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

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FDA THROWS UP IND ROADBLOCK, THEN REFUSES TO ANSWER INVESTIGATOR'S LETTERS ABOUT IT

The Food & Drug Administration last year reversed its long-standing policy of routinely approving investigational new drug applications from physicians and scientists of recognized competence, a practice which had facilitated clinical research and helped immeasurably in the development of improved cancer therapy.

(Continued to page 2)

In Brief

CANCER PROGRAM GETS SHOT IN ARM WITH OVERRIDE OF APPROPRIATIONS VETO; CARTER TO LEAVE NCI

OVERRIDE OF the HEW appropriations bill veto was a major victory for the Cancer Program in more ways than just the extra money it meant for the current fiscal year, important as that was. The size of the vote—310-113 in the House, 70-24 in the Senate—portends well for fiscal 1977 appropriations when Congress again will have to impose its will over the Administration's to adequately fund the Cancer Program. Moreover, House and Senate backers of the override effort repeatedly cited the need for continued support of the Cancer Program; cancer research in fact was the leading edge in the debate, indicating the legislators feel it still enjoys massive popular support despite the detractors who have been surfacing. Joseph Minish (D.-N.J.) told the House that failing to override would "emasculate" the Cancer Program and submitted a statement listing 14 cancer control projects that would be curtailed or eliminated. Birch Bayh (D.-Ind.) told the Senate that the Administration's request for NCI "is nothing short of incredible," and referred to progress made in treating bone cancer. . . . **THE MESSAGE** may have finally gotten through to the Office of Management & Budget. OMB first indicated to NCI and other HEW agencies that recision requests would be submitted to Congress cutting health spending back to the President's budget. That would be a futile exercise, since Congress can kill such requests merely by ignoring them, although it could delay release of the funds for two to three months. HEW argued against this tactic, reportedly sold OMB, and OMB deputy director Paul O'Neill was scheduled to meet with President Ford this week to try to talk him out of it. If O'Neill is successful, the new money could start flowing in a few days, including that to NCI grants approved for funding but waiting for their money since last November. . . . **STEPHEN CARTER**, deputy director of the Div. of Cancer Treatment, will leave to become director of the Northern California Cancer Program. . . . **JAMES HOLLAND**, one of the most outspoken, effective and respected leaders of the Clinical Cooperative Group Program, suffered a myocardial infarction a few days before last week's meeting of Cooperative Group chairmen, which he heads. He is reported progressing satisfactorily at Mt. Sinai Hospital in New York.

FDA CAN'T EXPLAIN WHY LETTERS GO UNANSWERED AFTER FIVE MONTHS

(Continued from page 1)

The new policy has changed the ground rules, threatens to impede clinical research with unnecessary and interminable delays, and—in the opinion of many investigators—is withholding treatment that might help hundreds of otherwise doomed cancer patients.

The new policy basically is this: Instead of approving an IND on the basis of the competence of the investigator and his institution, FDA is requiring detailed information on the history of the drug, its composition, design of the study, and other material investigators feel would be too burdensome to provide.

Investigators might learn to live with the new requirements, at considerable cost in clerical time and delays. But it has become apparent that FDA was not prepared to handle the increase in correspondence and information flow generated by the new policy. The result has been a near-total halt in approval of INDs for oncologic drugs.

M.D. Anderson's difficulties with an IND application for the drug Peptichemio reveals a classic example of a bureaucracy incompetent to respond to its constituents.

Gerald Bodey, deputy head of M.D. Anderson's Developmental Therapeutics, outlined the difficulties in a memo to Emil Freireich, his chief:

"On March 28, 1975, I submitted our IND application for Peptichemio and on April 23, 1975, the notice that we were permitted to order the drug was sent to us. Subsequently, we received the drug and initiated our studies.

"On Sept. 3, 1975," Bodey continued, "I received a phone call from Dr. Robert Young of FDA [group leader for oncologic drugs] informing me that it was FDA's impression that we had not initiated our studies because they had raised questions regarding the IND application. They had a record of a phone call to me on May 9 or May 10 informing me of this. I had no recollection of this phone call and I received no written interdiction at that time. As a result of the Sept. 3 telephone conversation, I received the enclosed letter of Sept. 6, which in effect ended our studies of Peptichemio, since we had already exhausted our initial supplies."

The Sept. 6 letter to Bodey was sent by William Gyarfas, director of FDA's Div. of Oncology & Radiopharmaceutical Drug Products, a division of the Bureau of Drugs. Gyarfas wrote:

"After a more comprehensive review of your proposal, it is determined that the notice [IND application] is deficient according to the following sections of form FD 1571:

"1. A complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage, is not provided.

"2. Complete information about such [outside the U.S.] distribution and investigation has not been submitted.

"3. An accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation for the information of clinical investigators has not been provided.

"4. An outline of the phase or phases of the planned investigations has not been provided.

"Further, the protocol should be revised to meet the guidelines for a well-designed clinical investigation. Section 314.111 of the Code of Federal Regulations, copy enclosed, contains a helpful outline.

"At this time it is necessary to restrict the study as follows:

"1. Investigation with this agent is limited to Dr. Bodey. All patients receiving the drug must be under the personal supervision and care of Dr. Bodey.

"2. Investigations are only to be conducted at the M.D. Anderson Hospital.

"3. Administration of the drug is limited to the quantity presently in Dr. Bodey's immediate possession.

"4. No new protocols can be initiated without prior clearance from this Administration.

"5. The initial dose may be raised to 35 mg./M^2/day four times three days at intervals not less than three weeks apart if prior experience supports such an increase. All further escalations of the dose must be in increments not greater than 5 mg./M^2 with at least three subjects per dose observed carefully for at least four weeks each. Dose may not be raised above 50 mg./M^2/day four times three days at intervals not less than three weeks apart without prior approval by this Administration.

"6. No more than 20 additional subjects can be enrolled in this study.

"We may communicate with you should any questions arise as a result of further review of your Notice [application]."

Bodey not only objected to some of Gyarfas' demands but also was offended by the implied lack of confidence in M.D. Anderson's competence. Bodey wrote back on Sept. 15:

"You should be aware of the fact that the decisions that you have transmitted in this letter have resulted in cessation of the studies of Peptichemio; not because of any desire on our part to discontinue investigations of this drug but because the restrictions make it impossible to effectively conduct a clinical trial. We consider this most unfortunate since the patients who were receiving this drug have terminal cancer and there is no other form of therapy available for them and there is a possibility that this particular drug might be of benefit to these patients.

"I object to the insinuation that the protocol was 'not a well designed clinical investigation' since this protocol has been designed and reviewed by experts

in the field of clinical investigation. I also find it incomprehensible that a 'more comprehensive review of your proposal' was not conducted until the end of August when we had received notice in a letter dated April 23 that the protocol had been reviewed and we were now permitted to obtain drug for the study.

"I would be interested in knowing on what basis the decision was made that 'no more than 20 additional subjects can be enrolled in this study.'

"We have made every effort to cooperate with FDA in submission of this IND. It has been particularly difficult to accomplish this since the manufacturer of the drug is in Italy. Raising new questions and objections to the study so many months after its initial application has succeeded only in preventing us from carrying on a study of this drug which might be of potential benefit to patients who are dying of malignant diseases.

"Your statements concerning deficiencies in providing information state that we have not provided 'an accurate description of the prior investigation and experience.' Are you implying by this statement that the published data that we have submitted is inaccurate? We have submitted all of the published material available to us at the time of submission of this application which we considered to be sufficiently substantial to permit us to do the studies which we had planned in our protocol.

"I have contacted the manufacturer in Italy regarding the request for additional information on the composition of the drug and an updated report on any other studies that might be available. I would appreciate receiving from you, in writing, information regarding how the following restrictions can be removed:

"(1) Limitation of administration of the drug to patients directly under the personal supervision and care of Dr. Bodey.

"(2) Limitation in the quantity of the administration of the drug to the quantity currently in our possession (this drug supply has virtually been exhausted at the present time).

"(3) Limitations in dosage escalation as prescribed in your letter.

"(4) Limitation of the number of subjects.

"(5) At what point in time you will have completed raising any questions regarding this protocol so that we can be assured that our studies can operate smoothly without further interference on your part.

"I appreciate the concerns on the part of FDA regarding potential toxicity, proper control of drug preparation, etc., but it is unfortunate that these concerns have prevented clinical investigation of a potentially effective drug for patients with terminal cancer being administered by competent clinical researchers."

That was Sept. 15. When more than a month went by with no response from Gyarfas or anyone else at FDA, Bodey wrote again, on Oct. 20:

"On Sept. 15, 1975 I sent you a letter asking for specific information on how we could correct some of the problems that have arisen with our IND. 11,442, Peptichemio. Subsequently, we have received more drug from Italy, but because of your interdiction, are not able to continue our studies with this drug.

"At the present time, I have not received a reply from you regarding my letter and I am disturbed by the fact that we are having to deprive terminally ill cancer patients from receiving a medication that might possibly benefit them. I think that this is of sufficient importance that it deserves prompt attention.

"I have contacted Dr. DeBarbieri in Milan, both by letter and by telephone in an attempt to get the additional information which you have requested. However, I would appreciate your permitting us to continue studies with this drug while we are awaiting this further information. I recognize the problems that you have raised regarding this drug, but I also recognize the fact that we have patients for whom no other therapy is available who might benefit from this drug and that this delay is preventing them from receiving such potential benefit. Your attention to this matter would be greatly appreciated."

Despite the urgency in Bodey's pleas, Gyarfas did not respond. Finally, early in November, Leo Collins, consumer safety officer in Gyarfas' office, phoned Bodey and told him they had never received the Sept. 15 letter. Bodey immediately sent three more copies, but he might as well have saved the postage, because he has yet to receive an answer.

The Cancer Letter phoned Gyarfas seeking an explanation of why Bodey's letters had not been answered. Here's how the conversation went:

CL: Dr. Gyarfas, we're doing a story about the difficulties Dr. Bodey and Dr. Freireich have been having with you concerning their INDs, and . . .

Gyarfas: You're not going to put your name on a story with only their side included, are you?

CL: That's why I'm calling you, to give you an opportunity to comment.

Gyarfas: The Food, Drug and Cosmetics Act requires us to see that good science goes into clinical research.

CL: Are you saying that Dr. Bodey's IND application wasn't good science?

Gyarfas: What he submitted was good, but it wasn't complete.

CL: How about letting him go four to five months without responding to his letter?

Gyarfas: I don't know. I'll have to look into it.

CL: Is it a clerical problem? The Cancer Program must have generated a lot more clinical research, and more IND applications. Are you understaffed?

Gyarfas: No more so than other divisions.

CL: Well, do you have any idea at all why it takes so long to respond to an investigator's questions about why you're holding up his IND?

Gyarfas: You weren't listening. I said I don't know why. I'll have to pull the file and check it out.

At the risk of being presumptuous, ***The Cancer Letter*** suggests that Bodey's letters weren't answered because no one in Gyarfas' office knew how to answer them. How does an FDA medical officer who may or may not have much if any clinical investigative experience tell a prestigious institution like M.D. Anderson that he knows better than its staff how a clinical trial should be designed? How does he justify his arbitrary dosage limits against a protocol designed by people who see thousands of cancer patients a year?

An FDA medical officer sometimes has a gut feeling about a drug in an IND proposal but he may not have the time or experience to adequately document his reservations. He can ask for more information and hold up the IND until he gets it. That may have been the case with Peptichemio, but the impression is that FDA went a little farther, and threw in some restrictions that were not justified. When Bodey pressed for an explanation, rather than back down, Gyarfas (or his staff member) handled the problem by just not answering Bodey's letters.

They did have one excuse for delaying. Bodey was unable to obtain from the Italian supplier of the drug, one A. DeBarbieri, in Milan, details on its composition. He wrote, asking for a statement of the quantitative content of aminoacid in the side chains of the drug; the aminoacid sequence in the side chains; any information available on whether the molecule remains intact after injected intravenously; and steps taken to insure the same drug composition from lot to lot. He followed up with phone calls, but at last word still had not received the information.

If that information is really necessary to the safe conduct of clinical trials, FDA could have said so and based its delay on that. The other issues appear to be matters of judgment, with M.D. Anderson's pitted against that of FDA, and FDA wasn't ready to back down.

Another theory was offered by an FDA staff member, who asked to remain anonymous.

"You should see those baskets, with the masses of mail and paper spilling over. It's unbelievable. And the mail in and out isn't handled like it is in your office. It's got to go to three or four stops, where it's approved, checked out, routed, copies made. I can understand how a letter can go unanswered for four months. It's not good, but it happens."

Freireich and Bodey have another IND which has been blocked by FDA, for the drug tetrahydrouridine. This drug is an inhibitor of the enzyme which inactivates another important cancer chemotherapy drug, arabinosyl cytosine. The IND application was filed July 9, and Gyarfas sent his notice of disapproval Aug. 20. Gyarfas wrote:

"The following list identifies the parts under FD Form 1571 that were either omitted or inadequately submitted. The failure to submit adequate information under these parts compels us to conclude that it is not reasonably safe to initiate clinical studies. Until the additional required information is received and you are told that we conclude it is reasonably safe to initiate clinical studies, the studies you propose may not be legally conducted under this IND. Your submission of additional information must be in triplicate.

"1. Enough details about the investigations to permit scientific review have not been provided.

"2. The description of prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation is insufficient.

"3. An outline of any phase or phases of the planned investigations must be provided. Protocol DT 75-38 is too broadly written to be meaningful.

"4. A complete toxicological profile of the drug tetrahydrouridine, including the combination with Ara-C. This should include administration by all routes proposed.

"5. A repeat dose study should be done in at least two different animal species, as recommended in Cancer Chemotherapy Reports, 3 and 4, January 1973.

"None of the five points raised in the letter were points of substance in our personal opinion," Freireich said, "and they are nonetheless extraordinarily difficult to fulfill with a resubmission. We are still anxious to proceed with this drug and are preparing a response which we are not very hopeful about."

There seems to be three aspects to the problems in FDA's oncology division:

—The disorganized, or perhaps over-organized, and understaffed system for processing mail.

—Understaffing of the entire division, particularly with medical officers, in view of the increasing workload generated by the growth in cancer clinical research.

—Failure to acknowledge the differences between firms who might carelessly or willfully submit incomplete or inaccurate data in pursuit of profits, and research instititions in which peer review mechanisms—approved and monitored by NIH—are supposed to prevent gross excesses.

The National Cancer Act in both the original and revised editions totally ignores the role FDA plays in clinical research. Apparently no one considered the increased demands the National Cancer Program would place on the Div. of Oncology & Radiopharmaceutical Products, and no provision was made in the Act for beefing up the division's capabilities. The problem is further complicated by the fact that FDA's appropriation is not considered with the rest of HEW, by the House and Senate HEW Appropriations Subcommittees. It is handled by the Subcommittees on Agriculture, Environmental and Consumer Protection, who have no voice in cancer research funds.

The problems can't be attacked successfully until FDA, particularly the Bureau of Drugs, accepts a

commitment to do whatever is necessary to facilitate cancer clinical research, at the same time maintaining its consumer protection role—those functions are not incompatible, providing they are reasonably administered.

Once that commitment is made, ways could be found to get FDA the resources it needs. NCI could transfer funds, and probably could lend some of its expert consultant slots provided by the Cancer Act. When the Act is up for renewal next year, provisions could be added, authorizing positions and/or funds earmarked for the oncology division.

RAUSCHER SAYS HE MAY LEAVE, BUT WILL STAY AT LEAST THROUGH JUNE

NCI Director Frank Rauscher edged closer last week toward the long-rumored announcement that he will leave his prestigious but salary-limited position for a far better paying one outside government.

Rauscher told a meeting of the American Assn. of Cancer Institutes that he was in the process of negotiating terms and conditions with his prospective employer, including the date when he would make the move. But he insisted he had not yet definitely decided to leave NCI, and in any case would stay at least through June.

"I don't want to leave," Rauscher recently told ***The Cancer Letter.*** "I haven't decided that I am going to leave. But the pressures are building. I'm almost at the point where I simply have to make a move."

Rauscher's salary has been frozen since 1969, except for a 5% increase government executives got last year, the first time in six years those at the top level of $36,000 have had a raise. Rauscher has received offers tripling that figure and including other perquisites.

One condition Rauscher has set on other employment: It can have no connection with cancer research in any way. "I'm not going to be like a Pentagon general who retires one day and shows up the next with a fat job selling tanks to the Army. The only way I'll do it is to go out clean, into a job with no relevance to cancer."

That probably cut down the list of prospective employers somewhat, although Rauscher did not rule out working for an organization that does business with NCI as long as his job was not involved. One firm mentioned in the rumor mill was the Whitaker Corp., parent company of Microbiological Associates, one of NCI's major contractors.

Rauscher made his mark as a virologist and isolated a mouse virus that bears his name. He moved up to head NCI's Etiology (now Cause & Prevention) Division, and was chosen in 1972 as the first director of the National Cancer Program and to head NCI after passage of the National Cancer Act. Some congressmen, including Chairman Daniel Flood of the House HEW Appropriations Subcommittee, were cool to Rauscher at first because he wasn't an MD. Rauscher eventually won them all over, now without question is the Administration's most effective spokesman on Capitol Hill. He has also been effective in explaining the Cancer Program to the public, an effort that involves encouraging realistic expectations as well as selling.

As an administrator, Rauscher moved cautiously at first, then finally made some tough reorganization decisions, mostly involving the consolidation of treatment functions.

Rauscher was appointed to the job by President Nixon largely on the recommendation of Benno Schmidt, with the concurrence of other members of the Cancer Panel and other leaders in the cancer effort.

Schmidt told ***The Cancer Letter*** this week that "I have strong hopes a way will be found to keep him. He's done an outstanding job, and would be extremely difficult to replace."

Speculation on who Rauscher's successor will be if he does leave has become the dominant conversation piece among NCI staff, advisors and just about everyone else with an interest in the Cancer Program. Two names come up in nearly every discussion: Tom Frei and Vince DeVita.

Emil (Tom) Frei is director of the Sidney Farber Comprehensive Cancer Center which is affiliated with Harvard Univ. One of the most respected cancer clinical researchers in the country, Frei probably could get a leave from Harvard for a few years, go on active duty with his PHS commission and thus do better salary-wise than Rauscher. He could put in enough time for PHS retirement (he has 17 years now).

All NCI division directors, and Rauscher's deputy, Guy Newell, are automatic possibilities, if the appointment goes in-house. But DeVita has emerged as the NCI strong man, after he won for his Div. of Cancer Treatment the responsibility for most NCI treatment programs. He handled the reorganization smoothly but firmly, and displays the kind of persuasiveness and wit in dealing with his advisory committees that has made Rauscher so effective.

Other directors of comprehensive cancer centers are at the top of the speculation list. Among these are Gordon Zubrod, long-time NCI executive, former DCT director, and director of the Miami center; Gerald Murphy, Roswell Park director, member of the National Cancer Advisory Board, chairman of the Cancer Control & Rehabilitation Advisory Committee and secretary of the UICC; and John Durant, Univ. of Alabama, chairman of the Southeastern Cancer Study Group.

Another name mentioned but quickly withdrawn was that of R. Lee Clark, president of the Univ. of Texas System Cancer Center, member of the President's Cancer Panel, and president-elect of the American Cancer Society.

"I've already got enough to do," he said when told

at the meeting of the Assn. of Community Cancer Centers in Jacksonville that he was one of the objects of speculation. He probably is the only cancer scientist in the world whose prestige is already so great that it would not be enhanced by the NCI directorship.

"WE NEED YOU," EVERYONE TELLS ACCC; GALE KATTERHAGEN ELECTED PRESIDENT

Assn. of Community Cancer Centers members held their second annual meeting last weekend in Jacksonville, Fla., and they heard this refrain from every speaker who is participating one way or another in the National Cancer Program: "We need you."

Representatives of comprehensive cancer centers, representatives of rural and metropolitan hospitals, NCI executives, and state and national representatives of the American Cancer Society all agreed that ACCC must be involved in the effort to bring the benefits of cancer research to cancer patients.

The organization is working directly to that end and has completed the planning phase of its grant from the NCI Div. of Cancer Control & Rehabilitation to establish relationships between community centers on the one hand and the comprehensive centers and clinical cooperative groups on the other, with the goal of improving clinical investigations in the community centers.

Four comprehensive centers and three cooperative groups agreed to participate in the demonstration/implementation phase of the project, provided DCCR awards the funds to complete it. A site visit team met with ACCC members involved in the project in Jacksonville.

The four comprehensive-community center relationships that will be developed with the grant are USC-Bakersfield, Hutchinson-Tacoma, Miami-Jacksonville, and Alabama-(community center to be selected).

The cooperative groups participating will be the Children's Cancer Study Group A, Southeastern Oncology Group, and the Radiation Therapy Oncology Group.

ACCC received $100,000 for the planning phase of the grant and was asking about $500,000 to implement it. The project would be completed in one year, according to the schedule.

If successful, the project would be used to show other community and comprehensive centers how to develop their working relationships, assisting each other in treatment, research, community outreach, communication, and education programs.

"We must be interdependent," Jack Hartmann, associate director of the Hutchinson Comprehensive Cancer Center, told the group during the workshop on components of a community cancer program. "The Cancer Program won't work unless comprehensive centers and the ACCC work together. . . Without you, the cancer control program won't work."

Lee Clark, president of the Univ. of Texas System Cancer Center, said in his keynote address that one in five cancer patients were cured in 1946 when he opened M.D. Anderson. "It's now one in three, and I hope it will be one in one when I'm still around to enjoy it. If that happens, ACCC will have a lot to do with it."

Clark said the five-10 year lag in getting research results into practice is the problem that can best be tackled through ACCC.

Gordon Zubrod, director of the Miami Comprehensive Cancer Center, echoed Clark's statements.

"Pessimism is not warranted in light of what we've learned in the past few years about the management of cancer," Zubrod said. "We're in a position now to join forces to reduce sharply mortality from certain kinds of cancer. We've got to try to find ways of translating research into the hands of physicians faster than we have."

Zubrod pointed out that penicillin and atabrin were discovered in the 1920s yet did not come into effective medical use until World War II. Methotrexate was discovered in 1948, "but we didn't learn how to use it in osteosarcoma until 1974. How many lives were lost in the interval?"

The opportunity to speed up transfer of research knowledge came with the Cancer Act, Zubrod said. "The comprehensive center is a window to the research world for the practicing physician."

Gale Katterhagen, Tacoma, was elected president of ACCC, replacing James Donovan, who remains on the board of directors and will continue as principal investigator for the grant. Donovan recently left private practice in Bakersfield to become director of cancer control activities and cancer research center development for the West Coast Cancer Foundation in San Francisco.

(A complete report on the ACCC meeting will appear in next week's issue of ***The Cancer Letter****)*

FOURTEEN NEW STUDIES FUNDED BY TOBACCO RESEARCH COUNCIL

Fourteen new scientific studies dealing with various aspects of smoking and health have been announced by the Council for Tobacco Research—U.S.A. Inc.

Among them are projects on the inhibition of cancer by different chemicals, the influence of nicotine on pregnancy and the effects of cigarette smoke on the body's disease-fighting system.

Grants are made by the council following a review of applications for research support by a scientific advisory board currently consisting of 11 physicians and scientists.

Recipients of new grants, their institutions and the titles of their research projects:

Sonia Buist, Univ. of Oregon, "The role of alpha-one antitrypsin deficiency as a risk factor in the development of chronic airways obstruction."

Hugh Evans, Jewish Hospital, Brooklyn, "Relation-

ship of non-MM phenotypes and lung disease among infants."

Gad Feinstein, Tel Aviv Univ., "Studies on peptide bond specificities, active site and inhibition of human leucocyte proteases which are implicated in the pathogenesis of pulmonary emphysema."

Lars Friberg, Karolinska Institute, Stockholm, "Causes of death in relation to smoking habits and other behavioral and environmental factors. A study on the Swedish twin registry."

Stig Kullman, Univ. of Lund, Sweden, "Influence of smoking on human fetal growth and post-natal development and on fibrinolysin in the blood of pregnant women. Accumulation and/or damage to human placental and fetal lung tissues of nicotine."

Joseph Lauweryns, Univ. of Leuven, Belgium, "The neuro-epithelial bodies: their role and structure as intrapulmonary neuro (chemo) receptors in normal and various physiological, pharmacological and pathological conditions."

Herbert McKennis, Medical College of Virginia, "Transport and metabolism of amine constituents of cigarette smoke."

Carl Pierce, Harvard Medical School, "Biology of suppressor T cells."

Irene Wang, Medical Univ. of South Carolina, "Genetic differences in the in vitro metabolism of chemical carcinogens by human and mouse tissues."

Lee Wattenberg, Univ. of Minnesota Medical School, "Inhibition of carcinogenesis by benzyl isothiocyanate and related compounds."

James Will, Univ. of Wisconsin, "Morphologic and functional correlations of the APUD cells of the lung."

Kohi Yoshinaga, Harvard Medical School, "Effects of nicotine on pregnancy."

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 NCI-CM-67083

Title: *Pathological monitoring services project*
Deadline: *March 24*

This project will include the pathological monitoring and examination of approximately 2,000 rodents (primarily mice) annually. The pathological examination will include the following organs and tissues: skeletal, muscle, bone, respiratory tract, from nasal passages to and including lungs, middle ear, heart, stomach, intestine, liver, spleen, kidney, reproductive organs, brain and skin.

Contract Specialist: T.R. Hardy
Cancer Treatment
301-427-7463

RFP NCI-CP-FS-61034-55

Title: *Support services for field studies*
Deadline: *Feb. 12*

The Chief, Epidemiology Branch, Field Studies and Statistics, NCI, wishes to contract with a highly-experienced organization for the purpose of providing computer programming and technical (non-professional), managerial, and clerical support for the field studies being carried out by research investigators of that branch. The field studies consist of investigations on cancer patients and high-risk groups, and are conducted in whatever locales within the United States may yield meaningful new clues to cancer etiology.

The potential contractor is expected to:

(1) Assist in establishment of new studies based on study designs and data provided by the Epidemiology Branch.

(2) Assist in data and biologic specimen collections for both descriptive and analytic studies.

(3) Assist in recording, computer programming, and summarizing data collected in order to permit detailed analyses of such data.

(4) Assist in typing, duplicating, filing, and referencing all data.

(5) Assign personnel anywhere in the United States for short or long periods as applicable, in order to carry out the particular studies desired.

The contractor must have its established offices and technical equipment within easy commuting distance of NIH, because of the necessity for frequent discussions and data reviews with research investigators.

The contractor must provide the following personnel, all of whom should be highly experienced: (a) a full-time management specialist with expertise in demographic or biologic research management; (b) 4 full-time medical abstractors/interviewers; (c) a one-half time nurse for collecting bloods and other specimens; (d) one and one-half time programmers; and (e) 1 secretary having scientific typing experience.

A resume of capabilities should not exceed 5 pages and should cover: (a) experience with related projects; (b) description of facilities and equipment; and (c) resumes of key personnel.

Responses should not include cost or pricing information. Responses directed specifically to the points mentioned herein are requested. Only those sources

which are considered to be qualified for this project will be invited to submit a proposal at the time a Request for Proposals is issued. Sources which are judged not to have superior qualifications will not be notified. Organizations interested should submit resumes of their qualifications and experience by Feb. 12.

Contract Specialist: Fred Shaw
Cause & Prevention
301-496-1781

RFP NCI-CM-67065

Title: *Study on the distribution, disposition and metabolism of antineoplastic agents*

Deadline: *Approximately April 12*

NCI is interested in organizations having the capabilities and facilities to perform the above titled project. The emphasis of this contract will be the development of a comprehensive pharmacokinetic model for disposition of a useful antineoplastic agent in a suitable animal model, and the further testing and refinement of this model in man. It is intended that the initial phase of work will be concerned with the preclinical studies, with commencement of clinical work only after analytical methods are established and a preliminary pharmacokinetic model has been determined in experimental animals.

The contractor shall: (1) measure concentrations and cumulative amounts of parent drug and metabolites where applicable in plasma, urine, feces, and relevant body tissues as feasible in animals and man; (2) determine drug-tissue interactions such as plasma protein binding, tissue binding, lipid solubility, etc., of parent drug and its metabolites; (3) develop a kinetic model which incorporates the above findings in a quantitative manner.

The principal investigator should be trained in analytical pharmacology, drug metabolism, and pharmacokinetics and would coordinate a staff having background/experience in several specialties such as: drug metabolism, disposition, pharmacokinetic modeling, and clinical pharmacology of antineoplastic agents.

Contract Specialist: J.M. Cooper
Cancer Treatment
301-427-7463

NCI, LITTON OPEN TALKS ON FINAL FREDERICK PACT BEFORE RECOMPETITION

NCI has started negotiations with Litton Bionetics for the final renewal of its contract to operate the Frederick Cancer Research Center before the job is opened again to competition. The contract has been renewed each year on a non-competitive basis since Litton won the award in 1972.

Later this year, NCI will issue an RFP inviting proposals for the cost-plus-fee-based-on-performance contract. NCI hopes to have the RFP out by September. Starting date for the new contract after recompetition is Sept. 26, 1977.

The final term before recompetition will be for 15 months, with a three-month extension to make the expiration and starting dates just prior to the new fiscal year period of Oct. 1 to Sept. 30.

The contract with Litton has been the largest ever awarded by NIH since the first year. The total for the term now being negotiated probably will be between $25 and $30 million.

Other sole source negotiations:

Title: Detroit SSMA population-based cancer registry
Contractor: Michigan Cancer Foundation.

Title: Comprehensive cancer center communications network
Contractor: Illinois Cancer Council.

Title: Demonstration for reimbursement in cancer control
Contractor: Blue Cross Assn., Chicago.

Title: Breast cancer detection demonstration project
Contractor: Virginia Mason Research Center, Seattle.

Title: Immunoprevention of spontaneously occurring neoplasms
Contractor: Microbiological Associates.

Title: Epidemiologic studies of drug induced cancer
Contractor: Johns Hopkins University.

Title: Bay Area (San Francisco) resource for cancer epidemiology
Contractor: California Dept. of Public Health.

Title: Etiologic studies of cancer in New Jersey
Contractor: New Jersey Dept. of Health.

Title: Development of laboratory animal virus diagnostic reagents and operation of a service laboratory
Contractor: Microbiological Associates.

CONTRACT AWARDS

Title: Study of mammary gland responsiveness to multiple hormones
Contractor: Scripps Clinic, $90,000.

Title: Breast cancer detection demonstration project
Contractors: Albert Einstein Medical Center, Philadelphia, $269,262; and Pacific Health Research Institute, Honolulu, $252,844.

The Cancer Letter—*Editor* JERRY D. BOYD

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