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MOVE STARTS TO STRIP ANTICANCER DRUG REGULATION FROM FDA AFTER NEW CHARGES IT IS DELAYING INDs

Problems encountered by clinical investigators in dealing with the Food & Drug Administration have flared up again at a time when Cancer Program advocates are preparing revisions to the National

(Continued to page 2)

In Brief

NCI NEEDS TO MOVE QUICKER ON FUNDING HOT NEW LEADS, RAUSCHER SAYS; HARLEY DIRKS QUITS

NEW METHOD is needed to "fund faster a guy who comes up with a good idea," NCI Director Frank Rauscher told the President's Cancer Panel at its meeting in Houston. "We can't pounce on a new lead in less than 12-14 months through a contract, nine months with a grant." Rauscher does have the authority to award grants up to $35,000 in direct costs without approval of the National Cancer Advisory Board. But they do have to clear NIH study section review, and Rauscher pointed out the study sections meet quarterly, so that authority doesn't speed things up very much. "We need special banks of ad hoc review committees. We should be able to fund in two to three months," Rauscher said, then added, "I make Tom King very nervous when I talk like that." King, director of the Div. of Cancer Research Resources & Centers which administers most of NCI's grant programs, said that special quick review committtees would have "inate problems." Also, the assumption that "burning new ideas are being generated at an accelerated rate is something I question" . . . . **NOW THAT** the FY 1977 appropriation for NCI has been settled, Cancer Program advocates must turn their attention to the 1978 budget. NCI had its hearing with the Office of Management & Budget last week, presenting its arguments for the $955 million it is seeking. HEW has recommended to the White House that NCI get only $798.1 million, totally unrealistic since it is $20 million less than NCI is getting this year. If history is any indication, the Ford budget to be released in January will be closer to the HEW figure. . . . **CANCER PROGRAM** won't be helped any by the resignation of longtime Senate HEW Appropriations Subcommittee staff director Harley Dirks, who invariably helped steer the subcommittee into making substantial increases for NCI over the President's recommendations and over amounts voted by the House. Dirks quit after it was revealed he had ordered printed the record of some hearings on the 1977 appropriations bill which never took place. What happened was that when the Administration didn't move fast enough in getting material to the subcommittee, Dirks canceled appearances of HEW and NIH executives but told them they could submit statements for the record. When the record was printed, the statements were made to appear to be responses to questions of subcommittee members, as if the hearing really had been held.

FREIREICH BLASTS FDA; DEVITA AGREES IT COULD BE MORE FLEXIBLE ON INDs

(Continued from page 1)

Cancer Act for submission to Congress next year. Those problems could result in demands that Congress remove from FDA the responsibility for overseeing clinical testing of anticancer drugs at nonprofit institutions.

Emil (Jay) Freireich, head of the Dept. of Developmental Therapeutics at M.D. Anderson, used the occasion of the President's Cancer Panel meeting in Houston to charge that FDA has resumed harassing clinical investigators after a period in which it had seemed that pressures from NCI (and perhaps from certain congressmen and even the White House) had caused the agency to be more reasonable in dealing with cancer drug research.

"As soon as the pressure was off, they were right back again," Freireich said.

FDA last year held up approval of seven investigational new drug applications when the agency suddenly decided to apply regulations it had developed primarily to control drug development by pharmacuetical manufacturers to clinical research sponsored by NCI, universities and other nonprofit institutions. NCI and its collaborators in medical schools and hospitals were stymied by what they considered nitpicking, trivial and sometimes ridiculous requirements with no logical application to them.

The explosive reactions that produced resulted in FDA backing down to some extent and releasing the INDs. It also resulted in an agreement between NCI and FDA for new procedures relating to the furnishing of experimental drugs by NCI to investigators, which FDA had threatened to halt. And NCI agreed to establish new reporting procedures and to more carefully monitor clinical trials.

Freireich cited three examples to show that FDA has resumed what he feels is unwarranted interference which has interrupted clinical research. Since last July M.D. Anderson's studies with thalicarpine and anguidine have been stopped entirely, and its maytansine study threatened by questions "which required elaborate responses" from the principal investigator, Gerald Bodey.

The thalicarpine study was stopped because of reports of the occurrence of mydriasis—"dilation of the pupil of the eye," Freireich told the Panel in a tone heavy with sarcasm. "This notification (by telephone) occurred after our phase I study of single dose therapy had already been completed. . . We received a copy of the letter approximately two weeks later, which indicated that the objection FDA had to the protocol was the occurrence of mydriasis, some vague statement about treatment dealing with toxicities observed in phase I. There was nothing of substance in the letter that could either guide us or indicate to us what the reasons for disapproval were. Nonetheless, we were forced to discontinue our study."

The anguidine study was stopped after FDA ordered that doses could not exceed 2.4 mg/m^2 "although we had already treated more than 20 patients at twice that dose without substnatial or serious toxicity," Freireich said. "Again, the reasons were not specified. Again, we had already proceeded beyond the point which we had been interdicted to proceed. Again, we were forced to discontinue the investigation."

Robert S.K. Young is FDA's group leader for oncology and is the agency's executive who is responsible for initiating the actions which have frustrated and infuriated Freireich, many of his colleagues and at times NCI staff members (he is not to be confused with Robert C. Young, who is chief of the Medicine Branch in NCI's Div. of Cancer Treatment).

Young told *The Cancer Letter* that M.D. Anderson's study with thalicarpine was not the only one involving that drug and that the order to stop it "probably was based on toxicities observed elsewhere." A DCT executive confirmed that, noting that the drug had produced EKG changes in a study conducted at the Washington D.C. Veterans Administration Hospital.

As for the anguidine study, Young said that while a dose higher than 2.4 may not have been a problem at M.D. Anderson, it had been elsewhere and "is a problem we had to work out."

Freireich told the Panel of another incident which he considered unwarranted interference in M.D. Anderson's internal operation:

"In August, this startling event occurred: Dr. Bowen, the chairman of our Surveillance Committee, received a telephone call from Dr. Young of FDA inquiring about procedures of our Surveillance Committee. He also indicated clearly to Dr. Bowen that our informed consent documents were deficient because we continuously referred to treatment as one of the potential benefits to the patients, which he thought was out of order. He subsequently telephoned Mr. Robinson, a member of our Surveillance Committee, who is an attorney, and had the same discussion with him, which was subsequently transmitted to us through a memo which Mr. Robinson prepared to record that phone call.

"In mid-September, Dr. Robert Benjamin, who is the chairman of two studies of new drugs for which we have our own INDs, received a letter from FDA asking for documents relating to Surveillance Committee activities and annual reports."

Young told *The Cancer Letter* that he had initiated the discussions with Bowen, Benjamin and Robinson after reviewing M.D. Anderson's patient consent statements. "Language in the statement seemed to give considerable prominence to treatment," Young said. "Informed consent cannot be coercive. If you

stress treatment, that tends to make it coercive. It can give the patient the feeling that if he doesn't go along and agree to participate in the experiment, he won't receive adequate treatment."

Young said he consulted attorneys outside FDA about the problem. Their advice was that stressing treatment in patient consent forms could be coercive.

"One way to approach the problem was to ask the institutional review committee to consider it," Young said. "So I called Dr. Bowen. We have a list of the committee members, and I asked Dr. Bowen if I could call one other member, so that we would have at least two opinions from the committee. I picked the lawyer, because the interpretation of 'coercive' is a legal thing."

Young said he asked for documents from the Surveillance Committee to assist him with his review of protocols submitted by Benjamin. Young noted that the committee had to approve the protocols before they were sent to FDA, and "we wanted to know what the committee had to say about them to help us in our evaluation."

Perhaps the most serious charge made by Freireich is that FDA is attempting to enforce its regulations in the same manner and to the same degree for anticancer drug development as it does for drugs intended for treatment of less serious diseases. It is "the application of the same principles for drug regulation which are used to avoid catastrophes for the development of drugs for very minor problems, such as sedatives, tranquilizers, pain remedies, etc.," Freireich said. "In those circumstances, of course, the potential risk so far outweighs the potential benefits that regulations . . . are quite stringent."

Application of those regulations to patients with neoplastic diseases is something else, Freireich insisted. "Absolutely new drugs are almost universally studied in patients with malignancies where the established modes of treatment offer no or very little hope for benefit. These patients have two needs. One is a desperate need for someone to attempt to reverse an inevitably fatal outcome and secondly, tremendous pressure for speed since any discoveries made after they die will obviously be of little benefit to those individuals. In that circumstance, of course, the potential for benefit is so enormous compared to small risks that such strenuous regulations are not only unnecessary, but naturally obstructive."

Young denied that FDA considered cancer drugs in the same category as headache remedies and tranquilizers when enforcing regulations.

"They are much more stringent in other divisions," Young said. "The dilemma of cancer patients is taken into consideration in making judgments." Young said that when the charge was raised previously by Freireich and some of his colleagues, it was brought to the attention of FDA Commissioner Alexander Schmidt. "The commissioner feels that the regulations should be applied but that we should take into consideration the seriousness of the disease."

Panel Chairman Benno Schmidt indicated he was surprised by Freireich's assertions. "I was under the impression we had gone some distance in getting this problem turned around," Schmidt said. "You sound like it is just as bad as it ever was, if not worse."

"That's the reason I'm here," Freireich said. "This is typical of the regulatory process. While we're being reassured, the same problems are going on. If there has been progress, I don't know what it is."

Vincent DeVita, director of the Div. of Cancer Treatment, did not attend the Panel meeting. He later told ***The Cancer Letter*** that FDA's rigidity on INDs was still a problem. "We haven't made much progress there. . . Many of the points holding up INDs are relatively minor."

The progress that has been made includes the distribution of drugs "which has worked out very nicely," DeVita said. New reporting procedures and monitoring of clinical trials have also been areas of agreement with FDA.

DeVita said that Young "really isn't asking for more than is in the regulations, but he could be more flexible. We aren't 100% clean, but we know where the problems are."

A new problem on the horizon is the indication by FDA that it may require the filing of separate INDs for each new drug combination. "That could really tie us up in knots," DeVita said.

The move to legislate FDA out of anticancer drug development regulation, except for that done by industry, is an alternative "that would be preferable to us," DeVita said. "The regulations were written for industry." If that happens, NCI would have to assume more responsibility in overseeing clinical trials than it now has. "We may be underestimating the work load, but it still would be preferable," DeVita said.

KING ADVISES CENTERS TO EMPHASIZE REGULAR PROJECT GRANT APPLICATIONS

Cancer centers may have a better chance of getting increased support from NCI by emphasizing regular research project grants and by submitting more "tightly knit" program project applications, Thomas King, director of the Div. of Cancer Research Resources & Centers, told an audience at Duke Univ.

King spoke as part of the dedication ceremonies for the Duke Comprehensive Cancer Center's first two buildings—The Edwin L. Jones Basic Cancer Research Building and the animal laboratory and isolation facility.

King warned that the task of ordering program priorities "will become increasingly more difficult, and the competition for new and renewed support more severe." But he said that "we intend to meet as best we can prior commitments to our most meritorious ongoing research and research support projects.

"We do not envision a curtailment in support of

cancer centers. To do so would markedly weaken their local impact and national value," King said.

King said, "It is encouraging to witness the genuine spirit of collaboration that has developed here at the Duke Univ. Comprehensive Cancer Center since 1968 when an exploratory grant award was made to help you develop a long-range plan for this complex. This in turn led to the construction program, the first phase of which is now completed."

Cancer Panel Chairman Benno Schmidt said that the federal government cannot afford to abandon basic cancer research support. Schmidt said he was worried by the notion developing in Congress that "irrelevant" basic research should be weeded out from "relevant" basic research.

It is the total of the science base that becomes relevant," Schmidt said. "Any building block that elucidates cell structure or mechanisms is relevant, although it may not seem so when described separately in advance."

Wolfgang Joklik, chairman of Duke's Dept. of Microbiology & Immunology and director of basic research at the cancer center, said the public often ignores the basic research that comes before a medical breakthrough.

Penicillin applications and a vaccine against poliomyelitis were built "on an infinity of bits of information from laboratories where there was no thought of either curing bacterial infection . . . or protecting mankind from poliomyelitis. Basic scientists are seeking answers where we don't know the questions," Joklik said.

The Jones Building, with its 74 labs, doubles the amount of cancer research space at Duke. The animal laboratory is a four-module containment facility allowing researchers to work safely with microorganisms of known or unknown danger to man. A $5.6 million grant from NCI helped finance the buildings. The center's third structure, a four-level clinical research building, is scheduled for completion by the end of 1977.

William Shingleton is director of the Duke Comprehensive Cancer Center.

M.D. ANDERSON DEDICATION INCLUDES "SIMPLE MESSAGE" FROM BETTY FORD

First Lady Betty Ford, speaking at the dedication of M.D. Anderson's new $70 million facilities, said she had a "simple message for all of you who worked so hard to create this fine institution—thank you for a job well done. As a former cancer patient, I know that without institutions such as this one, I wouldn't be alive."

Mrs. Ford, who underwent a mastectomy two years ago, pointed out that Sept. 26 was the second anniversary of that event. "I'm happy, healthy, and grateful. In a few weeks, I'll complete my chemotherapy."

Two days after Mrs. Ford's surgery, the preliminary findings in the breast cancer studied headed by Bernard Fisher and supported by NCI were reported, in which the drug L-PAM was found to increase by five-fold the disease free rate of mastectomy patients with positive lymph nodes.

Mrs. Ford eas found to have four positive nodes, and the L-PAM regimen was recommended for her.

"At the time of my mastectomy, I was pleased to see the response to it," she said. "It prompted many women to get a check up."

Former Texas Gov. Allan Shivers, who is chairman of the Univ. of Texas System Board of Regents, revealed the secret of the university's success in obtaining financial support from the state for its cancer facilities.

"Every year when Lee Clark (president of the Univ. of Texas System Cancer Center) goes to the Senate Finance Committee with his budget needs, the hearing always ends with the chairman asking, 'Dr. Clark, are you sure that's all you need?'"

Albert Owens, president of the Assn. of American Cancer Institutes, said, "These buildings are a great achievement, but they are an even greater challenge. More is required. Cancer remains an unsolved problem, a national health problem of the first order."

Clark was scheduled this week to be named president of the American Cancer Society at the annual meeting of the ACS Board of Directors in New York, succeeding Benjamin Byrd Jr. R. Wayne Rundles, professor of medicine at the Duke Univ. School of Medicine, was to be elected vice president and president-elect.

FREDERICK RFP OFFICIALLY HELD UP; NCI PROBABLY WILL REJECT MORE DELAY

Issuance of the RFP for recompetition of the contract for operation of the Frederick Cancer Research Center has now been officially delayed. NCI sent out an amendment to its original synopsis announcing the RFP; the amendment said the delay was "due to more intensive review."

The delay was made necessary when the ad hoc committee chartered to help write the scope of work for the new RFP insisted it needed more time to delve into the FCRC operation (*The Cancer Letter*, Sept. 24).

Ronald Defelice, NCI contract officer for FCRC, said that RFP requests already received will be honored and need not be renewed. Defelice may be reached by phone at 301-663-7148.

No new date for issuing the RFP has yet been established, but it probably will be soon after the committee meets again, in mid to late November. NCI feels that the RFP must go out before the end of the year, in early December if possible. Committee members had suggested that the contract with Litton Bionetics be extended six months to permit that much additional time to develop a new RFP. NCI is not expected to go along with that request.

MOLONEY CONVINCES MOST (BUT NOT ALL) NCAB MEMBERS OF VIRUS PROGRAM VALUE

Viral oncology, the field which stimulated intense public and congressional interest in cancer research in the 1960s, has not enjoyed any growth in NCI support over the last three years, and in fact both budget and personnel for the Viral Oncology Program have decreased slightly during that time. Demands of other programs have been partially responsible, but more important have been criticisms of the program's size in relation to the fading of the dream that it would produce vaccines to prevent cancer.

John Moloney, associate director for viral oncology at NCI, acknowledged those points when he described the program's extramural contract operations to the National Cancer Advisory Board. He followed that with a discussion of the program's new "research thrust" and some of its recent accomplishments which seemed to convince at least some Board members that viral oncology is still a very important part of the Cancer Program.

"The goals of the program have changed," Moloney said. "We are no longer solely concerned with the search for, the characterization, the isolation of that nice little round virus particle which might have something to do with cancer, then take that particle, produce a vaccine and go out and cure and prevent cancers in men.

"We feel we have become somewhat more sophisticated. We have developed within the program highly refined techniques of procedures for the detection of viral and subviral components in both normal and malignant tissues. Through coordinating efforts of the program, the virologist and molecular virologist, the experts in molecular hybridization, the immunologist and molecular immunologist have identified endogenous and exogenous tumor viruses in normal and tumor tissue of many mammalian species including subhuman and human primates. They have identified the oncogenic portion of the viral genes and have located these in the host cell with highly defined viral probes, developed within the program.

"We are studying and learning something of the nature, the character, the mechanism of transformation of the normal cell to malignant state, and the degree of viral gene expression in such transformation. Whether this expression is in terms of the synthesis of a specific protein, or whether it is a group of proteins packaged as a virus particle, we feel it is only through such studies that meaningful, specific preventive or control measures can be developed.

"In this respect, our viral oncology scientists have developed and are developing specific biochemical and immunological tests for the identification of groups and individuals at high risk to cancer, and are working with chemotherapists and can advise an appropriate therapeutic regimen. Additionally, they can judge, through the various probes they have developed, the prognosis of a patient in therapy."

Board Chairman Jonathan Rhoads asked Moloney to name "two or three of the accomplishments you're most pleased with."

"We've put a lot of emphasis into studies of the RNA tumor viruses and the role these viruses play in the induction of cancer," Moloney answered. "For example, the program has permitted David Baltimore to come up with his polymerase studies, reverse transcriptase findings, by making available resources to him. Additionally, the program supports such outstanding scientists as Dr. Spiegelman, Dr. Argyris, and some individuals in California who have been able to use the polymerase to detect certain viral or subviral components in both the normal and malignant cells. This is in the RNA field.

"We have in the program defined endogenous viruses versus exogenous viruses, viruses which are inate to every host cell versus the horizontal transmission of exogenous tumor viruses.

"We have been able to take a virus, split it up into its component parts, to identify specific structural proteins, and we hope oncogenic proteins associated with these viruses, and we can therefore characterize the various isolates that are coming out of the human cells, the animal cells, and so on.

"We have been able to take the nucleic acid information of these viruses, the actual viral genetic information, to split this up into the genetic information which has to do with the creation, the direction toward the synthesis of the structural protein and further identify the oncogenic, the trus oncogenic portion of these viral genes. Additionally, we have been able to locate these oncogenic viral genes in the host cell. This has been done in the avian field, the mammalian field, and very recently in a study about to be published, in the subhuman primate field.

"DNA virus, we have shown for example that under certain experimental circumstances that classic herpes viruses, those which induce fever blisters, can indeed be oncogenic under the right circumstances.

"We have shown further that these herpes viruses turn on, switch on, or induce the expression of the classical type C viruses in the DNA field.

"In the area of breast cancer, Dr. Spiegelman, Dr. Sloan and others in the program have been able to show–let's take the mouse system–type B viruses induce breast cancer in the mouse. Other viruses, the primate virus, are also associated with breast cancer.

"We've been able to use these agents as probes, and probe into certain human breast cancer and come up with similar type of information in human breast cancer tissues.

"Dr. Spiegelman has been able to use specific proteins associated with the mouse mammary tumor virus and track a mouse undergoing therapy. Whether it be chemotherapy or surgery, he can predict when an animal is going to go into relapse. He can tell you how effective a certain regimen is. He is now extending these studies into the human area and has some

very, very promising results which perhaps you can hear of in November (at the Board's next meeting, scheduled for Nov. 15-16)."

Benno Schmidt, chairman of the President's Cancer Panel, asked Moloney, "In view of the fact that we do have now more than a certain amount of scientific interest in this area, why not phase out contract research and rely on investigator initiated, grant supported, study section reviewed research?"

"If we did that, we wouldn't have a program," Moloney answered.

"Would we have the same amount of good research going on that we have now?" Schmidt persisted.

Moloney said that "There's a lot going in the grants area now that is not supported and should not be supported by the Virus Cancer Program. But a program assumes that you have a goal to obtain. . . . What is the most effective way to implement work toward achieving that goal? The contract mechanism has worked extremely well. It has brought together the finest minds in viral oncology, into a single group. Individuals do not feel they are being directed in any sense. It is true collaboration, with coordination of their efforts, toward specific goals. It has worked. Under the grants mechanism, you wouldn't have this type of coordinated effort."

"You're saying you have $23 million worth of better research, better reviewed, better coordinated, better calculated to provide results toward a goal," Schmidt said. "If that is true, that we have a better program here than if we relied on grants, then the next question is, shouldn't we be doing the same thing in immunology, or membrane physiology, or other areas that may be just as important?"

"We are in immunology," NCI Director Frank Rauscher said.

"That's not the same. Look at the budget," Schmidt said.

"There are only certain phases of research appropriate to the attainment of goals," Moloney argued.

Board member Harold Amos noted that contractors involved in the Virus Cancer Program include "most of the major people in the field. How much chance does a young investigator, say 30 years old, have of getting into the program?"

"Every chance," Moloney answered. Unsolicited proposals, many of them from young scientists, go through the program's peer review system and many are funded, he said. "We've also received excellent responses for CREGs (Cancer Research Emphasis Grants) from young investigators."

Board member Bruce Ames asked why David Baltimore was not being supported by grants rather than contracts. "He has ideas, he can compete."

"He has grants," Moloney said. "But he has a contract with us for a specific task, a specific goal."

Panel member R. Lee Clark commented that the Virus Cancer Program supports "a great deal of basic research that may not have any application to cancer."

Ames agreed that "this research illuminates a lot about virus mechanisms. You can defend it."

Board member Frederick Seitz said that many government agencies have "highly successful programs with contracts. The only concern is, do you have proper review. The only other argument is philosophical."

Board member Werner Henle pointed out that the Virus Cancer Program use of contracts has "permitted more money to go into the Cancer Program." Applications for virus research "do not fare well in grants review."

"Because a lot of scientists fell it is not ready," Schmidt said.

Rauscher suggested that the important question is, "Is the quality of what's being done as good as it would be with grants?"

Henle answered, "Look at the people involved."

"He's saying, Schmidt said, "that not only is it just as good, with good people, but those good people probably wouldn't be funded under the grants mechanism."

Ames suggested that NIH be asked to establish a new study section to review grant applications in the virus field. Rauscher pointed out that Moloney's review committees, dominated by non-government scientists, ensure "thorough review, true peer review. It is a very competitive program."

Amos agreed that the "quality and nature of review and the people in it are first rate. I don't believe you can do everything as well with grants as you can with contracts. You can do things with contracts that you can't do with grants, if the quality is there."

One board member was not convinced about the value of the entire viral oncology effort.

Philippe Shubik, who as director of the Eppley Institute is primarily interested in chemical carcinogenesis, noted that when the virus research effort started with the Virus Leukemia Program in the mid-1960s, "there was a provision that if the findings were negative, that would be the end of the program. I think they were negative, and that should have been the end of the program."

Shubik said it is his "personal view that there is ample evidence that originally many cancers seemed to be more likely of viral origin than is now the case. Consideration should be given to putting such a high priority on virus research. It is incredible that chemical carcinogenesis only now gets almost as much money as viral oncology.

"It is doubtful that so much money and priority should go into an area where the scientific underpinning is not sufficient to support it," Shubik said.

DISEASE-ORIENTED PROGRAMS MUST BE COORDINATED, RABSON TELLS NCAB

Alan Rabson, director of NCI's Div. of Cancer Biology & Diagnosis, made another strong case for the contract mechanism in appropriate situations. Major

contract programs are carried on in his division in immunology (*The Cancer Letter*, Oct. 8), diagnosis, the Breast Cancer Task Force and the basic research program at the Frederick Cancer Research Center.

Rabson told the Board about the Breast Cancer Task Force and FCRC programs.

Rabson said the BCTF is "an experiment in science management and approach." It is headed by Pietro Gullino.

"Why contracts rather than grants in the breast cancer program?" Rabson asked. He quoted Gullino: "If one accepts the premise we need a disease oriented program, then one has to coordinate the input of various disciplines in the study of a disease or a diseased organ, for example, breast cancer."

Rabson said this coordination in the BCTF consists of three components: First, definition of problems to be studied in the formulation of RFPs—"the RFP in the BCTF is the critical part of the whole program"; second, selection of proposals, done with the type of peer review "that matches anything in the grants program"; third, continual monitoring of progress.

"Gullino feels and I agree that the contract mechanism can operate in this way," Rabson said. "With the grant mechanism, coordination is difficult. The reality is that any research program with a specified goal must have a built in structure which permits (a) the definition of the goal; (b) the selection of an approach; (c) the monitoring of progress.

"This is the philosophy of the RFP in the Breast Cancer Task Force," Rabson continued. "The RFP is a question to the scientific community, with presentation of a problem and freedom of approaching it the way the investigators feel is most appropriate."

Rabson said he had discussed with Gullino the relative merits of investigator initiated research versus an approach such as he had just described. "Where the RFP is formulated by the best scientists, do scientists [who are awarded the contract] perform well when they don't formulate the broad question?"

Rabson said Gullino had pointed out to him that a number of distinguished scientists in the world had operated with this type of direction in their research. "This is not one of our contractors," Rabson said, showing a slide of Louis Pasteur.

"Pasteur made 10 major contributions to research, and at least three were in response to what in present day parlance would be an RFP," Rabson said.

Pasteur's studies of fermentation were initiated after an industrialist who had been having trouble in manufacturing alcohol from beets asked him if he "would be good enough to grapple with the problem involved," Rabson said. "In a sense, this is what the BCTF often does with its RFPs—it encourages the investigator to grapple with a certain problem."

The second type of directed research that Pasteur was involved with was a study of the diseases of wine, Rabson said. "This was not quite so gentle an RFP; it was undertaken at the command of Napoleon III, in 1863.

"His monumental work on the silkworm diseases was an area in which he had no interest until the minister of agriculture commissioned him to determine the causes of the diseases then destroying the silkworm industry in France."

Rhoads suggested that Pasteur may be "best known for his work on other projects which perhaps were grant supported."

The BCTF includes four major research areas—diagnosis, epidemiology, experimental biology and treatment. A technical review committee, chaired by a non-NCI scientist and including a majority of non-government scientists, is responsible for each area.

The Task Force meets once every two months in two-day sessions. The first day consists of reports from contractors on their programs; the second day, the four committees meet. "Everyone knows what's going on in all areas," Rabson said. "The groups get together, they interact, they come up with new ideas . . . It's a scientific exercise in coordination."

The technical review committees generate discussions for RFPs, they review and score proposals, and they follow each project. Dual review is provided by a steering committee, an NCI staff group which cuts across the division lines. The steering committee coordinates the efforts of the technical review committees and does the final writing of the RFPs.

Rabson said the basic research program is unique in that it is one in which the contractor proposes the nature and approach of the research. "It's the closest to real investigator initiated research that is done under a contract," he said.

The basic research program is carried out under the overall contract with Litton Bionetics for operation of the Frederick facility. Michael Hanna, director of the program, is a Litton employee.

"Hanna is primarily interested in tumor immunology, and the theme of that basic research program at Frederick originally was in the immunology of cancer," Rabson said. "It was to include interdisciplinary research in immunology, viral chemistry, cellular immunology, immunogenetics and the biology of metastasis. We have now added sections in molecular, cellular and systemic aspects of cancer."

William Pomerance, chief of the Diagnostic Branch in the division, said that diagnostic research is organized into "five areas of involvement"—breast cancer diagnosis, diagnosis, cytology automation, diagnostic radiology, and lung cancer. Research contracts totaling $8.7 million were funded in fiscal 1976, plus another $500,000 in support contracts.

Each of the research areas has an advisory committee. Pomerance said that "all projects are initiated by the committees. After discussion, deliniation and refinement, and some workshops, RFPs are prepared by staff and presented to the steering committee for final evaluation and determination of need."

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., NIII, 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 noted.

RFP NCI-CB-74118-37

Title: *Studies on the influence of chemical carcinogens*

Deadline: *Feb. 7*

NCI is interested in establishing a contract for studies on the influence of chemical carcinogens, including environmental agents, and/or hormones on viral gene expression in the initial events leading to mammary tumor development. A model system in which both viruses and chemical agents have been implicated in the induction of mammary neoplasms should be employed.

Contract Specialist: Robert Stallings
Biology & Diagnosis
301-496-5565

CONTRACT AWARDS

Title: Validation and utilization of microbial mutagenesis systems as prescreens for chemical carcinogens
Contractors: New York Medical College, $198,706, and Litton Bionetics Inc., $305,979.

Title: Biology of neoplastic liver lesions in mice
Contractors: Univ. of California (Davis), $499,204, and Univ. of Maryland, $185,472.

Title: Induction of colon tumors in guinea pigs
Contractor: Cornell Univ., $410,361.

Title: Automated system for HLA typing
Contractor: Stanford Univ., $42,234.

Title: Production and delivery of three HPLC interface systems
Contractor: Thermo Electron Corp., Waltham, Mass., $29,980.

Title: Cancer control radiologic physics centers
Contractor: Memorial Hospital, NYC, $87,533.

Title: Preparation of carcinogenesis bioassay reports
Contractor: Mitre Corp., $734,606.

Title: Study influence of interaction between environmental factors
Contractor: Univ. of Southern California, $90,055.

Title: Support services for field studies on cancer incidence
Contractor: Westat Inc., Rockville, Md., $109,901.

Title: SEER and third national cancer survey data processing
Contractor: GEOMET Inc., $74,790.

Title: Monitoring of biohazard containment facilities
Contractor: Enviro Control Inc., $233,000.

Title: Studies on in vitro malignant transformation
Contractor: Microbiological Associates, $205,157.

Title: Development of mammalian cell lines
Contractor: Microbiological Associates, $231,779.

Title: Four new alteration/renovation projects at Frederick Cancer Research Center
Contractor: Litton Bionetics Inc., $106,451.

Title: Computer support for cancer information dissemination
Contractor: IIT Research Institute, $84,784.

Title: Studies on in vitro transformation of mammalian cells
Contractor: Univ. of Texas (Galveston), $103,450.

Title: Immunotherapeutical trials with human tumors
Contractor: Hutchinson Cancer Research Center, $104,745.

Title: Studies of in vitro malignant transformation
Contractor: Hershey Medical Center, $56,973.

Title: Studies of the genetic and immunological factors in viral leukemogenesis
Contractor: Albert Einstein College of Medicine, $49,000.

Title: Study the influence of interaction between environmental factors
Contractor: St. Louis Univ., $185,332.

Title: Chemoimmunotherapy of actue myelocytic leukemia
Contractor: Mount Sinai School of Medicine, $71,167.

Title: Cervical cancer screening program
Contractors: Alabama Dept. of Health, $397,000; Tennessee, $192,000; and North Dakota Dept. of Health, $173,382.

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