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EMPHASIS ON EARLY DISEASE IN CLINICAL TRIALS, EARLY LUNG CANCER DETECTION SEEN AS "LANDMARK"

Two recent developments in cancer therapy—the decision by NCI to bring into clinical trials far greater numbers of patients with early disease, and the growing possibility that earlier detection and resulting effective treatment of lung cancer may drastically improve survival rates—have not created the excitement and acclaim at least one Washington observer feels they should have.

Nathaniel Polster, who has closely followed the National Cancer Program as a registered health lobbyist and newsman, thinks those developments are "a landmark in the world of science" and demonstrate the progress being made in cancer research.

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In Brief

EVALUATION OF POTENTIAL IMMUNOASSAY COMPONENTS SOUGHT; PROMISING RESULTS COULD LEAD TO CONTRACT

NCI IS OFFERING to help organizations which have identified potentially useful antigenic serum components to evaluate them. Coded serum panels are available for evaluating those assays with potential for the immunodiagnosis of cancer. Promising results may form the basis for a contract to support development of the immunoassay. Send preliminary data documenting a useful test to Immunodiagnosis Serum Panels, Bldg 8 Room 118, NCI, Bethesda, Md. 20014. . . . **DAVID VALERIO**, director of Hazleton Laboratories Life Sciences Div., has been named vice president of the company. . . . **MEETINGS:** International Conference on Integrated Cancer Management, Feb. 18-21 in Phoenix, sponsored by Good Samaritan Hospital and ACS-Arizona Div. NCI's Paul Carbone will give the keynote address, and the program includes presentations on bladder cancer, testicular tumors, prostatic cancer, head and neck malignancy, non-Hodgkin's lymphoma, leukemias, myeloma; pediatric, CNS and GI malignancies, radiotherapy, immunotherapy and hyperthermia. Astronaut Joseph Kirwin will be a guest speaker. Write to Robert Thoeny, program chairman, Director of Radiation Oncology, Good Samaritan Hospital, 1033 E. McDowell Rd., Phoenix, Ariz. 85006. . . . **WORKSHOP** and state of the art conference on school health education programs as they relate to cancer control will be held Oct. 12-15 in Denver. Suggestions for development of school health education programs in prevention, screening and early diagnosis of cancer will be solicited. Write to Carl Larson, Blair Bldg Room 7A01, NCI, 8300 Colesville Rd., Silver Spring, Md. 20910. . . . **CONFERENCE** on "Early Lesions and the Development of Epithelial Cancer" is scheduled Oct. 21-23 at NIH, Bldg 1, Wilson Hall, sponsored by the Div. of Cancer Cause & Prevention. Conferees will review what is known about the nature and biological significance of preneoplastic lesions in several epithelial systems that have been intensively studied.

NEW EMPHASIS ON EARLY DISEASE SEEN AS PROOF OF CANCER PROGRAM PROGRESS

(Continued from page 1)

Polster's excitement was touched off by discussions of NCI-supported treatment programs at the August meeting of the President's Cancer Panel, when the reasons for moving into emphasis on patients with early disease were described by NCI staff. It was noted then that getting those patients into trials would be a problem, since most of them are being treated at the community level and are not easily available to the larger centers where most of the research is taking place.

"That's a marvelous problem, a landmark in the world of science," Polster told ***The Cancer Letter.*** "Maybe some people who have not been following cancer affairs closely in recent years would miss the point. It needs to be made explicit from one end of the country to the other. It is, namely, that patients for therapeutic trials must now be recruited at early disease stage in large numbers. Heretofore, most of the medical experimentation involving cancer patients has centered on those with late stages of the disease.

"The reason for this is that therapy was so ineffectual, in face of the challenge of this fearful disease, that it was ethical only to put into clinical trials those patients for whom there was no hope of survival. In such cases, the therapies at hand could ethically be tested one against the other to see which ones were a tiny bit more effective than the others.

"Now, however, since the advent of the National Cancer Act of 1971," Polster continued, "therapy has advanced to the point where much can be done for the patients suffering from an early stage of the disease. A much higher percentage of cancer patients can be promised a normal span of life than ever before."

Polster contends that it now is unethical to deny patients with an early stage of the disease the therapeutic advances which have been established in clinical trials involving patients with advanced stages of the disease. "In fact," he said, "we owe it to the cancer patient, to the American people, to the world, to enroll in clinical trials thousands of patients with early stages of the disease.

"Such a landmark in the world of science, unfortunately, is apt to go without adequate notice in the lay press. Even in the scientific world the landmark is officially established only with the award—a Nobel prize, a Lasker award, or some other honorific notice. Until then it is not official.

"I think it is important to realize that the emotion, the intelligence, and the hard work that have gone into creating and developing the National Cancer Program have reached this state of fruition in 1975," Polster said.

Polster referred to remarks made at the Panel meeting by Vincent DeVita, director of the Div. of Cancer Treatment. (Part of DeVita's statement appeared in *The Cancer Letter,* Aug. 22). DeVita said:

"Now, in terms of the perspective, I like to think of cancer treatment this way. We have just completed a 75-year experiment in therapy. By that I mean that 75 years ago, in the late 1890s, surgery and radiotherapy really got off the blocks and began to evolve as the major treatment for cancer in this country and in the world. And for the first 50 years of this century we spent most of our time sharpening these tools as a form of cancer treatment. Then the very obvious plateau of the survival curves that took place in the 1950s was the result of the fact that the tools were perfected and could control the local disease, or if you like the TNM classification, the T and the N compartment in a cancer. (T=tumor, N=nodes, M=metastases). It began to uncover the major problem that we now face today, that is the people who have metastatic tumor. It turns out that no matter how extensively you push the local therapies one cannot, obviously, take care of patients with metastatic disease.

"In the last 25 years we have spent our time developing the systemic therapies, chemotherapy and immunotherapy, to the point where they are usable tools, two local—radiotherapy and surgery—and two systemic—immunotherapy and chemotherapy. . . .

"You have to identify a major cancer problem; identify the area within that problem to pursue; allocate the resources and at the same time continue to develop the four therapies I have talked about. Just as example, my radiotherapy colleagues tell me that they feel that with the sophistication of new radiotherapy equipment that local control might be achieved in another 60,000 to 70,000 patients a year by improvements in equipment alone; that is, people who appear to have localized cancer, but who are not able to control the T and the M compartment because of limitations in the equipment. (We thus have) a significant number of lives (to) be saved by improving (a) particular modality (and surgery along with it)."

DeVita went on to say that this number may represent the top quantity of people for whom therapy can improve the survival by using the two local approaches. He then explained the various phases of drug testing. Phase I is a standard initial testing of the compound in humans, he explained. It establishes the level of toxicology, or the level of dose which is safe to give humans without damaging them.

"It may not at all result in any information about the efficacy of that compound," DeVita told the Panel. "This makes them unattractive studies to do, and one has to organize them to get them done. Otherwise, people don't normally volunteer to (take part in) them.

"Phase II, if you have successful completion of the Phase I, (is used to) identify drugs that can be used safely in humans . . . developed for reasons of activity in animal systems. Then the phase II part is the testing against specific types of tumors, and we

have identified 10 target type tumors. Most of the common tumors are ones known to be responsive (and involves drugs tested in phase II).

"Now, you need to have the phase II capacity in order to keep . . . from logjamming at phase I. That is where we begin to dovetail with the disease-oriented study . . . .

"Phase III is when you take a compound that has gone through phase I and it has had identified activity against a tumor, and now one begins to compare it with an existing modality in phase IV, or the combined modality studies where you begin to orient yourself more toward the disease and look at the reason for failure in the disease and (in the application of that particular therapy).

"Now, there are some conflicts in here that have to do with patient resources, and I have to mention them because I think one of the main reasons for coordination in the (National Cancer Institute's) treatment program is to make sure we use the resources (economically).

"Phase I studies compete with phase II studies (in terms of the numbers of patients available for tests). That is, if you have a tumor in which you need to identify whether new therapy is effective and have to test drugs available, you also use the same tumor to do phase I studies. So you have some competing for resources (that is, patients available to enter various test protocols).

"Phase II studies could be new drug combinations as well as new drugs. So, you have some competition even in the phase II studies.

"Phase III studies are a multiplicity of types of studies, comparing old and new therapy, and it is here where the spontaneity begins to take place in terms of therapeutic research, unsolicited research. Once you have identified active compounds, for example, investigators have access to certain tumors and will begin to develop these phase III type studies, and in phase IV are the ones that I think are the studies of the next decade or combined modality studies, and that is the application of all these tools to the patients who are going to fail because as we know, over the years, they have had very high recurrence rate, and those are the patient resources that we have always had trouble getting.

"We have never, in many cases in the past, had any opportunities to pursue in that population, and I think now we do.

"So, we have used the contracts to develop a phase I capacity and more recently a phase II-phase III capacity so that we can move drugs out of the Drug Development Program into clinical testing. We have now also used the contracts to identify areas where we can collect the necessary resources, the patient with early tumor who has a high risk of recurrence. . . . But I just point out at this time that in spite of the fact that the contract program was evolved primarily as a drug testing apparatus to start with, that we have about 5,000 patients committed to the studies under the contract program. About 50% of those are patients who have localized or regional tumor where in the cooperative group program which has historically been mostly phase III type studies about 85% of the patients are primarily advanced disease, and the effort there is to move again more to the patients with localized tumor.

"That leaves about 325,000 patients a year out in the country who eventually die of cancer who don't go on to clinical trials. All of them, obviously, cannot. But there are a lot of patients out there with tumors which, if they were entered on clinical trials, would provide a good deal of information in terms of cancer treatment (and might, in fact, experience many more months of relatively comfortable life under the kinds of treatments we now know to be more effective than those available as recently as 10 years ago)."

Panel Chairman Benno Schmidt: "And would fare better than they are faring?"

DeVita: "They may well fare better, yes. Some of them obviously would be research efforts. So, I assume that a lot of the leads we are pursuing are going to work out, and the answer would be, yes. The patients would obviously benefit."

Polster also referred to comments by Roger Halterman, program director of the Clinical Investigations Branch of the Div. of Cancer Research Resources & Centers.

"I would like to make one comment that I think relates directly back to Vince's comments about patient resources. I think as an Institute at this point . . . we are all faced with a serious problem. We are in a new era of treatment research. We all realize that we have to reach patients that, to date, we really have not reached. We need to get hold of the early disease patients.

"Up until now, most of the cooperative therapy study groups and organ site task forces deal with patients with advanced disease. As a matter of fact, a couple of the groups deal almost 100% with metastatic disease, and unfortunately, it does not matter whether you talk about grant directed programs or contract directed programs, the institutes and the people that we deal with on the outside also have the same difficulty of getting hold of patients with early disease. These patients are still out in the community getting treated by community physicians. It is not until a problem arises that a patient finds his way into a center. I think that is one of the issues that we really ought to bring up. . . . I think we are attempting to correct some of those problems. But I think we are not really going to get off the mark on any of these programs unless we can figure another way to do it," Halterman concluded.

Polster turned to progress being made in developing means to diagnose lung cancer when it is still operable.

"Lung cancer is one of the most fearsome of can-

cers because each person has only a limited amount of lung he can sacrifice to surgery. Also, it is the second most prevalent type, after colon rectum, with 91,000 new cases of lung cancer expected in the United States this year.

"The bad news is that the most recent figures indicate only 11% of lung cancer patients will survive three years. Phenomenal results with lung cancer, however, are beginning to flow from an NCI-supported project which began at three medical centers in 1971, the year the National Cancer Act was passed.

"We have all heard that early detection of cancer is the best pathway toward cure. The saying is more than a cliche. The scientific expression of that thought came in 1969, for example, when R.J. Jackman, C.A. Good, and O.T. Clagett showed that 45% of lung cancer patients were able to survive five years—well on the way toward being categorized as "cured"—if their disease was peripheral lung cancer up to 4 centimeters in diameter. Patients with tumors 2 centimeters or less in diameter had five years survival rates of 68%. So the scientific problem became one of detecting cancers when they were small.

"One of the institutes participating in the lung cancer study commencing in 1971, Mayo Clinic, has just released a progress report on this work which will continue for some years.

"Here is what Mayo authors Robert Fontana, David Sanderson, and others reported in *Chest,* the issue of May 5, 1975:

"'If peripheral lung cancers could be detected regularly while less than 3 centimeters in diameter, it should be possible to increase the five-year survival rate of patients with such tumors to approximately 50%. Half of all lung cancers are peripheral.

"'Theoretically, a five-year survival rate of 25% of all lung cancers should result from vigorous application of roentgenologic screening alone.'

"The most recent five-year survival rates for lung cancer runs 5%, compared to the attainable 50% mentioned by the Mayo doctors," Polster noted.

"As a matter of fact the Mayo study involves a detection by sputum tests as well as by x-ray. In the tests nine out of the first 33 patients diagnosed during screening showed no indication of the disease on their x-rays but did show it in the sputum test. Putting these two types of tests together detects more dangerous, but curable, cancer than either one of the tests alone. As Mayo doctors put it:

"'Mayo experience before and since beginning the Mayo Lung Project has been that most in situ or minimally invasive lung cancers are resectable, usually by lobectomy, with five-year survival rates of about 70%.'

"It should be emphasized again that the best five-year survival rates so far produced across the country are 9%," Polster said. "So the Mayo studies show tremendous progress is possible.

The Mayo doctors then conclude:

"'These data and the ability consistently to localize roentgenographically occult tumors indicate that theoretically a five-year survival rate of 20% of all lung cancers is possible by aggressive application of cytologic screening alone. However, there are certain aspects of lung cancer, and especially of roentgenographically occult cancer, that cause concern about the actual survival rate that can be achieved.'

"The 'however' sentence above indicates that there are still some difficulties in fully achieving some of the percentages mentioned by the Mayo doctors. More important, though, is that the entire Mayo project is essentially centered on surgery as a treatment for lung cancer. The project began years before the phenomenal results were announced in 1974 in the NCI-supported, 37-institution breast cancer project. In that project surgery was immediately followed by low dosage of chemicals given on an outpatient basis by pill, simply administered.

"Whereas the theoretical percentages of cures mentioned in the Mayo study might be difficult to achieve with surgery alone, there is little question that new theories of combining surgery with post-operative preventive medicine designed to ward off recurrence of the disease, would produce survivorship statistics well within the realm of the Mayo theoretical potential," Polster said.

"The simple matter of fact is that lung cancer for the first time in human history now becomes a disease about which it is reasonable to talk of 'curing'."

(Before he became a lobbyist representing volunteer health organizations, Polster was managing editor of Drug Research Reports.*)*

SENATE COMMITTEE EARMARKS NCI JOB POSITIONS, BACKS NEW CONSTRUCTION

The Senate Appropriations Committee last week went along with the request of its Labor-HEW Subcommittee and added $100 million to NCI's budget over the amount voted by the House (***The Cancer Letter,*** Aug. 8). Committee members hoped to get floor action on the massive Labor-HEW appropriations bill this week, get it to conference with the House and on the President's desk before the end of the month.

The Senate figure for NCI is $803 million for fiscal 1976, plus an estimated $22 million for training that will come along later when Congress enacts new authority for training programs. That would be a healthy increase over the 1975 appropriation of $691 million, but it probably won't survive the conference with the House.

Normal practice in the past on HEW appropriations has been for conferees to split the difference between the two bills. That would give NCI $775 million, enough, NCI staff members say, to continue the momentum generated in the cancer program and to fund significant numbers of new initiates.

NCI did not get all it hoped to from the Senate, but it did get 94 additional positions earmarked in the bill. If that goes through and becomes law, the Office of Management & Budget will have to abandon its freeze on NCI job positions.

The committee report on the bill said, "The committee notes that there is a critical manpower shortage within the National Cancer Program. To develop and maintain an expanded cancer effort effectively and efficiently, adequate manpower resources must be available. To date, these resources have not been provided. Of particular concern is the apparent lack of positions and beds in the Clinical Center for cancer research, and the committee directs that more funds be allocated for this important activity.

"Therefore, the committee has provided as an earmark of 94 positions over the fiscal 1975 authorized level and those just recently released, for the implementation of the National Cancer Program."

NCI also had hoped the Senate committee would earmark funds for new construction grants and thus block OMB from further efforts to withhold such grants. No such earmark was made, although the report did say, "It is the intent of the committee action that funds in this appropriation are to be used for new construction, as well as for alterations and renovations and construction of biohazard facilities. Funding of new construction projects as authorized in P.L. 93-352 is essential to the success of the National Cancer Program and must be continued."

That's clear enough, but it may not have the force of law that a specific amount included in the budget and marked for new construction would have. However, the intent of Congress frequently is interpreted by courts based on the language of committee reports. If OMB persists in blocking new construction awards, the affected institutions will have plenty of legal ammunition, including the specific authority of the NCI director to make those awards.

The report commented on the comprehensive cancer center program:

"The development of the comprehensive cancer center communications network has particularly pleased the committee because each center will have its own communications office whose activities include a telephone response system and a directory of cancer services available in the region. The committee notes that this service is being conducted in conjunction with volunteer groups and is pleased with this cooperation.

"The committee is satisfied with the progress to date in the development of geographically balanced comprehensive cancer centers to serve as a national resource for basic and clinical research and multidisciplinary patient treatment, as well as the community outreach and communication efforts. The committee looks forward to the designation of two or perhaps three additional centers prior to the end of fiscal year 1976."

Other comments in the report on the cancer program included:

"The National Cancer Institute has made significant progress in advancing the national effort to reduce the impact of cancer on people. The committee is impressed with the direction the program is heading and with the institute's efforts to develop, improve and evaluate new methods and techniques to detect and diagnose cancer at an early stage when the disease is most curable. The most promising projects underway include efforts to improve detection in the most frequent sites of cancer: breast, lung, large bowel and uterine cervix. Recent developments include automating the analysis of specimens of the Pap smears; the use of the flexible figeroptic coloscope to improve the capability to detect cancer; 29 projects established in cooperation with state and territorial health departments to reduce uterine cervical cancer.

"These results reflect the knowledge of the number and character of the scientific avenues ripe for exploration which must be investigated to provide the means to control cancer. The high priority opportunities and leads through the major research thrusts of cause and prevention, detection and diagnosis, treatment and rehabilitation and cancer biology must continue.

"NCI should initiate new programs and expand recently initiated high priority programs, such as nutrition, for which $6 million has been provided, environmental carcinogenesis, organ site programs, center programs, education and training programs, and should continue the development of critically needed scientific knowledge through strong support of fundamental research efforts. For example, the committee commends the expanded utilization of the Frederick Cancer Research Center in the areas of biocontainment and the testing of environmental carcinogens, and recommends the continued and further expanded use of these facilities as well as the close coordination of cancer related activities with other federal agencies.

"Activities in the institute's cancer control program progressed dramatically in the fiscal year 1975. Activities have now reached into all corners of the United States. Projects are conducted through demonstration, a newly formed communications n etwork conducted through each of the 17 comprehensive cancer centers, and other educational projects. Active involvement of the medical community, voluntary agencies, local hospitals and public groups is expected to continue. The committee is interested in the involvement of all of these groups, especially the community physicians in continuing education and is pleased at the direction taken by the cancer control program in this matter.

"The committee notes that testimony brought out the fact that there are 20 major tumor sites in the human body which must be actively investigated clinically with combination drug and immunotherapy

trials. The committee urges NCI to move ahead in this area with a portion of the additional funds we have provided.

"The committee is pleased with the continued and growing success of the outreach clinics and rural patient care programs. The committee encourages NCI to continue its initiative in this area and would support increased funding for this program in the rural New England area.

"NCI supports research training in accordance with the National Research Services Award Act. Under this authority the institute makes both individual fellowship awards and institutional awards. Although the budget estimate for 1976 only provides for individual fellowship awards, the committee believes that institutional awards under the NRSAA, when extended, must also be continued."

The committee voted $2,266,181,000 for all of NIH, an increase of $584,827,000 over the Administration's request, $115,426,000 over the amount voted by the House, and $328,822,000 over the 1975 appropriation.

"In the past years the Congress has strongly and successfully resisted the inadequate and unreasonable Presidential budget requests for the National Institutes of Health," the report said. "These insufficient requests would have fallen far short of matching the much talked about commitments to attacks on cancer, heart disease, veneral diseases, blindness, and environmental hazards had Congress accepted them. The fiscal 1976 budget request is no different than previous requests. . . .

"Although funds provided in this bill are sufficient to maintain the NIH research grant programs at their present levels with some modest increases, they are in large part committed to the support of on-going projects. As almost all biomedical investigations require several years to complete, NIH will usually support an approved research project for at least three years and often for much longer. It is obviously desirable to continue support of a project until it has been completed or judged that support is no longer necessary. At the same time, the result is that, in the absence of substantial increases, most of each year's funds are, in effect, committed to on-going projects leaving relatively little additional money for the support of new investigators or new ideas—which is obviously also desirable. The committee therefore urges NIH to consider whether a different balance between old and new projects is desirable and, if so, how this might be achieved without undue disruption of productive on-going research.

"As the total NIH appropriation now exceeds $2 billion, substantial annual increases should not be routinely expected and it would therefore be prudent to develop a policy for the most effective management of the research grant programs on the basis of relatively constant funding from year-to-year.

"Further, the committee understands that several grants and contracts at NIH have carried on for five to 10 years. The committee is concerned that the agency may become dependent or enamored with these projects and conduct only a cursory review of their usefulness, followed by automatic extension. Because of this, the committee requests that a report be submitted within six months containing the numbers of grants and contracts over five years old, as well as what steps will be taken to review and evaluate these projects."

The 94 positions were not the only ones earmarked in the bill. The report said, referring to all of HEW:

"The committee has specifically earmarked 881 positions in the bill for various health programs. The committee notes that the positions provided represent increased over those authorized in fiscal year 1975. However, the absence of a specific earmark should not be considered as denial of new position requests. While the positions are very few in number and nearly 2,000 below the 1972 level the committee feels that it is vitally important to include these positions within the bill. This action is necessary because of the repeated attempts by Congress to direct positions through report language which has fallen on deaf ears within HEW and OMB.

"The positions provided are to be used exclusively for programs, service, research, and grants and contracts management—not for program direction, the office of the assistant secretary of health, or the various directors of the remaining health agencies."

Contract Awards

BIG GET BIGGER: LITTON LANDS $4 MILLION NCI PRIMATE CONTRACT

Litton Bionetics, already by far NCI's largest contractor, added another $4.4 million project to its list when it was awarded a three-year contract to provide and maintain a facility for subhuman primates.

It is the continuation of a project already carried on by Litton, but was offered in recompetition this year. Litton's was the only proposal submitted.

Other awards:

Title: Stimulation of immunity to virus associated and tumor associated antigens in animals
Contractor: Mt. Sinai School of Medicine, New York City, $360,000.

Title: Replication of oncogenic RNA viruses and its relation to human cancer
Contractor: Columbia Univ., $955,000.

Title: Investigations of oncogenic viruses in non-human primates
Contractor: Litton Bionetics, $79,975.

Title: Induction of aryl-hydrocarbon hydroxylase (AHH) in cultured human lymphocytes
Univ. of Wisconsin, $71,437.

Title: Study molecular events leading to transformation by RNA oncogenic viruses
Contractor: Litton Bionetics, $100,000.

Title: Resynthesis of bulk chemicals and drugs
Contractor: Monsanto Research Corp., $558,947.

Title: Study of latent virus infections and the significance of C-type particles
Contractor: Southwest Foundation, $290,780.

Title: Cell biology facilities and tumor immunology
Contractor: Meloy Laboratories, $195,880.

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.

(Brief announcements of the following RFPs appeared earlier in ***The Cancer Letter.*** *More complete descriptions of the work to be performed follow)*

RFP NCI-CB-64013-39

Title: *The development of an immunodiagnostic method for the early detection of ovarian cancer in asymptomatic women*
Deadline: *Oct. 30*

The objective of this program is to establish an immunodiagnostic method of identifying the existence of ovarian cancer at any early stage of the disease and for serial monitoring of patients with ovarian cancer so that treatment can be more effective.

The incidence is about 17:100,000 women; this represents an increase of 300% from 1930 to 1968. This increase is incidence combined with a 5 year salvage rate somewhere between 20% and 30% and the persistent reported finding of 70%–80% of patients first seen for ovarian cancer being in stage III and IV, make it mandatory that we look for a method of determining the existence of ovarian cancer at an earlier stage, where the reported 5 year salvage is increased.

The contractor will seek to establish an immunodiagnostic test for the presence of early ovarian cancer in humans. Specifically:

a. The contractor will have available an immunologically oriented laboratory capable of recreating, identifying and purifying antigens and creating antisera.

b. The contractor will have radioimmunoassay capability, in order to perform large number of tests on patients and populations at risk.

c. The contractor should be able to go right ahead with human testing.

d. The contractor will determine the risks involved in administering this test, if any.

e. The contractor will have access to patients with carcinoma and have clinical staff associated with the project who have clinical experience with this disease.

f. The contractor will locate, identify and have access to a population cohort at high risk for ovarian cancer including expected laparotomy for suspicion of ovarian cancer. The contractor should first demonstrate that the assay can distinguish patients with known ovarian cancer from patients with benign gynecologic disease and from normal women. A study should then be designed to evaluate prospectively a population of women suspected of having ovarian cancer, to determine the ability of the assay to detect early cancer. Provisions should be made for adequate follow-up of all screened patients, to identify patients with subsequent development of clinical evidence for ovarian cancer.

g. The contractor will have available biostatistical and epidemiologic support where necessary in selecting populations for study and determining appropriate size thereof.

Contract Specialist: Thompkins Weaver
Biology & Diagnosis
301-496-5565

RFP NCI-CB-63927-39

Title: *Development of topical chemotherapeutic agents for mycosis fungoides*
Deadline: *Oct. 30*

Although mycosis fungoides has been treated with some success by topically applied nitrogen mustard, there is reason to believe that some of the newer cancer chemotherapeutic drugs may be more effective by the same route. Safer and more effective topical drugs would not only be a valuable improvement in the treatment of this disease, but might point the way toward better treatment of more common skin diseases, such as basal cell epithelioma and psoriasis.

NCI is undertaking animal testing of the dermal irritancy and percutaneous absorption of a series of cancer drugs. From this and other information it is expected that approximately 30 drugs will be tested by topical application in mycosis fungoides patients. Proposals are sought for such clinical testing.

The contractor shall have the capability of clinically evaluating selected drugs by topical application in mycosis fungoides patients. The following protocol is suggested, involving two phases: first, patch testing for effectiveness, and second, extended clinical trials for effectiveness, and safety. Specifically:

A. Drugs: The drugs to be tested in each phase will be selected and provided by the National Cancer Institute, together with information on pharmaceutical formulation, dermal irritancy, percutaneous absorption, and other aspects as required. The contractor will file IND applications with the FDA, separately for Phase 1 and Phase 2.

B. Phase I: Clinical Trials. A small number of the most effective drugs from Phase I will be selected by NCI for clinical trial at prescribed concentrations and total dosage. The latter will be limited by what is known of systemic toxicity and percutaneous absorption. Medication will be applied to all lesions at prescribed intervals of one to seven days until the total dosage is reached. Patients will be carefully observed for at least six weeks to measure effectiveness and toxicity, and thereafter as required by the patient's condition. Standardized objective measures will be devised for systemic toxic effects. A period of six weeks of documented stability must pass before another drug trial is begun. Each drug will be tested in ten to 15 patients. The observed results will be evaluated against the known course of the disease with standard treatment, and against results with topical nitrogen mustard, which may be included here. Phase two is expected to require one to two years for completion.

Contract Specialist: Thompkins Weaver
Biology & Diagnosis
301-496-5565

RFP NCI-CB-63994-39

Title: *Periodic screening of relatives of patients with medullary carcinoma of the thyroid using calcitonin radioimmunoassay*

Deadline: *Oct. 30*

The development of radioimmunoassays for measurement of circulating calcitonin has been found to be very useful in the detection and diagnosis of MCT. Studies of kindreds with familial MCT have shown that elevated calcitonin levels, particularly after stimulation with calcium or pentagastrin, correlated well with the presence of tumor, and sometimes indicated subclinical disease. These tests appear to be the most accurate screening test for the presence of MCT. It will be important to determine how useful a periodic screening program of MCT families will be in early detection of tumors, and particularly in increasing the frequency of successful treatment of the disease and thereby increasing survival.

The contractor shall establish a cohort of patients with MCT proven histologically and large enough to offer a statistically adequate number of family members. The contractor will screen family members by determining their serum calcitonin levels by radioimmunoassay methods for the determination of patients in families who have MCT during its early stage of development and the long term follow-up of these families for the purpose of determining the natural history of the disease and the effectiveness of therapy.

Specifically, the contractor will emphasize the following points:

a. Determine the best and simplest provocative test for identifying patients who have MCT but who also have normal basal concentrations of immunoreative calcitonin. The normal response to stimulation should be established with appropriate control individuals.

b. Monitor at appropriate intervals the family members with no initial evidence of disease to identify early the patients who subsequently develop the disease.

c. Determine the effectiveness of calcitonin assay to detect and possibly localize (via differential venous catheterization) recurrence of tumor after surgical removal of the initial lesions. It may be desirable to obtain control data on patients who had thyroidectomies for other types of thyroid cancer.

d. In an effort to determine the efficacy of the screening and monitoring program, it will be important to establish its impact on the natural history of the disease. This may be approached by a retrospective analysis of the incidence of medullary carcinoma of the thyroid within each kindred and the length of survival after clinical diagnosis. This could be compared with the data obtained from the families now being screened. In addition, it will be helpful to determine the proportion of individuals detected within each kindred who have palpable thyroid nodules, elevated basal calcitonin levels, or elevated calcitonin only after stimulation; the histopathologic results, responses to therapy and length of survival could be compared among these groups and also with the retrospective data. A plan should be included for statistical analyses of these data.

Contract Specialist: Thompkins Weaver
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SOLE SOURCE NEGOTIATIONS

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

Title: Activation of C-particles and induction of cancer by immunologic and non-immunologic methods

Contractor: Massachusetts General Hospital.

Title: Production of sarcoma and leukemia viruses

Contractor: University Laboratories Inc., Highland Park, N.J.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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