (stage 3 and 4) who were treated with chemotherapy is extremely low five years following the start of their chemotherapy. And the frequency of relapse approaches zero after seven and one-half years.

The levamisole study was conducted by Peter Wright, Lucius Hill, Arthur Peterson, Charles Bagley, Lloyd Johnson and Edward Morgan at Fred Hutchinson Cancer Research Center, Mason Clinic, Swedish Hospital Medical Center and Univ. of Washington Hospitals.

"The purpose of our report is to emphasize an unexpected finding that became evident in the course of our prospective, double blind, randomized trial to evaluate the effects of levamisole given in combination with intrapleural BCG in patients with fully resected, non small cell lung cancer. Treatment with levamisole has led to immunosuppression and an unanticipated increase in tumor recurrence rates in patients receiving intrapleural BCG plus levamisole, as compared to intrapleural BCG alone.

"Levamisole was used in this study in combination with intrapleural BCG because earlier studies had suggested that both intrapleural BCG and levamisole had potential antitumor activity in lung cancer patients when each was used as a single agent. Moreover, since each agent was thought to have an independent mechanism of action, i.e., BCG to limit local tumor growth in the lung and levamisole to limit the spread of distant tumor metastases, we anticipated that the effect of intrapleural BCG and levamisole used together could be additive, or possibly synergistic. This study was of potential importance because earlier studies indicating possible efficacy of levamisole or intrapleural BCG in lung cancer had not yet been confirmed at the time our study was initiated. Moreover, although chemotherapeutic agents have been used with great advantage in combination, there was no evidence prior to this study that two immunotherapeutic drugs could be used successfully in combination.

"Thus, there were two principal objectives addressed by our study: the first was whether we could confirm the earlier reports of McKneally suggesting benefit from treatment with intrapleural BCG alone; the second was whether we could demonstrate an improvement in the effect of intrapleural BCG alone by the addition of levamisole.

"These two objectives have only been partly realized. With regard to the first objective, our results have shown a substantial trend favoring patients receiving intrapleural BCG alone as compared to patients who received placebo.

"We have observed a 44 percent reduction in recurrence rate and a 48 percent decrease in mortality in patients receiving intrapleural BCG alone as compared to patients receiving placebo. These differences suggest ultimate treatment effects of substantial magnitude.

"It should be emphasized, however, that these differences have not yet achieved the usually accepted degree of statistical significance with p values of approximately .10.

"With regard to the second objective, an unexpected result has been observed. Patients receiving the combination of intrapleural BCG and levamisole have shown a 19 percent increase in recurrence rate and a 27 percent increase in mortality when compared to patients receiving placebo. These differences from placebo are not large and statistical tests do not indicate that they differ significantly from the results observed in patients who received placebo alone. Nevertheless, these results indicate dramatic differences in recurrence rates and mortality among patients who received BCG depending upon whether or not the patients were also given levamisole.

"The explanation for this effect of levamisole is not fully understood at the present time. One possibility is suggested from additional findings which indicate that treatment with levamisole has resulted in suppression, rather than an increase in the host immune response to intrapleural BCG vaccination. It should be emphasized that an important rationale in the initial design of our study for the use of levamisole in combination with intrapleural BCG was the anticipation that levamisole as an immunorestorative agent might increase the host response to intrapleural BCG, as well as manifest systemic antitumor activity itself.

"Using the PPD skin test as an indicator of the patients' immune response to BCG, our results indicate that conversion of the patients' PPD skin test from negative to positive after treatment with intrapleural BCG was substantially reduced in patients receiving levamisole in combination with intrapleural BCG as compared to BCG alone. Since PPD conversion has been correlated with a favorable outcome in our study in patients given intrapleural BCG, the suppression of PPD conversion by levamisole may thus limit the potential antitumor effects of BCG.

"It is also possible that the effect of levamisole observed in our study may be independent of its influence on the host immune response to BCG or related to a nonimmunological mechanism, but we have no direct evidence to support these possibilities. No significant increase in noncancer related mortality could be ascribed to the administration of levamisole.

"These results, although unexpected, nevertheless indicate that treatment of lung cancer patients with levamisole and BCG has had definite immunological and clinical consequences. The consequences have been to suppress (rather than enhance) the patients' immune response, and to possibly increase (rather than decrease) tumor recurrences after surgery, as

was originally hoped. These results indicate that treatment with the combination of intrapleural BCG and levamisole will be of no benefit in the treatment of lung cancer following surgery. They suggest the possibility, nevertheless, that the combination of levamisole and BCG could conceivably be used with some benefit for other diseases, such as autoimmune or inflammatory diseases."

FISHER: CHANGING CONCEPTS OF BREAST CANCER, A HETEROGENEOUS DISEASE

"That an hypothesis is reasonable is not sufficient to allow for its acceptance. The fact that it does not coincide with preconceived opinions is not justification for its rejection."

Bernard Fisher's Karnofsky Lecture at the American Society of Clinical Oncology meeting was a stirring summary of the research in which he has participated, from the laboratory to the clinic, which is having a profound effect not only in the treatment of breast cancer but also in the scientific perception of the disease.

Although Fisher has made countless presentations on the National Surgical Adjuvant Breast Project clinical trials, his Karnofsky Lecture further refined his analysis of information which is continuing to flow from those studies:

* **Heterogeneity of breast cancer.** "Information from NSABP trials indicates that there are a number of significant variables which affect the prognosis of patients with primary disease. Tumors possess differing histopathologic characteristics which relate to patient outcome. Infiltrating duct carcinomas with no recognizable special type of histologic structure have the poorest prognostis while mucinous or colloid cancers are associated with a good prognosis. . . . The degree of axillary lymph node involvement influences prognosis. We were the first to demonstrate that greater incidence of recurrence accompanies increased number of positive axillary nodes. A sharp rise occurs when four nodes are involved. This led to grouping patients with positive axillary nodes into those with 1-3 or 4 or more. Our findings indicate that differences in age influence patient outcome; women 49 and less have significantly worse prognosis than those 50 or more whether considered overall or relative to degree of nodal involvement. . . . We have concluded that age, nodal status and pathologic characteristics variably affect prognosis, indicating the heterogeneity of the disease.

". . . Currently accumulating information [indicates] that not only is there heterogeneity between tumors, but that individual tumors are comprised of a heterogeneous population of cells which express their differences in unnumerable ways. . . .

"Results from three sequentially carried out clinical trials by NSABP support the concept that just as there is heterogeneity between and within primary tumors, so are metastatic micro-foci dissimilar and that their response to therapy is disparate. There was a significant increase in disease free survival in all patients 49 and less. The improvement noted was greater in those with 1-3 positive axillary nodes than in those with four or more positive nodes. In both groups, however, it was essentially unrelated to the number of therapeutic agents employed. In those with four or more positive nodes the two drug combination was slightly superior to the one or three drug regimens.

"An improvement in disease free survival occurred in women 50 years of age or more when two drugs were employed. This was due to the significant benefit observed in those with positive nodes. Patients with 1-3 positive nodes failed to demonstrate a benefit whether one, two or three drugs were employed. A significant but similar improvement in survival was observed in those 49 and under when any drug regimen was employed. In neither nodal category was survival significantly improved by two or three drugs. There is to date a striking improvement in survival in patients 50 and over with four or more positive nodes. The results are similar whether two or three drugs were used."

* **Current concepts providing the basis for adjuvant chemotherapy.** "Those concepts contend that the greater the amount of tumor present in a host the more drug is required to produce a favorable response, and that failure to cure may be due to excessive tumor burden. It is also considered that anticancer agents should be increasingly more effective the earlier the disease when there are fewer cells with a higher growth fraction, fewer biochemically resistant cell lines and better drug penetration. Current hypotheses also relate cell kill to first order kinetics, i.e., that a constant percentage of the total tumor cell population, irrespective of population size, is killed by a given effective dose. Those concepts, as well as pharmacodynamics, have been used as arguments to explain why tumor cells escape destruction by chemotherapeutic agents.

"The finding that increasing therapy from one to two drugs in patients 50 and over resulted in improved survival for those with a putatively larger tumor burden (four or more positive axillary nodes) whereas those with a presumably smaller one (1-4 positive nodes) were unaffected, challenges the concept that chemotherapy is more effective when there is less tumor present to be eliminated. It is generally accepted that there is a correlation between degree of nodal involvement and total body burden of tumor and that 1-3 positive nodes indicate an earlier stage of the disease in which there is less residual metastatic tumor. It is assumed that if a primary tumor is present for additional time there will result a greater number of positive nodes as well as increased metastases.

"Our contention has been that subsets of patients with negative, 1-3 positive, or four or more positive nodes have tumors with different biological and/or host characteristics which account for the degree of nodal involvement. The divergent response to chemotherapy in the two postmenopausal nodal groups is more likely due to the differences in the tumors comprising the two groups than to tumor burden. That finding is also disconcerting when considered in light of the current hypothesis relating cell kill to first order kinetics. Based upon that concept it might have been anticipated that the women whose tumors were associated with 1-3 positive nodes would have demonstrated better results from their treatment than those with four or more positive nodes. Since the finding is the opposite of that anticipated, it is highly likely that the disparate results in the subsets are due to the fact that the tumors are biologically different...

"In view of these results, one cannot readily predict what the effect of chemotherapy in negative node patients might be. Perhaps it may be more difficult to achieve a salutory effect from chemotherapy in such patients than in those with more aggressive tumors."

*** Value of adjuvant chemotherapy for postmenopausal patients.** "The observation that patients 49 and under with 1-3 positive nodes responded to L-PAM while identically selected patients 50 and over with the same nodal status, and presumably the same tumor burden, were unaffected by one, two or three drugs is likewise difficult to explain utilizing current concepts. To ascribe such findings to the difference in menopausal status and to an alteration of the hormonal milieu induced by chemotherapy in those women who are younger possesses logic. Unfortunately, that simple explanation does not suffice in view of the response by the subset of postmenopausal patients with four or more positive nodes.

"The finding that this subset responded significantly to two drug chemotherapy, even better than did those 49 and under with four or more positive nodes, eliminates the popular belief that adjuvant chemotherapy is beneficial only in premenopausal women.

"Once again it would seem that the difference in response to chemotherapy by the two 1-3 positive nodal groups is more likely due to the fact that the tumors, in women comprising the two subsets, are biologically different.

"Our findings support the thesis that metastatic cellular heterogeneity is an important factor to be considered when assessing therapeutic response and that current concepts which presently govern the use of chemotherapy should be reappraised in light of our observations.

"Preliminary results obtained from another NSABP protocol in which tamoxifen was employed further emphasizes the heterogeneity of breast cancer, and that therapeutic responses may be influenced by biological differences. In that study involving 2,000 patients, two findings have been obtained to date which are particularly relevant to this discussion. One observation clearly demonstrates that the distribution of quantitative ER values is different in tumors from patients 49 and under and those 50 and over. In the older age group, 39 percent of tumors have ER values greater than 50 fmol/mg protein while in the younger age group only 16 percent have similar quantitative values. Secondly, it would seem that tumor heterogeneity relative to quantitative ER receptor status may be correlated with therapeutic response."

*** Chemotherapeutic resistant cells.** "The failure of all populations to respond uniformly to any of the regimens of therapy cannot be viewed negatively. That finding may be considered an important contribution of our studies. We now assess the use of adjuvant therapy from a different perspective. The results suggest that a chemotherapeutic agent, or a combination of agents, can be used as a probe to identify subpopulations of patients whose metastases have cells with common or differing biological properties. A probe which fails to demonstrate an effect indicates that in the metastases being treated there were insufficient cells possessing sensitivity to the particular agent and that it was, thus, an inappropriate choice. A favorable alteration in treatment failure by a therapy probe indicates that a sufficient number of the heterogeneous cells within certain tumors were sensitive for some defined, or yet to be defined reason. If, however, micrometastases are comprised of cells with divergent characteristics, it is highly likely that the use of systemic therapy, unless effective in completely destroying all tumor cells may be removing sensitive populations, modify metastases so that their characteristics and growth are different from what they were prior to the use of the therapy.

"Prolonged continuous use of chemotherapy might permit nonsusceptible populations to grow unrestricted. Those cells may self replicate or produce dissimilar resistant clones. It has been considered that drug resistance is a pharmacologic phenomenon. In our opinion, lack of complete response to therapy is due to the dominance of nonsensitive cells; not cells which became chemotherapeutic resistant, but cells which were never sensitive to the chemotherapeutic agent to begin with.

"Building upon findings in an orderly, sequential fashion provides the best opportunity to define the degree and type of therapy required for a particular subset of patients. The addition of one appropriate agent may be sufficient to eradicate metastases in a particular subset. It then becomes unnecessary to administer to that subset the additional therapy required for eradication of other subsets. . . . There then becomes a rationality to the seemingly irrational

use of chemotherapy regimens in the myriads of clinical trials being carried out around the world—most of which are concerned with hitting the home run but are only too apt to leave men stranded on base."

HELLMAN: MANIPULATING THERAPEUTIC INDEX USING MAN, MOUSE, MACHINE

Samuel Hellman, like Bernard Fisher, is one of the world's premier investigators in the therapy of breast cancer. The director of the Joint Center for Radiation Therapy at Harvard, Hellman presented the Rosenthal Lecture at the American Assn. for Cancer Research, "Improving the Therapeutic Index in Cancer Treatment."

Hellman's study in which certain categories of patients are treated with a combination of breast conserving surgery (limited to tumor removal) and radiation for local control now has median survival at more than five years. There is no difference in survival compared to conventional surgery.

"In the use of radiation in the treatment of this disease," Hellman said, "while we are primarily concerned with increasing curability, we are also concerned with decreasing morbidity—that is, separating the complication curve from the cure curve. One complication or undesired constant accompaniment of mastectomy is the cosmetic deformity produced by loss of the breast. . . .

"Thus far these techniques have similar cure rates to those of surgery, with preservation of structure and function. Careful beam definition is used to treat the tumor bearing volume. With careful understanding of the anatomic spread to regional nodes one can fashion a radiation plan which treats these areas and the breast, yet irradiates as small as possible a volume of normal tissue. Following this, temporary local implantation of radioactive material is performed because of its characteristic of permitting high local doses with much lower surrounding doses. This allows a much more effective tumor dose while sparing the normal tissues.

"Close cooperation between surgeon and radiation therapist is required to remove the gross tumor without distorting the breast. This allows a more moderate dose of radiation to be effective. Radiobiology and clinical radiotherapy have indicated that microscopic tumor may be controlled with lower doses of radiation than gross tumor both because of numerical as well as physiologic differences between the cells in the two circumstances.

"A moderate dose of external radiation therapy is given to the tumor bed and draining nodes following gross tumor removal and sampling of the axillary lymph nodes. This latter is done not so much for radiation treatment but to indicate which patients might be candidates for adjuvant chemotherapy.

"Following the external beam radiation, a temporary interstitial implant is placed into the tumor bed. As this treatment technique is an evolving one, we have had the opportunity to study the effects of variations in the radiation dose, use of the implant and whether the tumor has been excised on both local control and cosmetic results.

"Implantation has markedly improved local control in stages 1 and 2. There has been only one local failure in the 73 patients treated in this fasion. These results (and survival) are quite comparable to those with conventional surgery."

Hellman said local control data for stages 2 and 3 breast cancer with and without gross tumor removal "confirm the value of this type of limited surgery. . . . It also has allowed higher likelihood of control at the highest doses since without tumor removal even at these doses some larger tumors are not controlled.

"We have been impressed that not only has adjuvant therapy improved relapse free survival but it has also benefitted local control in patients with advanced disease." Analysis of Hellman's stage 3 patients receiving chemotherapy as compared to patients not so treated showed the combination of radiation and chemotherapy allows improvement in survival without significant increase in toxicity, since there is little overlapping toxicity, he said.

The results of the breast conserving procedures "may offer little if any advantage in survival over conventional surgery, but they offer a great advantage in cosmetic and functional results," Hellman said. "Survival in breast cancer, while it may somewhat depend on local control, is largely influenced by whether or not the patient has an occult micrometastases when first seen. No local therapy can affect this, but there is hope from new studies using adjuvant chemotherapy and/or hormonal therapy that survival may also be significantly improved. Hopefully, the use of limited surgery, radiation therapy with both external beam and interstitial radiation and, finally, adjuvant chemotherapy when indicated with achieve the dual goals of increased patient survival with preservation of function and structure."

Hellman opened the lecture by commenting that "clinical research, in my opinion, must be considered in the broadest of terms. Obviously, it includes research projects with humans or human material as the subject. I believe it should also include research suggested by clinical observations, even if the experiments themselves are performed in animals, on cells, or in test tubes. Clinical research is a vantage point: an orientation, a way of looking at problems. One brings clinical observations to the laboratory and laboratory implications to the clinic when they appear pertinent."

Improving the treatment of cancer "may require understanding the basic biology of normal tissues, understanding their alteration due to the disease or due to treatment, developing new therapies or improving old ones," Hellman said. "Goodman and

Gilman, in the *Pharmacologic Basis of Therapeutics*, describe the relationship between desired and undesired effects of therapy as the therapeutic index. In most circumstances, the therapeutic index between unacceptable damage to normal tissues and successful cure is small. Nowhere is this more so than in the treatment of malignant disease."

Hellman said the clinical research by his colleagues and himself pertinent to breast cancer has been performed "in man, mouse, machine, marrow and molecule attempting to manipulate this therapeutic index" to either increase the cure for some accepted level of complication or decrease the complications for some accepted level of cure.

Hellman noted that colleagues participating in his studies included William Bloomer, Glen Tonnesen, Ralph Weichselbaum, James Adelstein, Leslie Botnick and Eileen Hannon.

NCI CONTRACT AWARDS

Title: Characterization of HLA antigens of donors lymphocytes by sterotyping and cellular typing
Contractor: The Blood Center of Southeastern Wisconsin, $290,929.

Title: Phase I study of effect of immune stimulants on human immune response
Contractor: Sloan-Kettering Institute for Cancer Research, $115,000.

Title: Provision of animal facilities and conduct of tests and studies in support of viral cancer research, four month extension
Contractor: Litton Bionetics, $48,000.

Title: Cancer information clearinghouse and allied services
Contractor: CSR Inc., Washington D.C., $1,003,197.

NCAB IMPRESSED BY FCRC; NIH TAKEOVER WILL NOT OCCUR FOR YEARS, IF EVER

Members of the National Cancer Advisory Board last month were left with a somewhat uncomfortable feeling by what some perceived as a move by NIH to take over the superb facilities developed for the Cancer Program at Frederick Cancer Research Center. Their discomfort was brought on by the statement presented to them by NCI Acting Director Vincent DeVita which said that the long term NIH-NCI objective for FCRC "is to gradually transform the facility from a contractor to a federal operation (***The Cancer Letter***, May 23)."

The Board then spent a day at the center, touring the labs and production facilities and listening to presentations by Michael Hanna, director of FCRC for the contractor, Litton Bionetics, and his staff. Board members seemed to be impressed by the quality of the work, qualifications of the scientists, and importance of the research and resources production to NCI and the Cancer Program.

A Board subcommittee will consider the various options DeVita offered as possible directions which could be taken when the present contract with Litton Bionetics expires in September 1982. DeVita would like to have the general shape of FCRC's 1982-87 operation outlined by fall so that RFPs can be ready for release by mid-1981.

During and after the tour of FCRC, Board members and others felt that questions relating to the NIH proposals needed answering:

* Why should a first rate operation, which seems to have overcome administrative problems encountered earlier and which is contributing significantly to the Cancer Program, be phased out to make room for expansion of NIH intramural labs?

* Even if FCRC remains largely a contractor run facility, would a sizeable growth in NIH intramural staff there change the "chemistry" of the operation?

* Has the decision been made that the Cancer Program no longer needs the research and resources produced at FCRC and that the facilities there can be better used by the National Institute of General Medical Sciences, National Institute of Dental Research, etc.? If so, by whom? Should not such a decision be made only after consultation with the NCAB, President's Cancer Panel, and perhaps others?

Although NIH Director Donald Fredrickson and other NIH executives may consider FCRC as the eventual answer to their space problems and would make it into "NIH North" if they could, that will not happen for a long time, if ever. Fredrickson and his staff are realistic enough to know they may never get enough positions for a total takeover of FCRC; even if they could it would be difficult to justify on a cost basis or the best use rationale.

The space crunch that will be brought on by the renovation of older buildings on the NIH campus may not be as severe as it first appeared. The renovations probably will proceed one building at a time, and as of now, the displaced labs will be accommodated in space on campus.

There could be additional moves of NCI intramural labs to FCRC. The National Institute of Allergy & Infectious Diseases and National Institute of Neurological & Communicative Disorders & Stroke may expand the labs they are presently operating at FCRC. It is not likely that other institutes will move any people there within the next five years.

NCI executives agree that the work being performed at FCRC is high priority and high quality, and the plans they are developing for recompeting the contract will not include provisions for reducing the scope of their program there. The nature of the contract could change significantly, however.

One change that is being considered is the suggestion that the contract be split up into two compo-

nents—one for the biology (or basic research) program, the other for everything else. Among the options suggested by DeVita was that as many as six contracts could be awarded—for central management support; science research to include biology, biological and chemical carcinogenesis, and biological markers; science research to include virus production and the fermentation pilot plant; animal services; biohazards and environmental control; and science services to include the chemical services laboratory, central histopathology service, etc.

Six contracts would be more costly to administer and probably would be less satisfactory for the scientists working under them. More feasible would be another of DeVita's options, three contracts—one for central management and administrative support, one for research programs, and another for resources and services.

NCI staff in the early discussions on the recompetition are seriously considering splitting out at least the biology program. They feel that some universities might be interested in competing for that part of the operation. Without the basic research elements, other organizations might be more interested in competing with Litton Bionetics for the rest of the program (when the contract was offered for recompetition in 1977, no one bid against LB).

HHS CARCINOGEN HANDLING GUIDELINE PROPOSALS PUBLICATION COMPLETED

The draft of guidelines proposed by the Dept. of Health & Human Services for intramural laboratories handling chemical carcinogens was published in the last two issues of ***The Cancer Letter***, except for the following (this completes publication of the proposals):

V. Situations Requiring Special Consideration (continued)

The toxicity and carcinogenic potency are also important factors to consider when selecting safeguards. For example, experimental data suggests that the carcinogenic potency of aflatoxin B1 is magnitudes greater than that of chloroform.

A. Higher Risk Situations

Careful judgment must be given in the selection of safeguards for any proposed use which involves a known highly potent chemical carcinogen. Also, operations that involve either large quantities of chemical carcinogens or complex procedures having a significant potential for producing aerosols or contamination create a higher risk of exposure. When these or similar situations exist, special consideration should be given to instituting additional safeguards beyond those described in Section IV. Attention should be given to the need for additional or more frequent changes of protective clothing, personnel showering, use of respirators, restricting the use of chemical carcinogens to either a glove box or other completely closed containment system, special handling of exhaust air from primary containment devices, work area access control, and environmental monitoring of laboratory activities.

B. Lower Risk Situations

Where the principal investigator, in consultation with the safety committee and the safety officer, determines that less stringent safeguards can be used to provide protection, the safeguards selected should require at a minimum, strict adherence to good laboratory practices. The laboratory worker should not eat, drink, smoke, chew gum or tobacco, apply cosmetics or store food in areas where the chemical carcinogens are used or stored. Hands should be washed following the completion of a procedure in which chemical carcinogens are used.

The laboratory worker should develop the habit of keeping hands away from mouth, nose, eyes, and face. A fully fastened laboratory coat and gloves should be worn when handling chemical carcinogens. Mechanical pipetting aids should be used for all pipetting procedures.

Operations involving volatile chemical carcinogens and the preparation of dilute solutions or the removal of small amounts of a chemical carcinogen from stock quantities should always be performed within a laboratory-type hood or glove box. The work surfaces should be covered with stainless steel or plastic trays, dry absorbent plastic backed paper or other impervious material.

Stock quantities of chemical carcinogens should be the minimum quantity required for efficient use; the primary container should be stored in an unbreakable outer container. The outer container should have affixed to it a label with an appropriate warning such as: CAUTION – POTENTIAL CANCER HAZARD. The stock quantities should be maintained in a secured and appropriate storage area when not in use.

Recommendations for decontamination and disposal described in Section IV should be followed.

C. Animal Experimentation

The laboratory practices and eingineering controls described in Section IV should be followed for all animal experimentation when chemical carcinogens are used. In selecting specific safeguards, careful attention should be given to animal care and housing methods, bulk chemical storage and dispersement procedures, dosage preparation and challenge procedures, waste management and disposal practices, and personnel protection requirements. These safeguards should be described in the safety plan.

Experimental animals should be housed so that potentially contaminated feed, feces, urine and bedding can be handled in a controlled fashion. Animal care personnel should wear a completely closed jumpsuit or its equivalent, laboratory issue shoes or booties, head cover, and gloves of suitable material. Clean clothing should be provided daily, or more frequently as the situation dictates. Personnel should be encouraged to shower when they leave the animal care or dosage preparation areas. Under no circumstances should personnel protective clothing or equipment be permitted beyond the boundary of the animal facility. Personnel working in animal rooms where exposure to potentially contaminated airborne particulate material or vapors exists should be provided suitable respiratory protection (See Section IV-B-6).

All animal use should comply with the Animal Welfare Act, Public Law 89-544, 1966, amended in 1970 and 1976 (P.L. 91-579 and P.L. 94-279) and should conform to the Guide for the Care and Use of Laboratory Animals, DHEW No. (NIH) 78-23.

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