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DCT BOARD OFFERS PHILOSOPHICAL, SOME FINANCIAL, AID TO PROGRAM PROJECTS, SAYS THEY ARE "IRREPLACEABLE"

Some assistance—largely philosophical but including a limited amount of financial help—has been offered to NCI's beleaguered program projects by the Div. of Cancer Treatment Board of Scientific Counselors.

(Continued to page 2)

In Brief

TERRY TO LEAVE NCI FOR JOB AS VP OF REVLON HEALTH CARE GROUP; NCI TRACKING SOURCE OF BREAKTHROUGHS

WILLIAM TERRY will leave NCI to become vice president for biotechnology research and development of the Revlon Health Care Group effective July 1. His new position will include directing Revlon subsidiary Meloy Laboratories where he will develop a biotechnology research center, with major thrusts in immunology and molecular biology. Terry has been director of the Immunology Intramural Research Program in the Div. of Cancer Biology & Diagnosis and he also headed extramural immunology research before the two were split. He held those positions during the two years he also served as acting director of the Div. of Resources, Centers & Community Activities. Terry will complete 20 years with NCI June 30, but only 14 were as a PHS officer and thus will not qualify him for retirement pay. . . . **WHERE HAVE** the breakthroughs come from? NCI has undertaken a study to track the source of support for major developments in cancer research. So far, Director Vincent DeVita said, the study has found that "one of the major discoveries of the last decade actually came out of a center core grant, and that led to a Nobel Prize." Also, "I think we'll probably find that study sections don't support paradigm changes, but they did support the research that led to new paradigms." . . . **NCI WILL** propose a new mechanism, Career Investigator Award. They will be five year renewable awards, with peer review based on the track record of the applicant. They will not be reviewed project by project, but will be reviewed intensively, DeVita told the Div. of Cancer Treatment Board of Scientific Counselors. Some details remain to be worked out. . . . **BERNARD WEINSTEIN**, who served as acting chairman of the Board of Scientific Counselors of the Div. of Cancer Cause & Prevention at the Board's recent meeting in the absence of Chairman Peter Magee, said he was "very impressed" by NCI's decision to lower the grant payline from 180 to 185. "That will be a tremendous stimulation not only to young investigators, but to old investigators with young ideas," Weinstein said. He commended DCCP Director Richard Adamson and his staff for "handling the budget with imagination and in a productive way, establishing priorities, cutting contracts, and implementing the payback system (for resources)."

DCT BOARD APPROVES MORE, EARLIER NCI STAFF HELP FOR P01 APPLICANTS

(Continued from page 1)

In a year in which some P01s considered scientifically strong nevertheless face loss of funding because of the level NCI budget and the falling payline, the Board approved a policy of extending support for up to three months after expiration to competing renewals which scored above the current payline but at or below the 1981 fiscal year payline.

"This is not to allow grants to die gracefully," Board Chairman Samuel Hellman commented. "The purpose is to keep those grants alive which still may be funded by the end of the fiscal year."

Currently, the payline for P01s is a 185 priority score; last year it was 207. NCI's experience is that as the end of the fiscal year (Sept. 30) approaches, unexpended funds become available in some program areas for transfer to others. The possibility thus exists that some and perhaps all of those P01s scoring between 185 and 207 will be funded.

The NIH program project mechanism recently has come under fire from another direction, in addition to the budget crunch. The budget squeeze on traditional R01 grants has driven their advocates into looking around for additional money, and the big program projects with their large budgets have become a target.

DCT Director Bruce Chabner assigned Arthur Levine, his special assistant for scientific coordination, the task of writing a statement of the issues of R01s vs. P01s and developing a set of recommendations for debate and discussion by the division's Board.

"The question of P01 vs. R01 grants has been a topic of discussion throughout NIH for a number of years, and this discussion has been given much recent impetus as a consequence of declining budgets," Levine wrote. "The R01 mechanism is regarded by many as the cornerstone of biomedical research in this country. While the P01 is usually looked upon as an important and unique means of research support, it is by definition a more complex instrument than the R01. Consequently, the many advantages, disadvantages, and inherent ambiguities in the P01 process mandate a continuing redefinition of its purposes as research needs and funding limits evolve."

Board members were critical of Levine's suggested recommendations; Sydney Salmon called them "deplorable" because they "leave out science in favor of administrative matters." But Chabner said Levine's document "is not deplorable—it is a response to criticism. P01s are faring badly in priority scores and are targets for criticism" In any case, the recommendations were only suggestions offered to the Board and did not represent NCI's position.

In the end, the Board approved a motion incorporating the major thrust of Levine's recommendations:

- Program projects are valuable, essential, and an absolutely irreplaceable mechanism for DCT.
- NCI program staff should become involved with P01 applications early in their development, critically evaluate preliminary outlines of P01 proposals. Staff should take an active role during the site visit to assure that the same stringent criteria are evidenced in each reviewer's and committee's critique.
- Review of P01s should consider the synergistic aspects of the proposals—the whole should be greater than the sum of its parts. Levine suggested that the four stringent criteria for P01 awards should be integration of the parts, quality of each part, synergism, and cost/management efficiency.
- NCI should have maximum flexibility in negotiating the final awards, using sliding scales within an acceptable funding range, such that only unquestionably strong research is funded fully and the greatest diversity of research ideas is permitted.

Some of Levine's suggestions "would kill program projects," one Board member said. Chief among those was that "unacceptable projects within the P01 should be assigned a score of 500 and included in the cumulative priority score."

Chabner said that current policy is that disapproved projects are to be taken into account is assigning priority scores but that no specific scoring penalties are attached.

Salmon objected. "Institutions are not penalized when several R01s submitted by their investigators are disapproved."

"What's being done is appropriate," Hellman said. "You can't have a P01 with three approved projects and 20 disapproved. If the character of the P01 remains intact, it's okay to pull out the bad ones."

The Board also objected to the suggestion that, at least in DCT, the ratio of P01 to R01 funds "should be significantly less than 1:1."

Hellman resisted that approach. "Let's avoid relative ratios," he said. "Based on merit, some years it could be 50-50, others it could be 70 percent in favor of R01s. Let the chips fall where they may."

The Board also was cool to suggestions that a budget ceiling be placed on P01s, that indirect cost rates should be fixed, and that a dollar limit should be placed on the total NIH support for any one investigator's laboratory, whatever the mechanisms of support.

Levine's report dealt with another problem, and offered a recommendation, which the Board did not get around to considering—support of departments with umbrella or block grants.

"There remains the problem of providing support for departments or divisions which have a critical mass (special resources, a special patient population, and/or unusual expertise), historic strength, and/or which serve a particular geographic need," the report

said. "It seems perfectly acceptable to identify these departments as such and to provide funds through an alternate mechanism, possibly administered by the Div. of Resources, Centers & Community Activities. However, work which cannot meet the [criteria he had listed for each project within a P01] should not be permitted to compete for the same grant pool as P01/R01 investigations. The Institute should decide how much money, if any, will be put into the sustenance of historically strong departments, independent of the absolute quality of their work at the moment, and allow such departments to draw only from that pool. One can readily defend the notion that a department which has a critical mass and a history of creativity will continue to be productive."

That suggestion could form the basis for further deliberations among NCI staff, their advisors and the scientific community.

DCT BOARD APPROVES CONCEPTS FOR NEW RFA, NEW AND RECOMPETING CONTRACTS

One new grant supported research effort and a host of new and recompeted contract programs were given concept approval by the Board of Scientific Counselors of NCI's Div. of Cancer Treatment. These were in addition to the approval of the concept of spending up to $3 million a year to support New Drug Discovery Groups (*The Cancer Letter,* June 11).

The Board approved issuance of a request for applications for a grant to study cocarcinogenesis in small animals irradiated in utero. The estimated first year award is $400,000. DCT staff rationale for the research:

The Low Level Radiation Effects Branch of the Radiation Research Program has as its major interest the effects of low levels of ionizing radiation on biological systems. For the purposes of the LLREB, low level is defined as acute exposures less than 10 rad. The major radiation effects occurring at these doses are mutagenesis, carcinogenesis and in utero effects. LLREB has specific interests in each of these low level effects including the influence of dose rate and LET.

Each year thousands of women are given radiodiagnostic examinations of the abdomen during pregnancy. The effects of these small doses of radiation on the developing embryo/-fetus are a matter of controversy. Several human studies suggest that doses of 1-2 rad may increase the postnatal cancer risk; however, other epidemiologic studies have not confirmed this. Factors such as gestational age at time of exposure and maternal health status are likewise not well understood. Clearly, the risks of radiation exposure during pregnancy must be more clearly defined in order to facilitate benefit/risk decision making in clinical practice.

The carcinogenic effects of low levels of ionizing radiation on the developing embryo and fetus in small animals are to be measured in order to define the risks of radiation exposure during development. Any small laboratory animal system may be used. Single cell, tissue and organ systems may also be used where appropriate, such as in investigation of mechanisms of radiation effects in utero. Proposed studies should evaluate cancer induction such as gestational age at exposure, maternal health and endocrine status should also be considered in the study design. Other factors which may be studied include dose rate and LET. Analysis of the data may include dose response curves at low doses and comparison of the types of tumors produced.

The Board approved four new procurements in radiation research which will be competed as contracts:

Comparative clinical NMR imaging studies. The total first year award was projected at $1.8 million, which would fund six institutions at $300,000 a year each ($200,000 plus indirect costs, based on $200 per patient per year).

NMR imaging is a radically new noninvasive method for diagnostic imaging that provides relatively high resolution (0.5 mm or less) images of all parts of the body without exposure to ionizing radiation. It holds the promise of providing differential tissue characterization without biopsy by noninvasive electronic measurement of tissue parameters. Technological improvements and clinical applications are proceeding rapidly on a worldwide basis. Scientists and clinicians can now see the potential for widespread diagnostic use. The current level of clinical investigation is limited principally by numbers of suppliers of the highly specialized equipment, by the cost of the imaging systems, and by lack of trained technical and clinical personnel.

Objective of this program is to carry out early comparative diagnostic studies using NMR and other ionizing radiation and ultrasound imaging systems to evaluate the capabilities and limitations of NMR imaging vis-a-vis the other modalities in the detection and diagnosis of various diseases and as a possible aid in the planning and assessment of therapy.

NMR imaging is one of several highly technical and expensive diagnostic imaging technologies that is undergoing a revolutionary rate of development and investigation of possible applications. Because NMR appears to have unique new capabilities, it is important to provide early clinical assessment of the present and potential state of this art in order to guide clinicians and technical developers regarding its uses and directions for improvement. Major economic costs and potential improvements in diagnostic capability are involved as well as possible major reduction in radiation dose to the population.

David Pistenma, who heads DCT's Radiation Research Program, said, "There is tremendous competition in industry to produce these, and efforts are being made by universities to acquire the equipment." He estimated the cost at $800,000 each. "I think we can define the role relatively quickly and compare with other imaging." NCI will not purchase any equipment; Pistenma said he expects six institutions will have the units installed and ready to operate by mid-1983.

Dose calculation for treatment with radioactively labeled antitumor antibodies. First year award estimate, $500,000, four years.

One of the most severe limitations in the delivery of tumoricidal radiation doses is the risk of injury to normal tissues surrounding the target volume. Interstitial and intracavitary irradiation are two long standing approaches to overcome this problem while intraoperative radiotherapy is a more recent area of investigation to overcome this limitation of external beam radiotherapy. The ideal radiation therapy system would be to have radioisotopes attached to tumor-specific antibodies which would concentrate the radiation dose in the vicinity of tumor cells whether in the primary tumor or in distant metastases. Advances in the development of monoclonal antibodies as well as experience with radioactively labeled tumor associated antibodies suggest that this may be a fruitful area of investigation in the next several years.

The purpose of this project is to develop methods for standardizing the calculation of radiation doses to tumors and normal tissues with the various isotopes (alpha, beta, or gamma emitters) likely to be used in therapy. Calculational methods must be correlated with three-dimensional anatomy [as defined by CT scanning, ultrasound, NMR, single photon emission computer tomography (SPECT), or positron emission tomography (PET)] and should be compatible with conventional radiotherapy treatment planning systems insofar as possible. Participating institutions will work individually on each of the tasks defined in the workscope for this project and also will participate in a collaborative effort to develop consensus criteria and guidelines for dose calculations with radioactively labeled antitumor antibodies.

It is essential that standardized methods be developed for calculating radiation doses to tumors and to normal surrounding tissues from radioactively labeled antitumor antibodies in order to understand the results of phase 2 clinical studies and to define criteria for phase 3 randomized trials. Unlike other uses of radioisotopes where the geometry is preplanned and then checked with x-rays, allowing for precise calculations, the distribution of radioactivity in conjunction with antitumor antibodies is uncertain until it happens. Thus, external imaging is essential to define the location of the radioactivity and must be quantitative in order to provide data for calculation. It also may be a dynamic process if the biological half-life of the antibody is significantly less than the physical half-life of the radioisotope. There may also be a need to repeat the dose calculations during the period of irradiation if the biological half-lives of the antibodies vary in different tumors or normal tissues.

Interstitial radiotherapy. First year award estimated $500,000, three years.

With the development of radioactive sources such as ^{125}I, ^{192}Ir, and ^{198}Au (which are much safer than ^{226}Ra) there has been renewed interest in the use of interstitial radiation therapy for the treatment of cancer. Thus, there are many more physicians performing interstitial transplants than ever before. There has also been an increase in the sophistication of calculations of dose distributions from interstitial implants. There is additional interest in interstitial implants in conjunction with hyperthermia for the treatment of selected cancers.

This collaborative effort is designed to enlist four to six leading institutions in a program: 1) to establish a limited registry of implant cases especially with regard to technique, dosimetry, acute and late toxicity, tumor response and/or local control; and 2) to develop guidelines for interstitial implants with various isotopes in each anatomic site alone and in conjunction with external beam radiotherapy or hyperthermia. This effect would provide a scientific foundation for the development of standards for interstitial radiotherapy and thereby would improve the delivery of interstitial radiotherapy throughout the country.

One of the presumed advantages of interstitial radiotherapy is the delivery of a high radiation dose to a well defined volume with minimal or no irradiation of normal tissues surrounding the target volume. Because innumerable techniques are used for the implantation of tumors in the same anatomical site, it is quite difficult to compare results among institutions. There is a tremendous opportunity to improve results of radiotherapy if criteria and guidelines for using this treatment technique are refined and made available to those physicians capable of performing implants. In addition to potentially improving the quality of interstitial implants in general, this effort may provide guidance and encouragement to additional physicians to learn the techniques of implantation.

Low LET treatment planning. Estimated first year award, $500,000, three years.

In the last several years, there has been increased sophistication of computerized treatment planning both for photon beams and for electron beams. These systems are becoming available to an increasing number of institutions each year. In parallel with this development, there has been an increasing availability of CT scanners for tumor and normal organ localization as well as developments in the use of ultrasound for this purpose. New developments include nuclear magnetic resonance imaging and better localization of tumors with contrast enhancing agents. These advances in tumor delineation and in computerized treatment planning have not been evaluated systematically by the radiotherapy community even though considerable effort has been invested in the development of hardware and software.

This effort will provide a focused evaluation of the capability of improving photon and electron beam radiation treatment dose distributions with presently available imaging systems and computerized treatment planning systems. This evaluation will include an assessment of the impact of improved treatment planning ranging from possible modification of simple treatments to incorporation of dynamic treatment wherein the patient, the gantry, and the beam collimators are moved simultaneously to optimize dose distributions. The results of the collaborative effort will be published as individual papers or in manual or book format.

By far the majority of radiation therapy treatments given in this country are with photons. Electron beam therapy and interstitial irradiation are used in a small percentage of patients individually and in no more than 10 or 15 percent of the patients in conjunction with external beam photon radiotherapy. Thus, the impact of improved low LET treatment planning on the results of treatment of patients throughout the country is potentially very great.

The Board gave concept approval to the recompetition of nine contract supported programs with an estimated first year award total of $11.3 million:

Clinical trials monitoring service. Present contractor is Mathtech Inc. Estimated first year award, $951,000, four years.

This is the phase 1 and early phase 2 clinical trials monitoring service. It provides two functions: 1) data management on a patient by patient basis of all phase 1 and some early phase 2 trials; 2) periodic site visits as required by FDA regulation.

During the first three years of this contract an information system was developed to monitor data on approximately 1200 patients in some 40 to 50 clinical trials. In addition, thrice yearly site visits are made to all institutions performing phase 1 trials.

Objectives: 1) Data monitoring of phase 1 and some early phase 2 trials of cytotoxic drugs and biologic response modifiers, 2) site visit monitoring of the same contractors, 3) to assist DCT in site visit monitoring of cooperative groups and noncooperative groups in investigational drug studies.

The monitoring of phase 1 trials will continue as under the previous contract. Remote data entry capabilities are expected to be added by the time this new contract is awarded. The level of effort of this contract for this segment will continue at approximately $551,000 per year.

Phase 1 and some early phase 2 trials of biologic response modifiers will be monitored in the same way as the cytotoxic drug program. BRMP estimates a requirement for approximately 500 patients per year. It is expected that this will require approximately $200,000 per year.

In order to assist DCT in site visit monitoring for trials other than outlined above, this contractor will provide clinical research associates (data managers) for the purpose of a) performing co-site visits with cooperative group monitoring visits, and b) organizing and performing site visits to nongroup investigational drug studies. The current budget estimate in-

cludes approximately 100 site visits per year at an annual figure of $200,000.

In vivo screening for antitumor activity. Present contractors are Arthur D. Little, Battelle Memorial Institute, IIT Research Institute, Mason Research Institute, and Southern Research Institute. Estimated first year award, $3,175,000, five years. See accompanying story on the Board's approval of major revisions in the screening program for more details on this recompetition.

Development of human tumor models for correlating in vitro drug sensitivity with in vivo response rate. Present contractors are Mason Research Institute and Southern Research Institute. Estimated first year award, $500,000, three years.

The current contract with Southern Research Institute is scheduled for incremental funding at approximately $2 million for its final year, 2/16/83-2/15/84. To facilitate competition of the major tasks (in vivo screening, detailed drug evaluation, tumor quality control, and preclinical model development) separation into discrete tasks and competition of each with closely related projects at other instititions is proposed. The Mason Research Institute contract is scheduled for recompetition in FY 83 and award in June 1983. Historically, approximately 15.5 percent of funds obligated to the Southern Research Institute contract have been expended in "associated model development." Accordingly it is recommended that $310,000 be reprogrammed from FY 83 funding and combined with $190,000 previously used for xenograft model development to form a single identifiable project area for competition at the $500,000 level, but not necessarily one contract.

The development of the subrenal capsule method as a screening tool has been completed and its use has permitted the conduct of the NCI preclinical tumor panel experiment. Heterogeneity (with respect to drug sensitivity) among subpopulations of cells within a tumor (e.g., lung xenograft) and variation in drug responsiveness among tumors of similar histology, whether animal or human, are well established findings. Past comparisons of preclinical and clinical activity and analysis of current tumor panel results do not suggest a positive correlation between efficacy in a given model and activity against other tumors of the same histological type. This may be a consequence of the limited number of tumors of a type included in past and present screening programs. There is a growing body of evidence suggesting that a model system composed of a number of tumors of the same histological type may, on the basis of percentage responders, predict preferentially for a reasonable clinical response rate. Pursuit of screens capable of measuring percentage responders among tumors of a specific type has been encouraged by the development of in vitro clonogenic assays. The results of the recent pilot study of clonogenic assays as large scale screens have provided the opportunity to address important questions related to the special requirements for screening large numbers of unknown materials.

A major consideration in developing this plan is the low plating efficiency of human tumor cells. The latter observation considered in the light of substantial evidence of heterogeneity among cells of an individual tumor indicates that selection pressure exerted in the in vitro cloning of fresh human cells is at least as great as the selection pressure exerted by serial transplantation in athymic mice. While the following represents the main task to be carried out, other tasks appropriate to the improvement of screening methods will be required as in the past.

Proposal: Development of two stage in vivo/in vitro human tumor screen using response rate as parameter for antitumor specificity of drugs.

Objective of this project is to determine whether an in vitro clonogenic assay, using transplantable human tumors grown in nude mice as the source of malignant cells, can be developed into a screening model capable of clinical predictability. In vivo human tumor xenograft screening currently is limited to too few tumors of any given histological type to provide presumptive information on expected clinical response rates. The use of clonogenic assays of fresh surgical explants for primary screening of unknown agents has the disadvantages of (a) low efficiency—less than half the tumors used exhibit an acceptable degree of clonogenicity in culture and (b) lack of selectivity in that a positive result indicates cytotoxicity only. In addition, the use of fresh surgical explants for screening in vivo or in vitro precludes confirmation of activity and analog comparisons. The use of a stable and reproducible battery of human tumors in an in vitro/in vivo model enhances the advantages and diminishes the disadvantages of both the in vitro and in vivo approaches. The feasibility of this approach has been shown in limited studies funded by NIH grants. Specifically, the plan requires the establishment of a battery of 10-15 human tumors of a histological type, e.g., breast carcinoma, as transplantable xenografts in nude mice. Selection of the individual tumors comprising the battery is based on the following criteria: (1) The tumors must be capable of transplantation and exhibit stable and reproducible growth characteristics over successive transplant generations; (2) the tumors must be capable of a high and predictable degree of clonogenicity (50-100 control colonies) in the Hamburger-Salmon assay when cells taken from nude mice are used.

Drug testing: (1) Compounds are screened in vitro against a battery of tumors of an histological type. (2) Compounds producing a 70 percent inhibition of colony forming units against any individual tumor are tested against the same tumor line in vivo to assess the degree to which the cytotoxicity observed in vitro reflects antitumor selectivity in vivo. (3) Overall activity is expressed as percentage responders, the same parameter used for clinical evaluation. (4) Only compounds that show in vitro activity are tested in vivo eliminating the need for in vivo testing and animal utilization for most agents. Having established that in vitro inactives are characteristically inactive in vivo against the same tumor, in vitro actives need be tested in vivo against responding tumors only.

Development and production of pharmaceutical dosage forms. Present contractor is the Univ. of Iowa. Estimated first year award, $350,000, three years.

This contract is a competition type service contract involving development of pharmaceutical dosage forms and production of these products for phase 1 or phase 2 trials. The contractor primarily develops and manufactures freeze dried dosage forms intended for intravenous administration, but also has the capability to provide a comprehensive line of other pharmaceutical products including infusion fluids, small volume sterile liquids, capsules, and tablets. The RFP will be similar to the original project plan except that shelf life studies will be eliminated in lieu of an award of a new shelf life surveillance contract. This change will relieve analytical time and allow additional support in product development.

Development of parenteral dosage forms for clinical investigation. Present contractors are the Univ. of Kansas and Univ. of Kentucky. Estimated first year award, $400,000, three years.

The Pharmaceutical Resources Branch monitors two contracts to provide dosage form development resources for difficult solubility and stability problems. Presently, the level of effort is about four technical staff years divided equally between the Univ. of Kansas and the Univ. of Kentucky. The workscope is essentially identical. The primary goal is to develop suitable pharmaceutical formulations of agents selected and assigned by NCI. The problems presented by these substances are severe (i.e., solubility improvements of 10^2 to 10^4). Physiologically acceptable approaches to improve the

solubility of these substances are relatively few in number (solvents, salts, complexes, surfactants, emulsions and reversible chemical modifications or prodrugs). The contractors are requested to provide an aceptable formulation as soon as possible using the most direct approach but development and evaluation of new methods are encouraged.

The Univ. of Kansas has held NCI contracts in this area of pharmaceutical science since 1972 and has developed formulation for a chemically diverse group of compounds. About three years ago, NCI recognized that increased resources were needed in this area and two contracts were awarded in 1980 to the Univ. of Kansas and the Univ. of Kentucky, each at a level of two staff years.

Based on the number of compounds presenting difficult solubility and stability problems encountered in the past three years, continuation of this project at an increased annual level from four staff years to six or seven staff years is recommended. The workscope will reflect this increase of level of effort but the objectives of the project will be similar to the current project. It is assumed that the annual work load will be between six and eight compounds requiring formulation research and development.

Analysis of chemical and pharmaceutical formulations. Present contractors are SRI International and Midwest Research Institute. Estimated first year award, $1,133,836, five years.

These contracts are a program resource which is responsible for the evaluation of bulk chemicals and formulated drug products for identity and purity. Reports of the analytical testing are used as a basis for assessing the suitability of bulk drugs or finished dosage forms for use in advanced antitumor screening, toxicological studies, formulation studies or for clinical trials. These data are also supplied to FDA as part of NCI's IND filings for new antitumor agents and related compounds. Historical summaries of the data are used in preparing specifications for the various bulk pharmaceutical substances. These specifications are used in procurement actions as well as for the routine quality control of these materials.

The contract with SRI International is the larger of the two. During the past calendar year, SRI has evaluated 106 lots of bulk and formulated drugs for identity and purity. Solubility and stability studies were completed on 13 different drugs. In addition to the more routine analytical assignments, SRI has performed additional studies in response to FDA inquiries regarding analytical data included in IND filings. Responses were submitted to FDA questions regarding aclacinomycin A, WR2721 and desmethylmisonidazole. Work is currently in progress to provide responses to questions regarding the chemistry of homoharringtonine and 5-methyltetrahydrohomofolate.

In order to ensure that the analytical chemistry needs of the program are adequately supported, the current 15 staff year level of effort will be increased to an 18 staff year level for the recompetition of the analytical package. This is necessary to ensure that the high priority needs of the program can be met promptly and that the current substantial backlogs can be reduced. The increased work load is due to the increasing complexity of new IND filings. In recent years FDA has required more extensive analytical data in support of IND filings. This in part parallels the evolution of high pressure liquid chromatography (HPLC) as a frequent method of choice for drug analysis.

Services in support of primary drug screening program. Present contractor is IIT Research Institute. Estimated first year award, $206,000, three years.

Major tasks of this contract are:

1. Evaluation of test results, requesting further testing of materials as required, scheduling them for timely review by the prescreen subcommittee and participation in these meetings.

2. Initiate requests for testing to screening contractors for those compounds designated for testing in additional test systems; assist in the evaluation of these test results and enter these evaluations to an on-line file which contains summary evaluation data and status information on all compounds being tested in the DCT panel of test systems. The contractor will also assist in the evaluation of test results and the establishment of protocols for development systems.

3. The current contractor provided the analysis and programming necessary to establish automated files for the prescreen subcommittee, operating committee, and a file for compounds of interest to staff. The contract will provide personnel to coordinate the data from staff for entry to these files and staff to record and enter minutes of the meetings of the operating committee. The operating committee file was designed to provide a management tool for NCI staff and include such data items as procurement requirements, screening test results, toxicology status and decision network status. This contract will also provide clerical support staff for data entry, typing and maintenance of files of selected agents and progress reports.

Primary genetic centers. Present contractors are Charles River, Harlan/Sprague Dawley, Leo Goodwin, and Simonsen. Estimated first year award, $4,476,000, three years.

These contracts serve as the nucleus for all breeding stock used throughout the DCT animal program. It is within these contracts that the pedigreed foundation colonies are maintained in associated flora isolators. From these isolatormaintained colonies, breeding animals are supplied to pedigreed expansion colonies, and, in some cases, directly to the large-scale production colonies. Breeding stock is then supplied from the expansion and production colonies directly to hybrid contractors, and to the research user in some cases.

It is NCI's intent to compete these contracts and make four awards, effective July 1, 1983, for a three year period. The contracts will operate as they have in the past.

Literature monitoring. Present contractor is Enviro Control. Estimated first year award, $110,000, three years.

The DCT Linear Array begins with compound acquisition. The chemical, biochemical, and biological literature is an excellent resource from which to acquire novel compounds. This project is designed to utilize the literature resource fully by providing timely access to the newest compounds and concepts appearing in the literature.

To date, 18 months into the project, approximately 1,100 compounds selected by the contractor have been received at NCI. The number received each month is still increasing; the latest monthly total was 121. Many more (14,700) have been selected by the contractor and requested through the mail. There is a wide variation in the response time from suppliers, so responses are still being received from even the earliest request letters. Aside from furnishing new compounds, NCI has gained many new suppliers because of this project. New suppliers generally mean new types of compounds. This project has been very fruitful in terms of acquiring highly novel structural types. Approximately 40 percent of the compounds received to date contained fragments (keys) never before tested by NCI. In addition, this project has identified potential radiosensitizing and radioprotecting compounds for acquisition.

This project has been very productive and the rate of return is increasing. We plan to continue this method of searching for active new types of compounds.

DCT BOARD APPROVES MAJOR CHANGES IN NCI DRUG SCREENING TUMOR PANELS

Major modifications to NCI's Drug Screening Program were approved by the Div. of Cancer Treatment Board of Scientific Counselors, changes that NCI said would reduce the cost of screening potential anti-

cancer agents by more than $1 million a year.

John Driscoll, director of the Developmental Therapeutics Program, told the Board that in the current panel of five transplanted mouse tumors and three human tumor xenografts, 92.4 percent of the compounds selected for further testing would have been picked up by only three—the L1210 leukemia and B16 melanoma mouse tumors and the human mammary tumor xenograft.

Driscoll recommended and the Board approved dropping the others from the panel—the colon 38 carcinoma, Lewis lung carcinoma, and DC8F1 mammary carcinoma mouse tumors, and the human lung and colon tumor xenografts. A new model, the M5076 mouse ovarian tumor which has been in development, will be added to the new panel.

The P388 leukemia prescreen will be retained to test 10,000 compounds a year, the same volume it has been handling.

Driscoll said the new panel would cut the screening cost from $5,695,000 a year to $4,675,000.

Board member Alexander Fefer questioned the decision to add the mouse ovarian tumor to the panel "just to pick up six to eight percent more" than the three tumor systems being retained from the old panel. Driscoll pointed out that while those three picked up 92.4 percent of all those selected by the old panel, "we don't know how many the old panel may have missed."

The old (current) panel was established in 1975 when the human tumor xenografts and additional murine systems were added to the L1210, B16 melanoma and Lewis lung tumors. The P388, which had been used for screening natural products, was switched to the role of prescreening, and the number of compounds going into the system was reduced from more than 40,000 to 10,000 a year.

Driscoll said that the screening program in the last seven years has demonstrated that solid tumors have selected compounds missed by L1210; that human tumor xenografts have selected compounds that were not selected by the murine tumor panel; based on the tumors evaluated, site of tumor origin is not a factor in drug selection; and that a positive correlation exists between the level of P388 activity and the percent of actives in other tumor systems.

The screening has been carried out through contracts with Arthur D. Little, Battelle Memorial Institute, IIT Research Institute, Mason Research Institute, and Southern Research Institute (See accompanying story on the Board's concept approvals). Approval of the new panel will require a reduction in total screening capacity. Most of those contracts are presently incrementally funded thorugh the 1984 fiscal year.

DTP staff said that "all have performed satisfactorily and the Drug Evaluation Branch prefers to not select one for elimination. Across the board reductions tend to increase the cost per test and are not cost efficient. Alternatively, the Branch is requesting approval to recompete the entire screening package one year earlier than originally scheduled. This recompetition would take place at an annual level $1 million less than was expended in FY 1982."

The new estimated first year cost of the recompeted contracts would total $3,175,000. The difference between that and the nearly $4.7 million cost of the screening program may be accounted for by the $225,000 a year contract with Jules Bordet Institute for screening and development of compounds from European sources which is not being competed now; portions of the Southern Research Institute contract other than in vivo screening which will be separated into discrete projects and competed at appropriate times; and various incidental costs.

SKIPPER, COHEN, BURKITT WIN 1982 GENERAL MOTORS $100,000 AWARDS

Howard Skipper, Stanley Cohen and Denis Burkitt are the winners of the 1982 General Motors Cancer Research Foundation prizes. Each will receive $100,000 and a gold medal.

General Motors said Skipper will receive the prize "for his contribution to an understanding of how fast growing cancers grow and how they respond to drugs." Cohen will be honored "for his discoveries contributing to an understanding of how cells grow and proliferate." Cohen is responsible for the discovery of the substance epidermal growth factor, a hormone like protein that regulates growth of many types of cells. Burkitt will receive his prize "for his identification of the childhood lymphoma bearing his name."

This has been a good year for Burkitt. Earlier, he shared the $50,000 Bristol-Myers Award with Michael Epstein.

ETHICS COMMISSION RECOMMENDS HHS TEST RESEARCH INJURY COMPENSATION

As expected, the President's Commission on Ethics in Medicine & Research recommended last week that the Dept. of Health & Human Services conduct an experiment to test the need for a program to compensate human subjects injured in biomedical research. The experiment would also test the feasibility of such a program in terms of administrative burden and costs.

The commission noted that "existing data suggest that the number of research injuries is not large. On the other hand, commentators often criticize the inability of our governmental system to respond to problems in advance of a crisis or catastrophe." By going ahead with the recommended experiment, "government has the opportunity to anticipate, rather than react, to headlines which may breed lasting public mistrust of science."

The experience with compensation for research injuries may also be helpful in evaluating the desirability and impact of possible programs to compensate for vaccine related injuries. The most recent experience with this problem was the indemnity program that was hurriedly included in the federal government's swine flu immunization campaign in 1976.

The term "compensation" refers to medical care and payment for lost wages and out of pocket costs provided to someone who has been injured. It does not refer to the payment subjects receive in some experiments simply for their participation. The experiment suggested by the commission would involve testing several alternative compensation plans; in each plan, compensation would be provided administratively through nonfault insurance without the need for judicial determinations.

Federal regulations now require that subjects be informed, prior to being enrolled in research, whether or not compensation will be provided in the event of injury. Currently, only a few institutions have formal compensation programs.

Compensation for injured research subjects has been proposed in governmental reports and scholarly journals for more than 20 years. But two objections have been raised: first, impracticality, and second, lack of need. The commission concluded that the best way to explore both of these issues was through an experiment in which HHS would provide funds to a limited number of research institutions to test several compensation programs with varying features over a three to five year period. The commission's report specifies a number of variables that deserve testing. As Morris Abram, the commission's chairman observed in releasing the report, "In the absence of such an experiment, we will be in no better position to resolve this persistent issue in five years than we are today."

Issues addressed by the commission were:

• Is there an ethical obligation to compensate injured subjects? The commission concluded that there is a moral obligation to compensate subjects for injuries that were caused by research, since research is an activity undertaken to benefit mankind generally and its costs ought not to fall disproportionately on a few people. Testimony from scientists and research institutions indicated that they generally feel themselves obligated to provide emergency medical care to injured subjects.

• Is the federal government, as a sponsor of research, obligated to establish a compensation program? Not necessarily; that depends upon whether injured subjects are not being fairly treated under the present system. To justify a formal program one must "demonstrate the existence of an unmet need and weigh that need against other needs in the public arena," the commission concluded. The current absence of definitive data on the incidence of injuries makes it premature for federal research sponsors to require compensation programs at research institutions; the absence of data does not, however, support the conclusion that injuries do not occur.

• How can it be established whether a program is needed? The experiment suggested by the commission would provide data on the rate and severity of injuries at participating institutions. Comparative data on the injuries at other institutions not providing compensation would be forthcoming if the federal agencies that support human research also adopt a recommendation made by the commission in an earlier report, "Protecting Human Subjects." Under that recommendation, scientists conducting federally supported research with human subjects would report annually the number of subjects who participated in each experiment and the nature and incidence of serious adverse effects that resulted, if any.

• What other information would the experiment provide? The experiment should indicate what effects would be expected in formal compensation programs. For example, will the availability of compensation generate an increased number of reported injuries? Will it produce a large number of specious claims? Through the experiment, different techniques for controlling a program's costs, both in claims paid and in administrative expenses, can be tested. The experiment would be designed to determine whether injuries resulting from a research procedure can be reliably distinguished from any adverse effects of therapeutic interventions or pre-existing illness. It may also be possible to discover whether the presence of a compensation program would make it easier for researchers to recruit subjects.

• Who ought to conduct the experiment? HHS, the major sponsor of human research, should design and administer the compensation experiment with appropriate consultation by other governmental bodies that sponsor or conduct human research.

The report, "Compensating for Research Injuries," has been printed and may be purchased from the Superintendent of Documents, U.S. Government Printing Office, Wahington D.C. 20402. The GPO Stock Number is 040-000-00455-6. Use that number when ordering. The price is $5.50 per copy.

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