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OMB PLOY WOULD DELAY FUNDING 1,500 NIH GRANTS FROM FY 1985 TO 1986; OTHER CUTS ARE CONSIDERED

The White House has decided, tentatively at least, to delay funding about 1,500 new and competing renewal NIH grants from the 1985 fiscal year until 1986 in what would be the Reagan Administration's most controversial action yet involving support of

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In Brief

FLORIDA OSTEOPATHS JOIN MEDICAL EXAMINERS, NULLIFY STATE'S LAW SUPPORTING LAETRILE

FLORIDA'S BOARD of Osteopathic Examiners voted 4-3 Jan. 12 for a resolution declaring laetrile harmful, reversing its previous stand. The action in effect nullifies a 1977 Florida law which blocked any effort to interfere with a physician's right to prescribe or administer laetrile. That legislation included a provision voiding the law if both the state Board of Medical Examiners and Board of Osteopathic Examiners ruled that laetrile is harmful. The Medical Board so declared in 1980, but the osteopaths twice voted to keep the law, contending there was no scientific evidence against the substance. Joseph Zavertnik, chairman of the Florida Cancer Council's Committee on Unproven Treatment Methods, said a change in membership on the Osteopathic Board accounted for the reversal. The Florida legislature last July killed a 1982 law permitting the manufacture of laetrile in the state. Zavertnik said getting the two laws off the books may not really change anything, since no one seems to know if there has been an increase in use of laetrile in the state, but "it does remove the sign of respectability from it, and that is all the proponents wanted".... **DEADLINE FOR** proposals in response to the RFP on a double blind evaluation trial of slit scan flow cytometer (RFP NO1-CN-55470-34, **The Cancer Letter**, Jan. 4) is March 26, not Feb. 4.... **JOHN CURRY**, who has been director of the American College of Radiology Philadelphia office, is the new executive director of the College. ACR headquarters in Chicago will be moved to the Washington D.C. area (Reston, Va.), in a new building scheduled for completion by December, 1985.... **ANNUAL MEETING** of the Assn. of Community Cancer Centers will be held in Washington March 13-17 with the theme, "Oncology: Surviving the '80s." The meeting will include "Advances in Cancer Control III," presented jointly by ACCC and the Assn. of American Cancer Institutes.... **NATIONAL CANCER** Advisory Board meeting Feb. 4-6 will include reports on NCI's Drug Development Program and support for information dissemination, as well as reports from the Board's various committees. The meeting will be closed all day Feb. 5 for review of grants, except for evening committee meetings.

GRANT FUNDING DELAY WOULD IN EFFECT CUT NIH BUDGET $37.7 MILLION IN 1985

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biomedical research. Approximately 270 of those grants would belong to NCI.

The ploy recommended by the Office of Management & Budget would permit NIH to "obligate" funds for 6,526 new and competing renewal grants, the amount provided for by Congress in the 1985 appropriations bill, but would fund only 5,000, the total number originally requested for funding in the President's 1985 budget.

That would permit the Administration in effect to impound about $215.5 million (with the average NIH grant costing a total of $143,700 a year) in FY 1985 without violating the law that requires cogressional approval for impoundment of appropriation funds. According to OMB's rationale, that would not be impounding but only delay of spending that amount one year. Since competing grants involve three to five year obligations, delaying funding this year would stretch out the delay for each subsequent year. Coupled with the White House' as yet unannounced decision to again ask for funding of 5,000 competing grants in the FY 1986 budget, the effect would be slash the NIH budget $200 million a year indefinitely--or at least as long as Congress goes along with it, which it probably will not.

NCI's share of the $215.5 million "stretch out" would be $38.8 million.

Although Congress can continue to appropriate money for more grants than requested by the Administration, there does not seem to be much it can do about the "obligate but don't fund until next year" effort, at least for this fiscal year. Congressional strategists are pondering what move to make next, and the grantees whose funds are delayed may consider legal action. It was a lawsuit by NIH constituents which forced the Nixon Administration to release illegally impounded NIH and other health funds in the early 1970s.

There are likely to be other hemorrhages in the 1985 NIH appropriations, these approved by Congress. In last year's Deficit Reduction Act, Congress directed that all agencies withhold amounts equal to 10 per cent of their original budget requests for travel, printing and consultants. There is a possibility that at NIH, consultants could include peer review members. Those amounts have not yet been determined.

In the same Act, Congress directed the Executive Branch to submit reports on actions taken to comply with the Grace Commission recommendations (which included a vast array of budget cutting suggestions), and to submit appropriate rescision requests to Congress in line with whatever actions are taken. The House and Senate both must approve rescisions before they go into effect.

Unless the Reagan Administration does more than give lip service to the Year 2000 goals, there is little chance those goals can be met if substantially increased funding for NCI is put off until 1988 or 1989, when the White House says the federal deficit will be brought under control. The programs and resources required to achieve the goal of reducing cancer mortality 50 per cent must have adequate funding starting in 1986, or they won't be in place long enough to have that kind of impact by 2000 A.D. As usual, it appears that Congress will have to provide the leadership while the White House sits on the sidelines.

DCT BOARD COMMITTEE TO RECOMMEND LIMITED START ON IN VITRO SCREENING

An ad hoc committee of the Board of Scientific Counselors of NCI's Div. of Cancer Treatment agreed last week to recommend to the full Board limited approval of DCT's plan for a major change in its Drug Screening Program.

DCT's Developmental Therapeutics Program had proposed that the emphasis in screening be switched from a compound oriented effort using induced and implanted tumors in mice to a disease oriented strategy using human tumor cell lines in vitro. A committee of Board members, chaired by Mortimer Elkind, met last week with a panel of individuals described by DTP Director Michael Boyd as representing "the world's best expertise in drug discovery and development" to discuss the proposal.

After the two day meeting, the committee decided to recommend that NCI go slow in making the change, suggesting that it start first with a limited number of cell lines in two or three diseases, leaving it up to DCT to determine which. The committee also said that the in vitro screens be carried out in parallel with the P388 mouse screen.

"I'm not sure I agree with that part of the committee's recommendation," DCT Director Bruce Chabner said. "The P388 has not been promising. We've used it long enough (10 years)."

The committee left it up to DCT to select which diseases will be the first to be targeted.

There was a consensus among the committee members that the number of compounds going into the screen should be reduced, and that NCI should not feel compelled to take to clinical testing any certain number of new drugs. Only those for which a high degree of confidence has been established should go into clinical trials, committee members felt.

The committee will submit a full report on the meeting to the Board at its meeting Feb. 14-15.

Chabner opened the meeting by commenting, "This

is an appropriate time to bring this group together, since it is the 30th year for the NCI Drug Development Program. We're very open minded and haven't made a decision that a change in the screening will occur. The consensus of the staff is that this is a significant opportunity, and that we should take advantage of it. There is no consideration of eliminating in vivo experimentation but just of introducing cell lines early in screening. The real question is, if we do accept the premise of cell lines, how do we integrate them into the pharmacology and in vivo screening? Our Board thought it was a promising idea that needs further work."

Boyd related the history of the screening program and described the cell line proposal (**The Cancer Letter**, Oct. 26). He said the Board of Scientific Counselors had asked the committee to address these questions: 1. Is the proposal justifiable? Are there better alternatives? 2. Is it technically feasible? 3. What changes or additions to the proposal should be considered? 4. What should be the priority of implementation relative to existing NCI screens? 5. What should be the timetable for implementation?

Daniel Hoth, chief of the Investigational Drug Branch in DCT's Cancer Therapy Evaluation Program, related "the clinical fate of drugs produced by the NCI program." From 1975 through 1984, NCI obtained INDs on 48 cytotoxic drugs, not including radiosensitizers. Five were dropped after phase 1 studies, four for unacceptable toxicity. Nine are presently undergoing phase 1 studies. Eleven are in phase 2 trials from which no evaluable data have yet been obtained.

Twenty three of those compounds have produced evaluable data from clinical trials, based solely on activity as a single agent. These include both published and unpublished data from more than 2,000 studies (included are some drugs screened prior to 1975). Nine were active in at least one disease, seven were negative and activity in the other seven was undetermined.

The nine active drugs were adacenomycin, against acute leukemia; AMSA, adult and pediatric acute leukemia; AZQ, lymphoma and glioma; bisantrene, lymphoma; chlorozotocin, islet cell and lymphoma; deoxycoformycin, CLL, non Hodgkin's lymphoma; mitoxantrone, breast cancer and lymphoma; and rubidazone, leukemia and lymphoma.

Hoth emphasized that those results "are not the final analysis of the value of these drugs." Trials are still going on, with many of those agents being tested in combinations with other drugs and modalities.

There were 50 evaluable drugs from pre-1975 screening, 26 of which were found active in clinical trials. Most of those were active only against hematological malignancies, but four were active against breast cancer, four against lung cancer, and two against melanoma. None were active against colon cancer.

Correlation of clinical results with activity found in the murine systems is still undergoing analysis, Hoth said.

NCI staff members and investigators from other institutions led discussions on the six targets for disease oriented drug development, describing the scope of clinical problems, current drugs available, cell lines and other models potentially available to support directed screening efforts. The six are lung, colon, breast, CNS and ovarian cancer and melanoma. Descriptions of in vitro screening approaches and procedures were presented; prospects for combined modality studies were discussed; and strategies for acquisitions and selection of materials were described.

Daniel Martin, Catholic Medical Center, New York, presented a paper in which he and colleagues from a number of other institutions (1) offered an in depth analysis of the murine and proposed in vitro screens and discussed other aspects of NCI's Drug Screening Program. Martin's presentation appeared to have had substantial influence on the Board committee. The paper follows, with some editing to conserve space:

Individual cancer investigators and institutions such as NCI are in general increasingly employing in vitro models. One reason is that there have been major advances in the development of human cancer cell lines in culture, and in the assessment of oncogene expression in these lines. There is a desire to focus studies on these new laboratory technologies with the hope that the study of human cancer will be more rewarding. Within this hope is the unsubstantiated hypothesis that human cancers may be different in some subtle but important way.

A major reason for this shift from in vivo to in vitro studies is cost. Despite the general requirement that NCI reviews of research grants should separate budgetary considerations from evaluation of scientific merit, criticisms are frequently voiced about the greater expense of in vivo tumor models. Emphasis is placed on less costly studies in vitro, and the grant review pink sheets often conclude critiques of animal studies with implications of excessive cost and a poor priority score. In addition, NCI has markedly reduced its contract supported research programs. Currently, only a single contract exists evaluating in vivo preclinical studies in combination chemotherapy. The economic basis of many decisions about animal tumor systems derives in large part from the low productivity of tumor bearing mice for primary screening.

A negative attitude has permeated study section peer review of therapeutic animal tumor research, leading to what we perceive to be improper and dangerous neglect of the field. Tumor bearing mice are indispensable for experimental therapeutics involving pharmacokinetics, immunologic mechanisms, biochemical pharmacology and combination chemotherapy. Absent ongoing investigations in these fields, the relevant new studies will be unavailable, or will be worked out in humans at much greater risk and cost.

Without the reasonable expectation of support, young investigators initially interested in in vivo experimental therapeutics will turn elsewhere. For example, despite the fact that both preclinical and clinical studies have long established that combination chemotherapy is more effective therapeutically than drugs employed individually, the unfortunate result of the above attitudes and events is that few modern studies of polychemotherapy have been conducted or are planned in preclinical in vivo systems.

Misperceptions of murine tumor models

Many clinical investigators believe that murine tumor models are not relevant to the human cancer problem because claims of anticancer activity for drugs in experimental tumor systems often were not verified when these drugs were used in human cancer patients. However, although there are a number of reasons for the poor correlation between animal tumor model determinations of drug activity and clinical efficacy, the most important is the use of different criteria for measuring activity in the two settings. Mere inhibition of solid tumor growth is used as the criterion for activity in the preclinical setting, whereas 50% or greater tumor regression, requiring the killing of two or more logs of the clonogenic tumor cells, is the acceptable criterion for activity in clinical trials. When different endpoints are used to evaluate data from chemotherapy protocols disparate results are obtained. When different endpoints are used in animal models and in the clinic, the lack of positive correlation between drug response of human cancer and animal models of human cancer should be no surprise. After all, even total lack of tumor growth during chemotherapy (which conventionaly would be considered very significant in experimental systems) is merely tumor stabilization as a clinical parameter, and is considered relatively insignificant clinically. There clearly has been a lack of effective communication and understanding regarding the significance of the difference between these two criteria for determining anticancer activities.

The opinions of laboratory oncologists regarding the chemotherapeutic predictive value of in vivo murine tumor models are ambivalent. On the one hand, they note that the models clearly have not been totally unsuccessful. Models are credited for the discovery of some 40 clinically active drugs that have radically altered the clinical approach to cancer therapy. On the other hand, the laboratory oncologist often seems dissatisfied with the tumor models. Some laboratory oncologists have faulted themselves for employing inhibition of tumor growth as an endpoint for activity in light of the different evaluation criteria employed clinically.

Unless the same endpoint for measuring therapeutic activity in the laboratory and the clinic are employed and a lack of correlation of chemotherapeutic activity is then demonstrated, murine tumor models should not be rejected as inherently false analogs of human cancer on the basis of the presently reported poor correlations. Rather, it is the methodologies that first need reordering. It may be that the design, interpretation and extrapolation to the clinic of the laboratory chemotherapeutic data need more revision that the tumor models.

Furthermore, the pressures to provide agents for clinical evaluation have resulted in numerous drugs with minimal activity in only one or two animal tumor models being accepted as clinical candidates. It is not surprising that such agents have failed in clinical trials. Agents with the greatest clinical utility, such as cyclophosphamide, doxorubicin and cisplatin have a high degree of activity in a broad spectrum of animal tumor models. We could readily improve the predictive value of animal tumor models simply by making our criteria for selection of clinical candidates more rigorous. If we are going to be more selective we must be prepared to have fewer new agents to evaluate in man in a given time.

. . . (NCI's proposed in vitro screening would take) compounds showing selective antitumor activity against one or a few tumor types (into) high priority development through preclinical pharmacology and toxicology studies to clinical phase 1-2 trials against the targeted tumor types. Compounds showing nonselective antitumor activity against many of the in vitro human cell lines would undergo further evaluation in an in vivo panel of human tumor xenografts, and following preclinical toxicity studies would enter into broad based clinical trials.

The efficacy of this in vitro approach to the discovery of new agents with clinical activity as compared to existing methods is completely unknown. An NCI study of the clinical activity of drugs active on the human tumor colony forming assay is as yet unfinished. Scientific caution would suggest launching a pilot study of this candidate method rather than making a total change in the drug screening methodology. At least there should be a

period of overlap (e.g. a few years) between the two approaches to see what the correlations are.

There are still other concerns. The environment of cells in vitro, which differs from that in vivo, may alter their chemosensitivity. Culture conditions may cause artifactual changes in the tumor cell cycle. Thus, extrapolations from tumor cell lines in vitro to tumor cells in vivo may not necessarily be valid. Many factors such as drug excretion and metabolism, tumor host interaction, and drug distribution cannot be studied or recreated in vitro. Since the toxic effects of potential new agents on normal tissues are not known, in vitro screening tests cannot suggest information about the therapeutic index. In vitro screening is not sufficient to characterize the positive compounds that are discovered. Murine experimental therapeutics are indispensible.

What might be the expectations for the number of potential new anticancer agents that might be identified by an in vitro human tumor cell line screen?

It is difficult to answer this question as there are no pilot data. However, it can be anticipated that, as with the in vivo murine tumor model screening program, the number of potential new agents will depend primarily on the methodological criteria that are employed. If a very rigorous endpoint of marked decrease in survival of colonies in the culture plate is employed, few compounds will be selected for clinical trial (and clinical investigators will be frustrated by the new system's poor productivity). If a very sensitive endpoint (tantamount to the inhibition of tumor growth employed in the murine tumor models) is the criterion for presumed anticancer activity, a large number of false positive agents will be sent for clinical trial (and clinical investigators will be frustrated by the new system's false over productivity, much as they were with the murine tumor model screening system).

Granting that the methodogical details and criteria will be satisfactorily worked out, and that some clinically active new anticancer agents will be found, what might be expected in terms of the degree of antitumor activity?

Cancer associated genetic instability causes biochemical cellular heterogeneity with a variable cellular overlap among all types of mammalian neoplasms, and this in turn leads to a variable chemotherapeutic correlation. The variability of chemotherapeutic response, which conforms to clinical experience, is a natural consequence of the somatic mutation model of cancer, and is precisely what should be expected. The assumption that there should be a common cellular heterogeneity for identical histologic types of malignancy arising from the same organ system is not warranted. Heterogeneity, or variability, cannot be expected to be duplicated from neoplasm to neoplasm.

Neither a magic bullet curative agent, nor an exact correspondence in chemotherapeutic sensitivity between histologically identical cancers, is an expectation compatible with our biologic knowledge of the heterogeneity of cancer. Heterogeneity makes the cancer problem harder to solve, but cure nevertheless can be attained by combination chemotherapy. Some leukemias, lymphomas, sarcomas, and some of the relatively uncommon carcinomas are cured by combination chemotherapy. Chemotherapeutic heterogeneity was the important original concept stimulating the promulgation of combination chemotherapy of cancer as opposed to single agent treatment, and curative progress with combination chemotherapy continues.

The cancer problem is more difficult than other medical problems; the proposed in vitro screening method cannot be considered analogous to sensitivity testing for antibiotics in patients with bacterial infection, where a positive test has a high correlation with clinical cure if the patient has normal immunologic and leukocytic function. . .

Combination chemotherapy with the newly found agent may be evaluated clinically (without initial preclinical in vivo trials), but in general this has not proven to be an effective way to conduct this type of research. Enhanced selectivity of a drug combination in vivo is demonstrably dependent upon the variables of sequence, timing, schedule, dose and dose ratio between agents. Given the infinite number of possible ways several drugs can be combined, only a minute fraction of these methods can be actually evaluated in patients. Clinical experience indicates that failure to obtain a positive result in the initial clinical trial usually results in a loss of clinical interest sufficient to preclude additional clinical investigation of a particular drug combination. It is therefore important to provide useful preclinical guidelines to aid the clinical investigator in selecting initially a sequence, schedule, timing and ratio of drugs in combination that will lead to positive results if such exist. Optimization can follow. It is precisely because the leap from preclinical models of whatever sort to the patient is so great that adjustment of many variables is necessary. Guidelines from in vivo murine model studies are useful. . .

It is a matter of record that concepts and biological principles having to do with tumor response to therapy carry across from the murine species to the human. Much of the conceptual framework and general principles of clinical cancer chemotherapy evolved from work on the murine leukemia L1210. Research on murine solid tumors provided an understanding of the basis for the need for clinical

chemotherapy. . . In contrast to the broad conceptual advances that have been made through use of murine tumor models, their utility as models to provide specific guidelines for drug treatment scheduling in cancer patients has produced uncertain correlations with clinical results. Analysis of these data reveals that judgment and knowledge must be employed to effect successful transfer of the details of the animal findings to the clinical situation.

Sometimes the model may be viewed as a means to produce a cookbook type prescription of a drug treatment schedule. A schedule found to be optimally effective in the model is assumed to be directly transferable to clinical scheduling. The classical example for this use is the optimal schedule for treatment of residual L1210 leukemia with methotrexate, confirmed to be effective for humans with leukemia as a maintenance therapy in the absence of manifest disease.

There are also clinical studies that do not correlate with successful preclinical findings in murine animal tumor models. However, when these reports are closely examined, the laboratory recipe has often not been properly followed in the clinic. . . Successful application of a "recipe" from a "cookbook" requires that the details of the recipe are closely followed, and that there is a close correlation between the situation in the clinic and the model. Much more often, however, there are clear quantitative differences (i.e. tumor mass, cell proliferation rate, a markedly differing degree of chemotherapeutic response of two agents that are to be evaluated in combination, etc.) between the model and the clinical situation that merit rethinking the recipe approach. One cannot translate what one sees in specific animal tumors to specific human cancers in a recipe like manner without taking into consideration the marked quantitative differences. . .

Experimental design including proper controls, sequence, dosage ratios, and the proper interval between drugs are among the important factors that require attention. Dosages and exposure times may be worked out in the laboratory, but unless the details are properly translated into the clinic with the aid of detailed pharmacological studies, the successful preclinical results may not be achievable in the complex clinical situation. If the details are not properly followed, the murine tumor model should not be faulted for a failure to predict a successful clinical trial.

The authors support the new investigations in in vitro screening. The human cell line screening proposal may well achieve better results than previous prescreens such as the P388 leukemia. In vitro screening may be useful prior to but not in place of in vivo animal model research. We believe that clinical frustration and disappointment with in vitro identified potentially active anticancer compounds will be minimized if appropriate in vivo test steps are interposed between the in vitro screen and single agent clinical trials. And most importantly, we believe that compounds identified as clinically active should be brought back to the laboratory and reevaluated in preclinical in vivo investigations to discover or optimize schedules, sequencing, time intervals and other details of combination chemotherapy.

As far as we are aware, no one is opposed to research that employs the in vivo animal tumor models. The trouble is that this type of verbal encouragement is insufficient to get the job done. Cost consciousness has led to actions such as the deletion of the murine models from the new in vitro screening proposal. This may be false economy. Without support, there will be no laboratories engaged in relevant research, and no ready cadre capable of expediting innovative and programmatic research on new drugs.

The supercedence of the in vivo murine tumor models by other methodology in the NCI Drug Screening Program may or may not improve the screening results. However, there is an immediate, unfortunate consequence of the deletion of the models due to the unproven charge that their drug sensitivity results are not sufficiently correlative to the findings in human cancer. Any official action taken in deleting the models from the program risks sending a signal to the research community that models are considered irrelevant to human cancer even in experimental therapeutics. Coupled with the growing cost motivated scrutiny of research studies on the more expensive in vivo animal models, it may unintentionally deliver a coup de grace to the employment of murine tumor models in therapeutic research.

Recommendations

Two recommendations are suggested:

An effective working group for in vivo preclinical treatment research could be forged by the engagement of four constituencies: the NCI administration, scientists involved in in vitro drug screening, in vivo experimental therapists concerned with elucidation of optimal methods for using drugs alone and in combination in tumor bearing mice, and clinical investigators involved in the early toxicity and activity trials. This working group could facilitate the discovery of active regimens for human cancer by considering the results of the in vitro screen, the results of the early human data on drugs classified as selective in the in vivo screen, and the in vivo xenograft data generated for the drugs classified as nonselective. The relevance

of in vivo experimental therapeutics for improving the use of the in vitro data, and the ability to optimize the early hints of human activity, including biochemical pharmacologic knowledge, could be explored by a small number of examples. If the value of in vivo experimental therapeutic data is not readily apparent the working group could be disbanded. If, however, the working group can prevent the decline by attrition and neglect of in vivo experimental therapeutics, while improving human cancer therapy, all interested parties will be well served. The long lags from animal demonstration to appropriate clinical application and validation might be diminished or eliminated. The product of this working group should be an improved prospect for discovery and early implementation of useful regimens for human cancer.

If the preceding recommendation is not deemed desirable, the following alternative is suggested: an advisory review group for in vivo preclinical treatment research in cancer. This is not a revolutionary suggestion, for a paradigm exists in the NCI Biochemical Modulation Advisory Group. The advisory group should consist of both preclinical and clinical investigative therapists, for there is a great need for a close interrelationship between these disciplines. Communication regarding the details of preclinical experimental findings may have a direct impact on the attainment of clinical success in that critically important time span when early clinical investigation is in progress. Feedback from the clinic regarding problems in the utilization of agents should be a prime determinant of complementary laboratory research.

The duties of an advisory review group for in vivo preclinical treatment research should include (1) review of all grant requests to NCI for in vivo preclinical treatment research with responsibility to recommend those they esteem to the Experimental Therapeutics Study Section for its final decision (This recommendation is not meant to imply that there is not sufficient expertise on that study section to adequately review grants on proposed in vivo therapeutic animal studies. It is recommended in the certainty that something needs to be done to prevent attrition and neglect of in vivo experimental therapeutics. The review group would have an advisory function designed to be a highly visible administrative mechanism that NCI views animal tumor models as integral to the effort against human cancer); (2) review of of requests for special in vivo preclinical studies in treatment research by an existing NCI contractor with responsibility to recommend those they esteem to DCT for its final decisions; and (3) responsibility to recommend to DCT any preclinical treatment findings that warrant clinical trial.

The institution of either recommendation will strengthen NCI's drug evaluation program by emphasizing the irreplaceable value of in vivo preclinical therapeutic investigation.

Gertrude Elion, Wellcome Research Laboratories and a member of the National Cancer Advisory Board, commented, "It's clear there is no way we can arrive at a consensus. There are differing viewpoints, and probably all are correct. There is no one way to do cancer research. None of us is omniescent. None of us is happy with randomized screening. The mouse is not a man, in vivo is not in vitro, tumor A is not tumor B, the tumor cell is not a normal cell, transplanted tumors are not spontaneous tumors. One of the questions raised is perfectly legitimate: just how good is the P388 at predicting compounds for antitumor activity?"

John Montgomery, Southern Research Institute and a member of the President's Cancer Panel, distributed a paper prepared by L. Simpson-Herren of SRI which included data claimed to support the conclusion that "when the screening tumors are evaluated for ability to predict for clinical activity or inactivity using cell kill as the therapeutic endpoint, the P388 system is a useful screening model."

"The main point is that use of cell kill is a valid measure of anticancer activity," Montgomery said.

"The question is whether or not you are assessing a compound appropriately," Elion said. "To assess for clinical activity depends on the dose schedule. We have to have some way of evaluating compounds in a biological system which simulates the human tumor."

Alan Rosenthal, Merck Sharp & Dohme Research Laboratories, suggested that a key issue is the apportionment of resources between rational discovery of drugs and the screening program.

"Our new National Drug Discovery Group mechanism is addressing that issue," Boyd said. He noted that NCI supports a number of grants studying biochemistry and other basic aspects of anticancer drugs. Implementation of the in vitro screening proposal would not be at the expense of those grants, Boyd said. But, "In the screening program per se, if we want to do something different, it has to be at the expense of what is already being done."

1. Earl Balis, Memorial Sloan-Kettering Cancer Center; Emil Frei, Dana-Farber Cancer Center; Abraham Goldin, NCI (retired); Gloria Heppner, Michigan Cancer Foundation; James Holland, Mt. Sinai Medical School; Janet Houghton and Peter Houghton, St. Jude Children's Research Hospital; Randall Johnson, Smith Kline & French Labs; Arnold Mittelman and Youcef Rustum, Roswell Park Memorial Institute; Robert Sawyer and Robert Stolfi, Catholic

Medical Center; and Franz Schmid and Charles Young, Memorial Sloan-Kettering. In addition, the paper was reviewed and supported by Emil Freireich, M.D. Anderson Hospital & Tumor Institute, and Bernard Fisher, Univ. of Pittsburgh School of Medicine.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda, MD. 20205. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring, Md., but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

SOURCES SOUGHT

CECS-RCB-Synopsis 190
Title: Biological Carcinogenesis Branch repository for storage and distribution of reserch resources.
Deadline: Jan. 23 for statement of qualifications.

Small business firms (no more than 500 employees) located within one hour driving time from NIH, Bethesda, Md., capable of functioning as a repository and distribution center for various biological reagents and possessing the following capabilities, are invited to submit complete information to the contracting office specified herein:

1. A minimum of 3,500 sq. ft. of dedicated floor space for low temperature storage of specially developed biological reagents and clinical specimens.
2. Ability to supply electrical power to accommodate approximately 40 government owned refrigerator/freezer units.
3. Ability to supply liquid nitrogen to 18 nitrogen freezers.
4. Availability of standby facilities in event of loss of refrigeration capacity.
5. Security maintenance of all storage facilities and continuous monitored central temperature alarm system for all refrigerator/freezers.
6. Capability to house and operate a government provided IBM/PC/AT and its ancillary software to maintain on line inventory for biological reagents.
7. Capability of operating a reimbursement accounting system whereby recipients of biologics are billed for materials and shipping costs by the repository contractor. These payments are substracted from the costs of operating the repository and are so indicated on vouchers submitted to the government for payment.

Information furnished should include the total number of employees and professional qualifications of scientists and laboratory technicians; a description of general and special facilities including the actual number of square feet available and indication of electrical capacity; an outline of previous projects; a statement regarding industrial security clearance, if previously granted; and other available descriptive literature.
Contract Specialist: Zaiga Tums
RCB Blair Bldg Rm 114
301-427-8888

NEW PUBLICATIONS

"Quit for Good," a new smoking cessation kit designed to help health professionals counsel their smoking patients more effectively. Each kit contains enough materials to help 50 smokers become, and stay, nonsmokers. For the free kit, write to NCI, Office of Cancer Communications, Bldg 31 Rm 10A18, Bethesda, Md. 20205.

Cancer Today: Origins, Prevention, Treatment," National Academy Press, 2101 Constitution Ave., Washington D.C. 20418, $9.95 U.S., Canada, Mexico, $12 elsewhere.

"What to Know About the Treatment of Cancer," by Vincent Anku, $7.95 paperback. Madrona Publishers, PO Box 22667, Seattle 98122.

"Chemical Carcinogens," edited by Charles Searle, $129.95 U.S. and Canada, $155.95 elsewhere. American Chemical Society, 1155 16th St., Washington D.C. 20036.

"Cancer of the Kidney," edited by Nasser Javadpour, $34. Thieme-Stratton, 381 Park Ave. South, New York 10016.

"Neutron Brachytherapy: An Advance for Bulky Localized Cancer Therapy," by Yosh Maruyama, $24 soft cover. Harwood Academic Publishers, PO Box 786 Cooper Station, New York 10276.

The following titles are available from Raven Press, 1140 Avenue of the Americas, New York 10036:

"Hodgkin's Disease and Non Hodgkin's Lymphoma: New Perspectives in Immunopathology, Diagnosis and Treatment," edited by Richard Ford, Lillian Fuller and Frederick Hagemeister, $95.

"Candidiasis," edited by Victor Fainstein and Gerald Bodey, $43.

"Mediators in Cell Growth and Differentiation," edited by Richard Ford and Abby Maizel, $98.

"Viruses as the Causative Agents of Naturally Occurring Tumors," edited by George Klein, $69.50.

The Cancer Letter _Editor Jerry D. Boyd
Published forty-eight times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.