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

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NCI NATURAL PRODUCT DRUG DEVELOPMENT TO GET NEW EMPHASIS; SUGGESTIONS OF CRITICS ACCEPTED

Anticancer drugs derived from natural products should start coming out of the NCI pipeline somewhat faster if a reorganization proposed by critics of the Drug Research & Development Program has its desired effect.

Div. of Cancer Treatment Director Vincent DeVita has agreed to the reorganization, which involves primarily creating three branches out of the existing Drug Development Branch. That branch now has responsibility for new synthetic compounds as well as natural products and for the pharmaceutical formulation and distribution of new drugs. There will be a branch now for each of those three functions.

Another novel suggestion accepted by DeVita is that the discoverer of a new drug should be permitted to participate in the decision making process once his drug has been selected for further development.

S. Morris Kupchan, Univ. of Virginia, is principal investigator for the university's contract with NCI for isolation of potential anticancer

(Continued to page 2)

In Brief

GRANTS TO GET BIGGEST SHARE OF NCI'S EXTRA $74 MILLION; A PR FAILURE IN PITTSBURGH

HERE'S HOW NCI will spend the extra $74 million Congress appropriated for fiscal 1976 over the President's budget: $54 million for grants, $16 million contracts, and $5 million for intramural programs and overhead including 79 additional staff positions ordered by Congress over White House objections. . . . **LOUIS WASSERMAN**, distinguished service professor at Mt. Sinai School of Medicine, has declined reappointment to the NCI Div. of Cancer Treatment Board of Scientific Counselors and thus gives up the chairmanship of that Board. Other members whose terms expire this year are Janet Wolter, Rush-Presbyterian-St. Luke's, and G. Lennard Gold, hematologist-oncologist consultant with NCI. . . . **DCT DIRECTOR** Vincent DeVita is soliciting names as potential replacement for his departing deputy, Stephen Carter. DCT also is still looking for a chief of its Laboratory of Experimental Chemotherapy. . . . **MEDICAL DEVICES** bill which will strengthen and clarify FDA's regulation of this growing field has finally been passed by the House, now goes into conference with the Senate version. It will have widespread impact on use and development of devices in cancer detection, treatment and rehabilitation. . . . **A PITTSBURGH** MD recently examined a woman with a suspicious breast lump, then told her she would have to have a biopsy. "In that case, Doctor, I think I should go to a specialist," she said to Bernard Fisher, who some day may win a Nobel Prize for his role in developing better breast cancer therapy. "You need a better PR program," quipped a colleague to whom Fisher had related his ego-deflating story.

NCI ACCEPTS "TEAM" CONCEPT IN DRUG DEVELOPMENT SUGGESTED BY CRITICS

(Continued from page 1)

agents from natural products. He presented the report of a drug development review team to the DCT Board of Scientific Counselors last week. The team was headed by Alan Sartorelli and included Richard Donovick, Norman Farnsworth, Walter Nickerson, Koppa Rao and Daniel Wang, along with Kupchan.

Kupchan told the Board that the slowness in advancing promising candidates toward clinical trials—three to five years sometimes, after an agent had been identified—was caused by three major factors: inadequacy of contract capability for developmental scale-up; inadequate staff for natural products in the Drug Development Branch; and the absence of a mechanism for involving natural products principal investigators in the program after they have found a new drug.

"It is considered essential that the discoverer should participate actively in the decision making process," Kupchan said. "After a drug has been selected for further development, a project team should be formed to guide further movements of the agent through prep lab development, formulation, preclinical toxicology, and clinical trials. The team should include the discoverer, the project officer or other basic staff scientist, and a clinician. Such a team concept will insure, among other things, that there will be advantageous utilization of the special expertise of the discoverer in the process research development and large scale preparation of the candidate agent. Furthermore, this innovation will insure that the clinical representation will acquire an intimate knowledge of the agent's pharmacological and chemical properties at an early stage to anticipate possible clinical problems."

Kupchan said the review team felt the scientific approaches, techniques, expertise and philosophy involved in the isolation of natural products "differ significantly from those employed in synthetic organic chemistry." The team suggested that the natural products effort be given administrative and scientific autonomy by creating a Natural Products Branch.

The review team also pointed out that the preparative laboratory contractors have been responsible for both synthetic and natural product isolation and recommended that the dual responsibility be eliminated. "It is our opinion that preparative scale isolation expertise of natural products cannot be assumed to be an attribute of persons trained in synthetic organic chemistry," Kupchan said.

DeVita noted that this last recommendation had already been implemented with the release of an RFP for natural products (*The Cancer Letter*, Feb. 27). He said the review team's suggestions in general were "palatable" and that most would be implemented. "There may be a few differences (in the changes to be made vs. the recommendations) but it will be in the spirit of the recommendations," DeVita said.

Natural products now "are sort of winnout out over synthetic compounds," DeVita said. "We need to have the capacity to move rapidly."

Board of Scientific Counselors member Harris Busch, Baylor, said that "the promise now is greater than ever."

Saul Schepartz, director of the Drug R&D Program, said that much of the expense in the natural product program is the actual identification and collection of material. The major expense with synthetic compounds is in testing, he said.

DeVita gave the Board copies of a report he had written summarizing quality control in the Drug Development Program. Portions of that report follow:

The clinical evaluation of new anticancer drugs differs from the evaluation of any other kind of drugs. Normal volunteers cannot be used. Initial evaluations are performed in cancer patients with advanced disease refractory to all standard therapeutic measures. Over the past 20 years the NCI Drug Development Program has developed and clinically evaluated over 50 new anticancer drugs. While all of these have been toxic to some degree and not all have been effective, there have been no toxicologic accidents in the first doses administered, which is a tribute to the rigorous preclinical evaluation these drugs undergo before clinical testing.

At NCI the logic guiding the Drug Development Program is embodied in the so called program logic—a decision network apparatus sharply spelling out the criteria for moving candidate anticancer compounds from one developmental step to another. This also provides a means of achieving optimal bounds among the various program elements and of allocating the necessary supporting resources according to the volume of work projected.

Drug development begins with the acquisition of compounds for evaluation. To date, over 300,000 synthetic compounds and natural product extracts have been acquired and submitted for evaluation at NCI by more than 2,200 suppliers. Current suppliers, domestic and foreign, include pharmaceutical and chemical industries, academic institutions, research institutes, government agencies, and contractors. Materials acquired or submitted for evaluation are screened against experimental tumor systems which have been selected to quickly eliminate inactive compounds and identify compounds with the greatest clinical potential. The most important components of NCI's screen is a transplanted mouse lymphoid leukemia (designated as L1210). Another transplanted mouse lymphocytic leukemia (designated as P388) is also used for all natural products because of its superior sensitivity for crude fractions. The combination of L1210 and P388 model tumor systems provides the program with a highly efficient first screen.

After initial activity is confirmed (at least 50% in-

crease in the life span of treated vs. untreated tumor bearing mice) the final decision is made regarding the further development of each compound under evaluation. This decision is based on considerations regarding the agent's chemical structure and other criteria specified in the linear array. When a drug has passed primary screening, it enters secondary evaluation to determine the schedule dependency, optimal route of administration, vehicle of administration, and activity against tumor cells in pharmacologic sanctuaries (e.g., central nervous system). Drugs destined for clinical trial on the basis of primary and secondary evaluation for antitumor efficacy and safety are further tested at the preclinical level in the specific disease-oriented animal tumor systems (e.g., mammary carcinoma in rodents).

Drug combinations and combined therapy modalities projected for clinical use are also studied at the preclinical level in a variety of systems in order to define factors related to scheduling which might influence the design of clinical protocols. Such studies are designed to provide the clinician with information relative to the optimal sequencing of drugs or drugs plus radiation or surgery to maximize antitumor specificity.

When a new agent meets criteria for activity, questions must be answered regarding dose range in large animals (dogs and monkeys), organ toxicity induced in both species, nature of this toxicity, predictability of toxicity, dependency of toxicity upon drug dose, manageability or reversibility of toxicity, and quantitative and qualitative consistency of findings within each species.

The acquisition of toxicologic information is required by law before a drug can be approved for clinical trial. In order to file an investigational new drug application (IND) with FDA, data must exist to show tolerated doses for each species (in mgs. of drug per kg. of body weight, or mg. of drug per square meter of body surface area) as well as optimum schedule and route of administration. Recommendations must also be made regarding the starting clinical dose, and warnings must be stated regarding potential toxic effects. The starting clinical dose is derived from studies in dogs and monkeys and is usually a small fraction of that dose which in animals causes minimal toxicity.

Approval of an IND signifies the beginning of clinical trial: clinical evaluation of a new agent proceeds in three phases. Phase I studies involve clinical pharmacology, toxicology as well as therapeutic evaluation. Patients entered in these studies always suffer from advanced disease refactory to all standard therapy. Patients whose death is estimated to be imminent (days to a few weeks) are usually not entered on trial. The aim is to establish the maximum tolerated dose (MTD) at the schedule tested, to determine the type and severity of ensuing toxicity and to assess the predictability, treatability and/or reversibility of this toxicity. If toxicity is manageable, and a tolerated dose can be determined, phase II studies begin.

Phase II studies assess the clinical activity of drugs against a group of 10 "signal" tumors in their most advanced stages. These include breast cancer, colon and lung cancer and leukemias and lymphomas. Objective response must be clearly evaluable in at least 15 to 30 patients for each signal tumor, generally by measurable indicator lesions. Drug evaluation is based on response intensity and rate, pharmacologic disposition, mechanism of action, and cell cycle sensitivity. A Phase II clinical evaluation must be completed before judging anew compound selected by the screen to be inactive.

If acceptable levels of drug activity are demonstrated against any of the signal tumors, Phase III studies (comparison with best conventional treatment) are initiated to define the exact role of a new agent in a clinic for optimal exploitation.

Thus, the Drug Development Program is totally unique in that it identifies new compounds for the treatment of cancer by first determining therapeutic efficacy and toxicity in animal systems and then conducting clinical trials in a population of patients with advanced cancer for which no therapy exists, 90% of whom will die of their disease within a year if no new drugs are identified. NCI entered this field because development of these drugs was and is costly and the opportunity for profit is minimal. Our data are generated under contract with primate research firms but without the influence of the profit motive. They are monitored by NCI staff and/or prime contractor staff on a weekly basis and through the use of frequent telephone communications and site visits.

The report outlined in detail various quality control procedures required of contractors in the program. It concluded:

In the aggregate, the quality and the quantity of the acute and subacute toxicology data obtained in the program prior to the institution of clinical trials provides a larger safety margin than any other group of drugs for far less fatal diseases. It must be emphasized repeatedly that the end point of cancer drug testing is not chronic toxicity but the ability to administer a drug to patients with advanced cancer without lethal, irreversible or unsuspected toxicity, under dire clinical circumstances created by the presence of advanced widely metastatic cancer. Since these drugs are never tested in normal human beings, the program reserves testing for teratogenicity and carcinogenicity to a later stage of drug development if and when the compounds have been demonstrated to have the ability to control tumor growth to the extent that life is prolonged.

Cancer chemotherapy is a unique kind of drug treatment, and unique approaches have been and should be utilized. Criteria evolved for the testing of other kinds of drugs cannot be applied to the cancer

situation. Normal volunteers cannot be utilized. Toxicity is inseparable from therapeutic effect and the utility of all cancer drugs are judged by the therapeutic index of their acute and subacute side effects.

There is an urgent need to develop new and better anticancer drugs. The patient with advanced metastatic cancer is the test system. Even drugs with considerable toxicity are acceptable for clinical use if the risk benefit ratio is considered realistically from the eyes of the population in question and the doctors caring for them. These patients need protection from unreliable, unethical experimentation but they also need protection from overprotection which impedes cancer drug development. Consideration of these patients as a unique minority group (350,000 per year) not spoken for by normal healthy persons is imperative. Chemotherapy is a cornerstone of the exciting new advances in cancer treatment today and will undoubtedly lead to further improvement in the control of cancer in the future.

FDA'S NEW GUIDELINE PROPOSAL MEETS MOST NCI OBJECTIONS; COMMENTS ASKED

The Food & Drug Administration has a new draft of guidelines it is proposing for clinical testing of antineoplastic drugs. Previous drafts have met with a variety of objections from NCI and investigators around the country, and the current draft reflects FDA's attempt to meet those objections.

DCT Director Vincent DeVita, who had objected to the last set of proposed guidelines, said the new draft was "much better" and was one NCI could live with. He had some reservations with provisions relating to pediatric patients and has already sent his suggestions for improving that section to FDA.

Those wishing to offer further comments should send them to FDA, Div. of Oncology & Radiopharmaceutical Drug Products, 5600 Fishers Ln., Rockville, Md. 20852.

The complete proposed guidelines follow:

INTRODUCTION

"General Considerations for the Clinical Evaluation of Drugs" contains suggestions that are applicable to most investigational new drug studies, and should be reviewed prior to reading these guidelines. The guidelines, for antineoplastic drugs, are provided to help an investigator formulate his plan of development of a particular substance in conformance with established FDA regulations. They should be construed as general directions, not a set of specific instructions. They are not, nor are they meant to be rules and regulations.

It is impossible to compose a set of general directions which will cover every clinical protocol imaginable for investigational drugs in this class. An investigator must use his discretion when applying the standards as set forth in these guidelines to his own clinical research. These guidelines are principally for cytotoxic chemotherapeutic agents. Their phase I studies are assumed to be those of a new drug substance, about which there exists no human data.

Before the initiation of a clinical trial, appropriate preclinical (animal) toxicologic and pharmacologic studies must be completed, analyzed and reviewed. For phase I studies, these should support the scientific rationale for testing in man, outline potential qualitative toxicities, and provide a reasonable guide in selecting and escalating the starting dose in man. As clinical studies progress, subsequent protocols must be based rigorously on conclusions derived from prior experience (preclinical and/or clinical). The submitted protocol should conform to accepted standards of design, and is the sole basis for its (own) regulatory judgment.

As most cytotoxic chemotherapeutic agents act by altering cellular metabolism and/or inhibiting cellular proliferation, pathologic and frequently physiologic, the risk versus potential benefit to the research subject must be carefully considered before clinical trials may begin. Many antineoplastic drugs also have oncogenic, teratogenic and mutagenic properties which should be carefully looked for and defined both preclinically and in the clinic. For these reasons cytotoxic compounds are usually not tested in normal subjects.

The use of research subjects, who have the disease of interest, often allows the concurrent conduct of phase I and phase II studies. Such trials are encouraged, when the study is designed such that the data gathered contributes to the attainment of the objectives of both phases.

Because cytotoxic antineoplastic agents as a class have a low therapeutic index, the treatment of most cancer with such drugs should be limited to those physicians who by medical training and experience are qualified in their use. Clinical investigators for these drugs must be qualified by scientific training and experience as an appropriate expert in this field. Investigators must have ready access to adequate laboratory, and hospital (support) facilities.

Protocols should be sufficiently detailed to allow reviewers (institutional, FDA, etc.) to determine whether the study is likely to attain its objectives without exposing the subjects to unnecessary risks. Therefore, all protocols should contain:

1. A clear and complete statement of the objective(s) of the study.
2. A description of the relevant target population.
3. The therapeutic indication of the test product.
4. The known properties of the test product.
5. The subjects' inclusion and exclusion criteria.
6. The methods to be used to confirm the diagnosis.
7. The criteria to be used to evaluate efficacy and safety and the methods to be used for their observation and quantitation.
8. The duration of the study.
9. The projected number of subjects needed to establish specific objectives of the study.
10. The level and type of control.
11. The level of blinding, where appropriate.
12. The proposed experimental design.
13. A randomization plan for assigning subjects to the treatment groups when appropriate.
14. The proposed procedures for auditing the data.
15. The proposed statistical procedures for analyzing the data, where appropriate.
16. The proposed procedures for documenting and summarizing the statistical segment of the study.
17. The proposed plan for presenting the data from completed studies.
18. The proposed procedures for presenting the conclusions of the study.

An efficient, well-ordered plan of development of a drug is highly recommended. The sponsor is responsible for coordinating and monitoring the research efforts of participating investigators in such a way that the conclusion that an agent is effective or ineffective, safe or unsafe is reached with the exposure of as few subjects as is possible or practical. Once substantial evidence has been gathered that an investigational new drug, administered in a defined manner is safe and effective, the sponsor has an urgent obligation to prepare his data, and submit an NDA (New Drug Application).

The FDA has a specific mandate to protect all persons receiving new drugs in the USA, and a continuing obligation to improve the public's health. This administration seeks to do this by promoting and fostering productive, innovative biomedical research, and preventing dangerous or unproductive clinical research. These guidelines represent one aspect of its efforts.

PHASE I STUDIES

I. Objectives

A. Tolerance. These studies should determine an agent's non-therapeutic effects, such as limiting toxicities, their degree of reversibility, and dose-response relationships. Schedules should be sought for maintaining patients at maximally tolerated doses over a period of time sufficient to allow recognizable neoplastic regression.

B. Pharmacology. For those agents administered orally, absorption and biovailability profiles should be determined. Rates of drug clearance from the plasma, biotransformation, and excretion should be established, and estimates of tissue distribution and concentration, should be obtained.

II. Population of Interest/Sample

Phase I subjects traditionally have histologically confirmed malignant disease, which at the time of the study is no longer amenable to conventional form(s) of therapy (which should be specified in the protocol). Meaningful, tolerance studies are carried out in subjects who are physiologically well compensated and who can survive a required minimum period of observation. Investigators must be prepared to document that "carry-over" effects of antecedent therapies have been dissipated, and that the effects of the investigational drug can be separated from the effects of concurrently administered non antineoplastic drugs and the disease itself. As the primary goal of phase I studies need not be a determination of therapeutic effect, research subjects need not have objectively measurable tumors.

III. Controls

As there is no conventional therapy to which the investigational drug's effect(s) can be compared, and since malignant disease has a high and predictable mortality historical controls can be used, so long as the historical control data base will allow a valid comparison to be made and the particular historical control used is relevant to the clinical situation in which the investigational drug is being tested.

IV. Research Plan and Informed Consent

Initial drug doses should be well below the level at which pharmacological or toxic effects might be expected.

Dose increases should be made in increments most appropriate to the slope of the animal toxicity curves. The dose should be carefully increased until a level is found which produces clear signs of a therapeutic or major non-therapeutic effect.

Effects of the drug, both therapeutic and nontherapeutic, are determined and validated by serial histories, physical examinations, and laboratory determinations. The latter should include general profile tests, and appropriate specific tests as suggested by preclinical findings. A careful search should be made for organ specific toxicities such as CNS, cardiac, liver or pulmonary toxicities which may not be predicted from the preclinical studies.

In view of the researcy nature of these studies, the possibility of no therapeutic benefit, and even serious nontherapeutic consequences, informed written consent as outlined by the Secretary, HEW, shall be obtained from each subject. Care should be taken to insure that the subject "be able to exercise free power of choice without undue inducement, or any element of force, fraud, deceit, duress, or other form of constraint or coercion." Additional financial obligations through participation must be explained. These stipulations should in nó way be construed as abridging the investigator's right to a personal conviction that he (investigator) only administers drugs with a therapeutic intent on his part.

PHASE II STUDIES

I. Objectives

A. Therapeutic effect. These studies should determine which types of tumors do or do not respond to the investigational new drug being studied. Dose-response and time-response relationships should also be determined concurrently.

B. Nontherapeutic effects. By careful documentation on nontherapeutic effects, and their dose-response and time-response relationships, an assessment is made as to whether these effects are tolerable in the context of the achieved therapeutic effect.

II. Population of Interest

Subjects should be carefully chosen in view of potential benefits with various tumor types generally assigned a priority for testing according to their potential responsiveness as suggested by preclinical or phase I studies. The disease state to be examined must be fully and carefully described in terms of all relevant prognostic factors that affect the natural history of the disease in question. For example, specification of the following factors may be necessary: age, clinical extent of disease, rate of progression of the tumor, response to previous therapy, state of nutrition, functional status of the subject, etc.

III. Sample

Patients whose histologically confirmed malignant disease is no longer amenable to conventional form(s) of therapy (which should be specified in the protocol), are candidates for study, if and only if, they also have objectively measurable malignant disease. Spatial measurements are preferred, but in some cases only temporal measurements will be available. To be meaningful phase II studies must be carried out in subjects who are physiologically well compensated and who will probably survive a required minimum period of observation. Investigators must be prepared to document that carry over effects of antecedent therapies had been dissipated, and that the effects of the investigational new drug can be separated from the effects of concurrently administered nonantineoplastic drugs and the disease itself.

As those subjects with spatially measurable disease will have had their disease quantitatively characterized before treatment, each of these subjects can also serve as his own control with respect to his measurable disease.

V. Research Plan and Informed Consent

The response variables (therapeutic and nontherapeutic) along with the methods by which they will be measured must be specified. A therapeutic measure (an index of clinically meaningful results) must be selected; for example, length of survival; 25% reduction in the sum or a 50% reduction in the product of the lesion's maximum diameter and its perpendicular maintained at least 30 days with no evidence of progressive disease elsewhere. Failure must also be defined.

Until a therapeutic failure is declared, or a meaningful therapeutic effect is documented, the subject should be dosed at maximally tolerated doses (schedules) as suggested by preclinical data, available clinical data, and the disease under study. Observations must be made over a period of time sufficient to allow all events of interest to occur (generally the subject's remaining life time.)

In view of the research nature of these studies, the possibility of no therapeutic benefit, and even serious nontherapeutic consequences, informed written consent as outlined by the Secretary, HEW, shall be obtained from each subject. Care should be taken to insure that the subject "be able to exercise free power of choice without undue inducement, or any element of froce, fraud, deceit, duress, or other form of constraint or coercion." Additional financial obligations through participation must be explained. These stipulations should in no way be construed as abridging the investigator's right to a personal conviction that he (investigator) only administers drugs with a therapeutic intent on his part.

VI. Statistical Design and Analysis

The sample size chosen for the study must be sufficient to accurately measure response characteristics using the chosen variables. Methods for the choice of sample size must be carefully documented with rationale consistent with Phase II goals. If a comparative trial is used, randomization methods must be completely documented with all stratification factors specified. If a comparison with existing literature is the goal, supporting documentation on the comparability of patient populations should be provided whenever possible.

Statistical analyses should be clearly described and referenced with complete data available for checking in a concise format. Each assumption used in an analysis should be stated and justified whenever possible.

Statistical significance should not be a goal or end in itself, but a guide in interpreting, and method of validating the accumulated data and derived conclusions.

PHASE III STUDIES

I. Objectives

A. Therapeutic effectiveness. Prior to a phase III study, substantial evidence has been gathered to determine whether the drug administered, in a defined manner, is a possibly effective (clinically meaningful) treatment for a particular neoplasm. In general, to be approved for a phase III study, there must be prior evidence that the agent is either superior to or no worse than a standard therapy, and thereby usable as an alternative therapy; of clinical benefit to a substantial proportion of patients, or of clinical benefit to a well defined group of patients. The phase III study is thus designed to definitively compare the experimental therapy, commonly by using a controlled randomized clinical trial, with that of an existing standard therapy.

B. Nontherapeutic effect. Substantial evidence is gathered to determine whether the nontherapeutic effects are tolerable (relative safety) in the context of the achieved therapeutic effect.

II. Populations of Interest

Subjects with tumors shown to be responsive in phase II studies. The disease state to be treated must be unambiguously described in terms of significant prognostic characteristics. Appropriate demographic and personal characteristics should also be included in defining this population. The population must be well defined.

III. Sampling

An adequate and representative sample must be obtained. Entry criteria and the method by which a valid sample is to be gathered and each subject characterized must be described. The most appropriate subjects are usually previously untreated, newly diagnosed cases. Well conducted, cooperative trials are suggested when no investigator alone can recruit a sufficient number of subjects over a reasonable period of time.

IV. Controls

The usual control group is one on "standard therapy" (active treatment) but historical controls at times may be appropriately used. The method by which the sample is to be divided must be completely de-

scribed as must stratifications and efforts made to avoid bias when assigning subjects to the various groups. The latter should be accomplished by random assignment of subjects to the various groups.

V. Research Plan

The investigative program must be soundly based on prior experience and findings. It must be carried out over a sufficient length of time to allow all events of interest to occur. The response variable, methods of measurement, a therapeutic measure, and failure must be defined. The most meaningful general response variable and that of primary interest is the length of survival of the subjects. This should not be an absolute goal in itself, however, and an honest attempt to assess the quality of life must also be made. Other response variables of interest are the rate of response, time to progression of disease, length of remissions, etc.

The method by which instruments and their operators are to be standardized, and their quality, reliability and precision established, maintained and assured must be presented. The method by which observations are to be faithfully recorded and bias eliminated or minimized must be described.

The use of innovative experimental designs where appropriate is encouraged. Crossover of therapeutic failures to the "other" therapy may be of use for some response variables.

VI. Plan of Analysis

Specification, in advance, of the method of data analysis will facilitate the carrying out of meaningful study. The appropriateness of the chosen statistical model must be justified in terms of the experimental material with underlying assumptions. The test statistic's level of significance and desired power for a meaningful specific difference must be specified in advance. The comparison to be made is between the experimental group and the active treatment (standard therapy) group or historical control groups. Survival curves estimates, response estimates, toxicity comparisons and other analyses are of interest.

The definition of the risks involved with the use of a therapeutic agent is an abiding concern. Relative safety in terms of benefit and risk should be established concurrently.

Combination Studies

The determination that a combination of agents is superior to single agents or other combinations should be conducted after it has been demonstrated that each member of the combination is clinically active (effective) alone, or when there is clear and convincing preclinical evidence that each member of the combination will materially contribute to the desired therapeutic effect. The design, otherwise, should be that of the appropriate phase. Efforts should be made to quantitate the contribution of each member to the therapeutic and nontherapeutic effects of the combination.

POST NDA APPROVAL

Since a drug's development is a continuing process, each physician who uses an agent has a responsibility and obligation that goes beyond the patient he is treating. By carefully characterizing his patient's disease, and making and recording his observations accurately, he may observe new, clinically significant therapeutic and nontherapeutic effects which he should bring to the attention of the medical community. Progress in the treatment of cancer with drugs will be facilitated if each practitioner is enlisted, in a meaningful way, as an investigator.

PEDIATRIC CONSIDERATIONS

In the effort to make new drugs available quickly for general use, care should be taken not to neglect patients in the pediatric age group. Too often, the information needed to administer agents properly to this group is not obtained during the initial phase of drug development, and these patients essentially end up as "therapeutic orphans." To avoid this situation, the following recommendations are made:

1. The initial testing of an investigational new drug should be done in adults.
2. Phase I tests in children should be based upon and begun as soon as valid, adult phase I data becomes available.
3. Phase I tests in children should be completed during the phase II tests in adults.
4. Phase II tests in children should be in progress, or a reasonable plan of phase II testing in children must be prepared, before the actual approval of the NDA. If the disease in question occurs in adults and children, initial phase II tests in adults are suggested.

FDA HOLDS UP ANOTHER IND; RAUSCHER HAS "EXCELLENT" MEETING WITH SCHMIDT

Just when it appeared that FDA was becoming a little more reasonable in evaluating IND applications for anticancer drugs, as indicated by the release of applications the agency had held up for months, another example of bureaucratic indifference surfaced last week.

An IND application for hycanthone, based on a protocol drawn up by investigators at M.D. Anderson, was one of four submitted by NCI which FDA refused to approve last year in its sudden policy change. It was incorrectly reported in ***The Cancer Letter*** March 12 that all four, including hycanthone, had been released by FDA. Hycanthone in fact was the only one not released, and NCI staff members asked for a conference with FDA to find out why.

John Penta, head of the Drug Liaison & Distribution Section in DCT's Cancer Therapy Evaluation Program, told members of the Phase I Working Group the outcome of that meeting.

Hycanthone has been used extensively to treat certain infectious diseases. Since FDA's Div. of Anti-infectious Drugs had had considerable experience with hycanthone, NCI's IND application to test it in cancer patients was referred to that division, rather than to the Div. of Oncology & Radiopharmaceutical Drugs. It was the Anti-infectious Drugs Div. staff which rejected the application.

Penta said the rejection was based on six points:

1. FDA objected to the use of the term "phase I trial" in the application, since the proposed tests were to be carried out with cancer patients and not healthy subjects as is the case with most non-cancer phase I tests. FDA said it perferred the phrase, "early clinical trials."
2. NCI had included as a part of the background information in the application the statement that as an anti-infectious disease drug hycanthone had achieved a 90% cure rate. FDA objected on the basis that "it's not quite that high."
3. The application said the drug "may be related" to some hepatoxic effects noted in some patients. FDA said the term "may be related" should be qualified by saying "it is speculated."
4. A previous protocol for hycanthone authored by another M.D. Anderson investigator had been submitted but was withdrawn. FDA wanted to know why his name was not on this submission (he had left the institution).
5. FDA asked for the CVs of the M.D. Anderson institutional review committee which had approved the protocol.
6. FDA wanted the protocol to make provision for potential teratogenic effects of the drug.

Penta said he asked the FDA staff members at the meeting, which included representatives of the Oncology and Anti-infectious divisions, to release the

IND immediately so that tests could proceed while NCI made the revisions they had requested.

"It became clear then that the Oncology division had not reviewed the application," Penta said. "In fact, no decision had been made as to which division would have the authority to act on it."

The fact that several hundred thousand patients have been treated with hycanthone, with all the toxicological data that has provided, should have made approval of NCI's IND almost automatic. Instead, it was delayed for months, and is still being held up even after the other INDs have been released, simply because FDA (1) was being nitpicky over terminology and (2) couldn't resolve a minor jurisdictional matter among two of its divisions.

DCT Director Vincent DeVita commented that "it's ridiculous to delay this for even one week on the basis of semantics." But he noted that "some progress has been made" as evidenced by release of the other INDs and by FDA's agreeing to NCI's proposals for classifying and distributing investigational drugs to physicians. DeVita also pointed out that NCI has not been in compliance with FDA regulations regarding the monitoring and reporting of clinical studies.

"We're not back where we started," DeVita said. "We've come a long way. The major problem is the delay of IND submissions over trivial points."

Charles Moertel, a member of the Phase I Working Group and also of FDA's Oncology Drugs Advisory Committee, said he thinks the problem can be resolved satisfactorily. "I hope that closer relations can be developed between FDA and NCI. In fairness, they have some problems. We need to develop mutual respect, an atmosphere of cooperation."

NCI Director Frank Rauscher and DeVita met later last week with FDA Commissioner Alexander Schmidt and some of his staff. Rauscher said it was "an excellent meeting" and felt that progress had been made in reaching a better understanding between the two agencies. The hycanthone matter was brought up and Rauscher felt it would be resolved, "although we still have some problems to work out" relating to INDs.

RFPs AVAILABLE

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

RFP NO1-CP-65764-59

Title: *Influence of repeated low dose irradiation on mammary gland carcinogenesis in estrogenized rats*
Deadline: *April 23*

The proposer is to define the operational variables which influence the synergism observed in animal models. Evidence has shown that in the use of rat strains a synergism exists with both x-ray or neutron irradiation and estrogen administration in the induction of mammary gland tumors. This evidence must be considered in view of mammographic exposure as well as incidental chest radiation during periods of high estrogen levels, e.g., during replacement therapy or steroidal contraception. The NCI is seeking proposals to address this problem within the limits of the RFP workscope.

It is estimated this work will require one full time PhD level professional, two trained technicians and associated staff support as required per contract year. A three year effort is anticipated.

RFP NO1-CP-67763-59

Title: *Resource for microscopic and autoradiographic technology*
Deadline: *April 23*

The contractor will serve as a resource for preparation and examination of tissues both for high resolution autoradiography (1 micron sections of plastic-embedded tissues) and high resolution light and electron microscopy. Microscopy will be used to provide data on (1) the pathogenesis of tumors of various target organs such as lung, colon, skin, pancreas, prostate, etc.; and (2) the localization of labelled compounds, including carcinogens into cellular organelles by autoradiographic techniques.

Potential contractors should not suggest specific research problems in their proposals. Such problems will be generated during the course of the NCI's collaborative research program, and at a time, specific tasks will be identified for performance under this proposed contract. Such tasks will be either (1) a professional, collaborative relationship in which the contractor participates in the design, execution and evaluation of the task as well as co-authorship of any resulting publications, or (2) performance of an NCI protocol under direction of an NCI project representative. Each task will be a relatively short study of less than six months duration. It is anticipated that from five to 10 such tasks will be initiated in any 12-month period.

It is anticipated that at least two two-year funded Basic Ordering Agreements (BOA) will be negotiated. Approximately $100,000 each year will be established

for potential support of relevant tasks. It is hoped that more than one contractor will be selected for award from this RFP.

RFP NO1-CP-65765-59

Title: *Glucuronidase, sulfatase and other deconjugating enzymes in the pancreas and its secretions*
Deadline: *April 23*

NCI has a requirement to study in vivo or in vitro the enzymatic potential of the pancreas and its secretions and other appropriate tissues for deconjugation of various chemical carcinogens in bile. Each of these two experimental approaches have their advantages and utilization of both concommitently by the same or different institutions may be attempted.

Proposers should assess various possible methodologies for research relevance and potential for meaningful results and subsequently provide a rationale upon which the conceptual approach is based.

RFP NO1-CP-65762-59

Title: *In vitro cultivation of normal, prostatic epithelial cells*
Deadline: *April 23*

NCI has a requirement to develop techniques or procedures to culture primary cells from epithelial elements of human and rat ventral lobe prostate having as many normal biological characteristics as possible. Normal cells established in culture must ultimately be characterized to confirm their being (a) normal, not BPH or carcinomatous, (b) of prostate origin, and (c) of epithelial region.

Contract Specialist for four above RFPs:
Harold Smith
Cause & Prevention
301-496-6361

CONTRACT AWARDS

Title: Incorporation of two additional renovation projects, and exapnded research effort in the viral oncology, cancer treatment, and NINCDS program areas at Frederick Cancer Research Center
Contractor: Litton Bionetics, $496,441.

Title: Organ culture assay of vitamin A analogs
Contractor: Southern Research Institute, $1,333,511.

Title: Breast cancer detection demonstration project
Contractor: Duke Univ., $227,715.

Title: Biostatistical and operational support for lung cancer
Contractor: State Univ. of New York, $120,357.

Title: Evaluation of assays for circulating tumor associated antigens: Clinical usefulness of CEA as an adjunct in the differential diagnosis of gastrointestinal cancer
Contractor: Emory Univ., $52,505.

Title: Analysis of IR-1, RQV-1 and closely linked genes
Contractor: Stanford Univ., $79,777.

SOLE SOURCE NEGOTIATIONS

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

Title: A study on UV photocarcinogenesis
Contractor: Temple Univ.

Title: Review and analysis of categorical citation information relevant to the Diet, Nutrition & Cancer Program
Contractor: Institute for Scientific Information, Philadelphia

Title: Prototype comprehensive network demonstration in head and neck cancer
Contractors: Roswell Park Memorial Institute and Northern California Cancer Program.

Title: Psychological aspects of breast cancer
Contractor: Montefiore Hospital & Medical Center, Bronx, N.Y.

Title: Prototype network demonstration project for breast cancer
Contractors: State Univ. of New York, West Coast Cancer Foundation, Institute for Cancer Research, New England Medical Center Hospital, Wilmington Medical Center, Downstate Medical Center, Oklahoma Medical Research Foundation, and Georgia Cancer Management Network.

Title: Demonstration of benefits of early identification of psychosocial problems and early intervention toward rehabilitation of cancer patients
Contractor: Childrens Hospital of Los Angeles.

Title: Demonstration of cancer rehabilitation facilities and/or departments
Contractor: New York State Dept. of Health.

The Cancer Letter—*Editor* JERRY D. BOYD

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