THE CANCER LETTER

P.O. BOX 2370 RESTON, VIRGINIA TELEPHONE 703-620-4646

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FDA ADVISORS OKAY NCI TOXICOLOGY PROPOSALS, WRITE NEW CLINICAL GUIDELINES, APPROVE AN NDA

The Oncologic Drugs Advisory Committee of the Food & Drug Administration approved new toxicology guidelines for anticancer drugs which will reduce the cost of preclinical tests by half and the time required by one-third; moved toward approval of guidelines for clinical trials of anticancer drugs; and recommended approval of the new drug

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In Brief

MARKUP OF CANCER ACT RENEWAL BILL OCT. 31; GARFINKEL NEW ACS VP FOR EPIDEMIOLOGY

KENNEDY SUBCOMMITTEE'S markup of S. 988, the bill that will renew the National Cancer Act, the National Heart, Lung & Blood Act, and other biomedical research authorities is scheduled for Oct. 31. It will be an open session of Sen. Edward Kennedy's Health Subcommittee, starting at 10 a.m. in Room 4232 of the Dirksen Building. . . . **E. CUYLER HAMMOND**, American Cancer Society vice president for epidemiology and statistics since 1967, has left that position to become director of the epidemiology training program at Mt. Sinai Medical Center. He will continue with ACS as a consultant and as co-director of Mt. Sinai's Environmental Cancer Research Project, operated jointly with ACS. **LAWRENCE GARFINKEL**, long an associate of Hammond's in ACS' epidemiological programs, will succeed him as vice president for epidemiology and statistics. . . . **NEW DRUG** seminar on L-asparaginase and daunorubicin has been scheduled by the Div. of Cancer Treatment of NCI for Dec. 17-18 in the Masur Auditorium at NIH. The seminar will cover the initial development of the two drugs, their pharmacology, toxicology and clinical activity. Clinical studies of daunorubicin will be discussed by Audrey Evans for pediatric tumors, Raymond Weiss for adult tumors and Bruce Peterson for acute leukemia. Charles Haskell and Mark Nesbit will report on L-asparaginase as a single agent in treating leukemia and other malignancies. James Holland, David Poplack and Joseph Simone will report on the role of L-asparaginase in ALL, treatment of relapsed ALL and optimal current treatment of childhood ALL. Peter Wiernik, Michel Boiron, Ronald Chard, Emil Freireich and Robert Gale will discuss use of anthracyclines in treating acute nonlymphocytic leukemia. . . . **"MANAGEMENT OF PATIENTS** with Terminal Cancer," a postgraduate course for physicians and other health professionals is scheduled for March 29-30, 1980, at the Shoreham Americana Hotel in Washington. It will be cosponsored by the Vincent Lombardi Cancer Research Center and the Office of Continuing Medical Education of Georgetown Univ. Contact 1980 Cancer Symposium, Lombardi Cancer Research Center, Georgetown Univ. Hospital, 3800 Reservoir Rd. N.W., Washington D.C. 20007. Registration is $150.

FDA ADVISORS SAY NO TO ESTRAMUSTINE NDA, APPROVE STREPTOZOTOCIN POWDER

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application for one agent and disapproval of another at the committee's meeting last week.

The Developmental Therapeutics Program in NCI's Div. of Cancer Treatment earlier this year asked the committee to consider preclinical guidelines which would limit toxicology testing to mice, eliminating the requirement for tests in dogs and monkeys. NCI also asked for other changes and simplifications, and submitted an alternative recommendation in which dogs would be used.

A key element of NCI's proposal was the request that histopathology and chronic toxicity studies not be required until the decision was made to move a drug beyond phase 2 trials.

The committee accepted a modified version of NCI's alternative proposal, feeling that testing in a species in addition to mice remains necessary until more definitive information is available on the mouse as a predictor of human toxicity. The committee went part of the way with NCI on histopathology, recommending that dog histopathology be performed prior to phase 2 studies and disagreeing with an FDA pharmacologist who argued that it should be done before phase 1 tests.

The potential for saving money is significant. NCI estimated that the existing procedures cost $100,000 to $120,000 per compound and that the cost with the committee's proposal would be reduced by approximately 50%. By using only mice, the cost would be $12,400 per compound without histopathology, $15,500 with, NCI had estimated; the incentive remains for eventually eliminating dogs.

The time saved also is significant. The existing toxicology protocol requires nine months to complete; with the committee's proposal, about three months.

NCI executives hope that the reduction in cost will encourage more institutions and pharmaceutical firms to participate in anticancer drug development.

The full committee accepted the recommendations of its subcommittee which considered NCI's proposal at a meeting last summer. The minutes of that meeting describe the new recommended procedure:

"The subcommittee concluded that there was convincing evidence that the mouse could serve as a useful predictor of quantitative drug toxicity in man. This judgment was based on the review of the studies of Freireich, et. al., Homan, Goldsmith, et. al., and Guarino. The recommendation in regard to murine toxicology is as follows: (1) Two schedules should be employed—single dose and daily times 5. From this would be computed an LD_{10}, LD_{50}, and LD_{90}. (2) The animals would be observed at 24 hours after injection and at least every seven days following the last treatment; the minimum observation time is to be 28 days, and longer if the animals have not fully recovered from the acute toxic effects of the drug administration.

"This should include measurements of animal weight, which if there has been a loss, should at least return to control values for the animal to be considered as having recovered. The subcommittee concluded that hematology, clinical chemistry, and histopathology studies need not be required in the murine studies. However, there was a strong recommendation that such investigations be encouraged, so that the true value of the mouse as a predictor of qualitative toxicity can be defined over the next 2-3 year period.

"The subcommittee concluded that an additional species must be tested for the prediction of quantitative, as well as qualitative toxicity. At the present time, the dog represents the logical candidate species, in view of the extensive background information available in the literature. There was considerable discussion among the subcommittee members as to the value of the dog as a predictor of qualitative organ system toxicity. The report of Schein, et. al., 'The Evaluation of Anticancer Drugs in Dogs and Monkeys for the Prediction of Qualitative Toxicities in Man,' *Clinical Pharmacology and Therapeutics in Man,* Vol. II No. I, pp 3-40, suggests that canine studies are of limited usefulness; suppression of bone marrow function is adequately estimated, but toxicity to other organs such as liver and kidney is grossly overpredicted.

"In addition, many clinically important toxicities have not been appreciated in past canine studies. At present, qualitative toxicity data from dogs is not utilized by most experienced clinical pharmacologists, who routinely anticipate the worst and expectantly monitor patients for possible adverse reactions. Nevertheless, some members of the subcommittee felt that the additional information may prove useful for specific agents, and should be prospectively analyzed for its value.

"Two dose schedules in dogs were recommended: A single dose and daily times 5. The initial dose should be 0.1 the LD_{10} (mg/m^2) in the mouse. One or more additional dose levels should be given to produce overt toxicity, so as to insure that all qualitative toxicities inherent in the test agent are produced. The defined levels of toxicity outlined in the current NCI protocol are not required. It was recommended that at least 4 dogs be included at each dose level, and that 2 animals be held for a 2 month period in order to observe for possible delayed, or irreversible toxicity. Measurements of hematologic and clinical chemistry paramenters, as well as gross pathology and histopathology, should be obtained on all test animals.

"The subcommittee made the recommendation that phase 1 trials of the new agent be allowed to

proceed upon completion of a 60 day observation period at the first dose level in dogs; this assumes that this species confirms the safety of the 0.1 LD_{10} (mg/m^2) dose predicted by the mouse.

"The subcommittee also recommended that the histopathology of all dogs be formed and analyzed prior to initiation of phase 2 clinical trials. This requirement should apply not only to NCI drugs, but also to all other individuals or institutions submitting a request for an IND for a new anticancer agent. David Richman, FDA supervisory pharmacologist, dissented from that position feeling that histopathology should be completed prior to phase 1.

"The subcommittee concluded that studies of carcinogenicity should be initiated for all cytotoxic agents and, if possible, that they be completed prior to formal NDA approval. Until the carcinogenicity studies are formally analyzed, the package insert should state that the agent under question should be regarded as a carcinogen, until such time as there are data from animal model systems to suggest otherwise. The specific model to be employed for estimating carcinogenic potential represents a difficult question which the subcommittee was not able to address in depth during the meeting. There was great concern expressed about the use of potentially carcinogenic drugs in patients receiving adjuvant chemotherapy, a situation where a relatively large percentage of patients may survive for a significant period of time so as to be at risk for the development of a second drug-related tumor. Studies of teratogenicity also should be completed prior to NDA approval, as well as an analysis of the drug's potential action on fertility.

"Lastly, the subcommittee concluded that there is an urgent need to better define the reliability of animal prediction of drug toxicity in man. The FDA should consider organizing a specific conference to deal with this important issue in drug development."

Committee member Charles Moertel questioned the decision to require use of dogs. "As you pointed out, dogs are not all that good a predictor," Moertel said. "You will not have the dog data complete until after phase 1 when you will already have people data, which is better. Why the expense and time for dog tests? You still will use the mouse for initial dose."

"Maybe not," said committee chairman Philip Schein. "If the mouse dose is too strong, you go to the species most sensitive."

"Has there ever been a case of a fatal first dose based on the mouse?" Moertel asked.

"I'm not sure," Schein said. "But we felt the mouse was not completely reliable."

"There is a second concern, of delayed toxicity," commented committee member Charles Haskell. "With nitrosureas, the dose in man was escalated too rapidly."

"The dog has never been inadequate in predicting a safe starting dose," Schein said. "The dog will be used here as a backup to the mouse in predicting safe starting dose."

"Perhaps it would be better to use a different species of mouse," Moertel said. Turning to NCI representatives, Moertel asked, "Are you satisfied with the approach and agree this is a good use of dollars?"

"That was the thinking of the committee," said Vincent Bono, chief of the Investigational Drug Branch in DCT.

"We're satisfied," said Saul Schepartz, DCT deputy director.

Moertel asked if NCI planned to continue developing the methodology and come back later with a proposal to use two strains of mice, eliminating dogs. Vincent Oliverio, director of the Developmental Therapeutics Program, said, "We're willing to come back later with another proposal."

Robert Dixon, chief of the Laboratory of Environmental Toxicology at the National Institute of Environmental Health Sciences who was a consultant to the subcommittee, charged that 25% of the compounds tested by NCI "never made it to clinical trials because of extreme toxicity." Schepartz and Oliverio disagreed. Schepartz said he could think of only six over the last 15 years.

"Will this abbreviated toxicity testing allow too many investigators to engage in clinical trials?" Dixon asked.

"We specifically said that other institutions would be encouraged to develop drugs," Schein said. "That's one of the reasons for all this."

The committee took up the draft of clinical testing guidelines which had been written by another subcommittee, made extensive revisions in it but approved the general thrust of the effort.

Previous attempts by FDA to impose guidelines for clinical testing of oncologic drugs had been opposed by NCI and investigators from other institutions. They felt that those proposals were too inflexible, would have inhibited clinical research and would have deprived many patients of the possibility of getting effective treatment.

It's a different situation with the new proposals, Bono told ***The Cancer Letter,*** "We can live with these."

The subcommittee wrote an introduction to the guidelines which carefully states:

"These guidelines . . . are provided to help an investigator formulate his plan . . . in conformance with established FDA regulations. They should be construed as general directions, not a set of specific instructions. They are not, nor are they meant to be, rules and regulations."

The proposals include directions for phase 1, 2, and 3 studies and include a brief mention of the basis for combination studies. In a discussion of controls, they note that "randomized control trials are always the preferred method" but concede that historical

controls may be used in certain situations.

The proposed directions for phase 1, 2, and 3 studies each include requirements for statement of objectives, defining the population of interest, and describing the research plan. Phase 1 studies should estimate the agent's acute, cumulative and dose limiting toxicities, dose and time response relationships, and the drug's pharmacology, the proposal states.

For phase 2 studies, the proposed guidelines state that the objective is to determine if a drug has antitumor activity, and to further define nontherapeutic effects.

For phase 3 studies, "the principal intent is to expand and define the knowledge about the therapeutic activity of a new drug," the proposal says. The new drug may be compared directly with an established agent or standard therapy, may be added to a standard regimen, and in certain circumstances may be taken directly from phase 1 to phase 3.

The committee made so many revisions that FDA staff will make up a new draft and circulate it to the members for further comment before final adoption of the guidelines.

The committee declined by a 5-4 vote to recommend approval of an NDA for estramustine for treatment of prostatic cancer.

It was an agonizing decision. Committee members acknowledged that the drug probably has helped many patients; that experience in other countries seems to have clearly established its efficacy; and that without NDA approval to permit its marketing, its continued availability depends on the willingness of Hoffmann-La Roche to supply it to investigators.

That last point remains in doubt. Donald Carlton, director of drug regulatory affairs for the company, said, "My recommendation to the company is that we've had it." The committee had refused to approve the drug at its meeting last June, contending that the evidence presented in support of the NDA indicated its benefit could be that of an analgesic derived from its estrogen component (***The Cancer Letter***, June 15).

Estramustine (Emcyt, the Hoffmann-La Roche trade name) is not available from NCI.

Gerald Murphy, director of Roswell Park Memorial Institute who heads the NCI supported National Pancreatic Cancer Project, presented results of NPCP studies for patients with advanced disease.

The company was asking approval for stage D prostatic cancer refractory to estrogen therapy and orchiectomy.

Some committee members felt that results cited by Murphy and Hoffmann-La Roche did not demonstrate increase in survival and that most of the benefits were in the subjective category. The chief benefit claimed was that the drug appeared to be related to "stable" disease observed in patients.

Moertel commented that two randomized double blind studies with estramustine, by the World Health Organization and the Univ. of Wisconsin, are two years along and asked why no results from those were presented.

"Those are for primary therapy, and we're not asking approval for primary therapy," answered George Gill, Hoffmann-La Roche assistant medical director for clinical oncology.

"You've been wrestling very hard, Dr. Murphy, with how to evaluate this drug," Moertel said. "It is very difficult. Since you are dealing with subjective changes, why has there been no double blind study at this stage? That is the traditional way to evaluate subjective changes."

"When you start a study, you never know where it will end," Murphy said. "We're not looking for long survival rates but for drug effect. We hope it will lead to treatment of earlier stages of the disease."

Insisting that survival is the important consideration, Moertel commented, "There is no evidence in these studies that Emcyt patients live longer."

"There are suggestions they do, but no proof," Gill said. "There are significant differences in the objective response rate."

"It produces more stability than standard therapy? Better symptomatic response?" Moertel asked. Gill said that it did.

"Aren't double blind studies indicated at this stage to assess the pain effect?" Moertel asked.

"I don't see how you could do it," Gill said. "What would you compare it against?"

"Estrogen, or standard therapy," Moertel said.

Murphy argued that with patients in that advanced stage of disease, randomized double blind studies were not practical and probably were not feasible.

"What do you think this drug is doing?" asked committee member Brigid Leventhal. "Why is it important to performance status but not survival? Why should people pay for this rather than Estrodial? Does it kill tumor cells?"

Gill responded that the drug localizes the disease by killing tumor cells.

Schein said there were two major issues: "Is this just another form of estrogen therapy? The company has provided us with evidence that it is not. Also, if we accept it as a therapeutic agent, we have to define stable disease."

Moertel said that Mayo had conducted a study of an agent in which it was given to patients at several stages of disease, including an advanced stage. "A small percentage had stable response. The stable responders did live longer than those with progression.

"I hope someone will ask me what that agent was," Moertel said. "It was a placebo."

Moertel said stable disease should be defined as no new lesions, less than 25% increase in the size of existing lesions, and no significant deterioration in performance.

"They don't have to get better, just stay the same," Leventhal commented.

Murphy said that the majority of patients receiving estramustine did improve.

Schein said the committee had to make a judgment. "Did patients live better, perhaps live longer?"

"I'm convinced the pharmacology data suggests it works differently than just high dose estrogen," Haskell said. "The data suggest that stable disease is better than progressive disease. There has been sustained interest in the drug for over 10 years in Europe and elsewhere. There is sustained interest in it as a palliative agent. The possibility of abuse is low I recommend approval."

Moertel argued, "There is a paucity of evidence due to the nature of the disease, and, I suggest, to the nature of the trials. They are based too much on subjective observations. People say they feel better. I'm not sure that sustained interest is good criteria. We have to get out of subjectivity, and get into a double blind study. If it works, we're home free."

"Palliative can be a very useful indication, and it does not exclude survival," Haskell said. "Can you ask NCPC to conduct a study using a drug they believe useful against a placebo or what they feel is a less effective therapy? I suspect not."

"The committee should take cognizance of the fact that you can't always do a double blind randomized study in a group of patients with advanced cancer," commented FDA staff member Bryant Jones. "You can't give cancer patients a placebo."

"I agree that there is a lot of inferential evidence," Moertel said. "What bothers me is that we must have certain basic criteria [to release a drug for marketing]. I think it is possible to have an appropriate double blind randomized trial. If it would produce similar evidence to that presented, there is no question it would be approved."

"It is not possible to further randomize a patient who has failed orchiectomy or estrogen therapy," Gill said.

"Want to bet?" Moertel asked.

The committee first voted 6-3 against approval, but the discussion continued.

"The problem is that there is a general feeling it is active," Schein said. "But we have the responsibility to have fairly conclusive evidence. The feeling is that we do not have the evidence from this presentation."

FDA staff member Robert Young said, "We've been struggling with the data for four years. I'm sure we would all vote for a phase 3 trial. It is not necessary to have objective evidence, but subjective results have to be demonstrated."

Gill complained that FDA delayed response for months after the NDA was filed in June, 1977. "We've never been asked by Dr. Young or anyone else to do another study. Maybe that's what FDA wants, but they have never asked us in two and a half years."

Committee member Sherman Kay said he was "not comfortable" with the decision against the drug. Committee member John Whitaker, who like Kay is a practicing oncologist, said, "The committee made a mistake in turning this down. We're taking a drug as good or better than anything else and saying, you can't use it."

Haskell offered another motion asking, "Is stable disease acceptable as clinical evidence of the efficacy of Emcyt?" This carried on a 5-4-1-vote, with one abstention. Whitaker, Haskell, Kay and committee member Jack White in favor; Moertel, Leventhal, and committee members Richard McHugh and Valerie Miké against; and committee member Carol Portlock abstaining. Schein broke the tie voting in the affirmative.

Haskell's motion to recommend approval was then defeated 5-4, with Kay joining Whitaker, Haskell and White in favor. McHugh, Miké, Leventhal, Moertel and Portlock voted no; Schein, as chairman, could vote only in the event of a tie.

The committee had no problems with recommending approval of an NDA for a streptozotocin powder (Zanosar), requested by Upjoin for treatment of islet cell carcinoma of the pancreas. The vote was 8-0, with Leventhal abstaining.

Streptozotocin is one of the compounds NCI makes available free to physicians through its "Group C" distribution system. Approval of the NDA, assuming FDA accepts the committee's recommendation, will result in removal of streptozotocin from the Group C list once the drug is on the market.

CTP STAFF SURVEYED ON PREFERENCE—N.C. OR BETHESDA; ASSURANCE GIVEN

When Joe Califano set up the hybrid National Toxicology Program, assembled from pieces of four agencies within HEW and with NCI contributing more than half the resources, many felt he had created a bureaucratic monster. Some allies of the Cancer Program feared it would result in an open end drain on NCI funds and manpower, controlled by others.

NCI's contribution consists of the staff and budget of the Carcinogenesis Testing Program. Ever since the advent of NTP, CTP staff members have speculated that they eventually would wind up in Research Triangle Park, N.C., where NTP is headquartered—or wind up out of jobs.

Those fears grew last week when CTP staff members were asked to state their preferences—bethesda or North Carolina—should all or part of the program be required to move.

The feeling that NTP might be fattened up at the expense of other areas of NCI has been fueled by the decision by NCI executives to provide additional positions to CTP even if it means cutting back staff in other programs.

NCI is caught in a tug of war over position ceilings

between Congress and the White House. The congressional appropriations committees provided in the FY 1980 money bill for 2,065 positions for NCI. This specifically included 28 additional slots for the Carcinogenesis Testing Program, to be added to the 52 already authorized.

The White House, however, has interpreted the congressional position figures as ceilings, representing the maximum numbers that could be hired, rather than an obligation to actually fill that number of slots. The Administration thus chooses to ignore the legislative history of position authorizations. The appropriations committees acted, especially in the case of NCI, to overcome White House imposed position ceilings which committee members felt were hampering the programs involved.

In the 1979 fiscal year, Congress had asked for 2,057 positions for NCI, but the Whte House cut that to 1,915. NCI started the year with more than 2,000 positions filled, and had trimmed that only to 1,973 by Sept. 30. It seems unlikely that the Administration's level for NCI will be anywhere close to the 2,065 asked by Congress and may remain at the 1,915 level.

NCI executives would like to go along with the intent of Congress and provide the full 80 positions requested for the Carcinogenesis Testing Program. To do that, they would have to cut back on other programs by whatever number under 2,065 the White House establishes.

The irony is that CTP hasn't been able to fill all 52 positions it has been authorized.

NCI executives told ***The Cancer Letter*** this week that there is no basis for any fears that CTP employees will be forced to move to North Carolina against their wishes. The survey of staff preferences was part of a long range planning process to help determine how much, if any, of the program would be moved and if some part is moved, who would go, executives said.

"The overriding principle is that, for the foreseeable future, there will be a continued presence in Bethesda for the Carcinogenesis Testing Program," one executive said. "A second principle is that no one will be compelled to move."

An effort will be made to carry on the program with staff in both locations. As new staff members are hired, they may be asked to work in North Carolina, but that probably would depend on the nature of their jobs.

In any event, it would be impossible to make any moves before May, 1980, because no space is available. No laboratory space will be available until late in 1981.

Further, it is unlikely that any commitment to move a significant number of NCI people will be made until after HEW reviews the National Toxicology Program next year and determines that it is workable. Califano had asked, in his instructions establishing the program, for a review after two years. The White House has reminded Secretary Patricia Harris of that requirement.

Guest Editorial

WHO DIRECTS OUR RESEARCH?

By Ernest Borek

Investigator initiated and peer reviewed research has become a shiboleth as sacred as motherhood. Supporting the initiative of imaginative investigators should, of course, be a primary goal of all agencies, private and public The history of American science amply documents that there is first rate talent among us.

However, originality must be recognized and appreciated by the agencies which are charged with the evaluation of research proposals. The quality of research is circumscribed by the limits of imagination of the members of the review bodies.

At the present time, the review process at NIH, with which I am familiar on both sides of the deadlines—applying and reviewing—is a disaster. The reason for this stems in part from the conditions of our time, but less obviously from faulty strategy in the choice of reviewers. There has been a persistent dictum for the choice of members of the review groups at the NIH: choose young scientists because they have and can appreciate fresh ideas.

In the biological studies, history provides evidence to the contrary. Avery was 68 when he described the most important biological discovery of the century. Lwoff and Monod were 50 when they made their signal contributions to biology.

Many young scientists selected for service on study sections, review bodies or site visits have become visible not by their originality, but by fierce competition for publications in fields opened by the originality of others.

I had to evaluate the CV of a 37-year-old chairman of one of our study sections. He had 250 publications! I made a real effort to search for any increment in our total knowledge from that mass of papers but found none.

In turn, such people can only appreciate and understand science as they practice it. Their critiques, which fortunately have become available from "pink sheets," reveal their limitations. Alas, some of these have been directed at me and I can speak from experience.

In a recent application, I have proposed *inter alia* to study the mechanism of the high turnover of tRNA in tumor tissue, which we had unequivocally established. I proposed to search for some nucleases which might cleave the aberrantly modified tRNAs or pre-tRNAs in tumor tissue. The critique that came back stated that no such enzymes are known to exist. The priority I received put me on the waiting list. I am still waiting.

My program director, who is highly intelligent and is widely knowledgeable, symphathized and suggested that I resubmit to the same study section and meet the criticisms and expand the background for the rationale. I did and I quote the encouragement I received for this effort: "The molecular mechanisms underlying the phenomonon merit investigation, even though these are to a large extent unexplored."

Descriptions of experiments including obvious minutia are demanded. Another review group chided me as follows: "Most of the work proposed is feasible and is worth pursuing. Dr. Borek has the expertise for carrying out the experiments, although the effort proposed would hardly justify a three-year grant." As a personal aside, I may add that in a long career of fairly fruitful research, I have never known six months ahead of time what I was going to do next. If I did, I would have given up science for an equally boring but more remunerative career.

Accomplishment is measured not with new knowledge contributed, but with the number of publications. One study section I know of sets three to five publications a year as the requisite proof of accomplishment. A colleague showed me the following gem in his pink sheet: "He has made some interesting observations in the past and it seems likely that the proposed experiments will yield publishable results." Since he was deemed wanting in his quota, they cut in half his grant—with the aid of which he made the "interesting observations." Never having made an "interesting observation," the reviewers have no concept of the difference in effort needed between finding something new and polishing someone else's finding.

The program directors at NCI, who are by and large far more capable than the reviewers, are helpless. They merely tell you to study the critique of the study sections and resubmit to the same group for a new review. This means that the study sections not only review research, but direct it to the level of their experience and understanding. At this rate, original research will either vanish or will have to be bootlegged.

Pasteur said, "A good scientist must have the capacity for astonishment." I wish the administrators at NIH would insure that every study section has at least one member who has been astonished at least once.

It is generally accepted by staff at NCI that study sections in basic science find research with possible clinical applications anathema. An experience of mine some 12 years ago confirms this. I submitted for a competitive renewal the grant which had supported the work of my students who discovered the nucleic acid methylating enzymes. I reported that the tRNA methylating enzymes are aberrantly hyperactive in six different tumors and that we found altered tRNAs—the first qualitatively different biochemical component in a cancer cell. And I outlined some development of these findings. I was utterly flabbergasted in those halcyon days of funding to find that I was not fundable. Through sources which I will not reveal, I had access to a paraphrase of the critique: Borek has discovered six new enzymes; he ought to purify them before he goes mucking in cancer." Today you can hardly find an issue of a journal devoted to cancer without some extension of our early observations, but no one has been able to isolate a pure, eukaryotic tRNA methyltransferase. They fall apart during purification.

Originality does not fare too well in reviews of larger grant proposals either. I have served for several years on the Cancer Centers Review Committee, and did the best I could to counteract evaluations based on traditionalism or, sometimes, jealousy. I recall vividly a site visit I led to Fox Chase Cancer Center seven years ago, when some clinical members of the team snickered at the emerging efforts of Barry Blumberg. Fortunately, I was able to counteract some of the pejorative written reports before the full committee. I was told this was the first substantial support for Dr. Blumberg's work.

Another member of that institution, Beatrice Mintz, who is possibly our ablest embryologist-geneticist, also had a rough time with her grant support. Yet, I said seven years ago Mintz alone is worth the whole Fox Chase grant.

Of late, youth has been tapped for members of site visit teams for the evaluation of cancer centers. This is unfortunate for several reasons. The number of young cancer researchers pullulated in the past eight years because, like Willie Sutton, the bank robber, "That is where the money is." Many members of this pool are totally unsuited for the evaluation of such complex enterprises. They may have a narrow expertise, but lack judgment. I had some of them in mind when I described the obnoxious reviewers at a meeting at NCI and which was published in the Dec. 16, 1977 issue of ***The Cancer Letter:*** "Some feel that they represent OMB; some think they are running a PhD program; some want to show how much they know; worse, some want to create the center in their own image."

N.B. Nothing in the foregoing article applies to any member of the Study Section which is about to evaluate my competitive renewal for funding of our studies of the molecular mechanism of carcinogenesis by carcinogens which are negative in the Ames test.

Ernest Borek is adjoint professor of microbiology at the Univ. of Colorado Medical Center and director of basic oncology at the AMC Cancer Research Center. His service as a member of NIH study sections included a term as chairman of the Cancer Center Support Grant Review Committee.

NCI CONTRACT AWARDS

Title: Clinical Oncology Program, continuation
Contractor: Allentown Hospital, $246,403.

Title: Human melanoma: Evaluation of BCG immunotherapy of patients without detectable disease after removal of tumor containing lymph nodes, continuation
Contractor: UCLA, $145,641.

Title: Approaches to cancer patient management: A synopsis of the network program experiences (head and neck cancer)
Contractor: Illinois Cancer Council, $221,959.

Title: Development of a course on prevention, focusing on cancer, for nurse practitioners or physician's assistants, 3-year contracts
Contractors: Northeastern Univ., Boston, $231,566; Baylor College of Medicine, $364,513; Bowman Gray School of Medicine, $220,047; Univ. of Washington, $285,816; and Memorial Hospital, New York, $294,356.

Title: Pain control in cancer
Contractors: Rehabilitation Institute of Chicago, $365,904; University Hospital, Boston, $453,675; Univ. of California (San Diego), $379,794; Jefferson Medical College, Philadelphia, $490,174; Univ. of Washington, $336,962; Montefiore Hospital, Bronx, $378,377; and Univ. of Wisconsin, $430,999.

Title: Development of large area solid state images receptors for x-ray imaging
Contractor: Xerox Corp., Pasadena, Calif., $166,303.

Title: Diagnostic and prognostic significance of a newly discovered alkaline phosphatase in cancer patients
Contractor: Univ. of Wisconsin, $58,000.

Title: 18 alteration/renovation/maintenance/upgrading projects at Frederick Cancer Research Center
Contractor: Litton Bionetics, $251,645.

Title: Resource to provide rodent disease diagnostic laboratory support for monitoring the health status of animals used by the NCI Carcinogenesis Testing Program
Contractor: Univ. of Alabama, $663,861.

Title: Breast Cancer Detection Demonstration Project, extensions
Contractors: Univ. of Pittsburgh, 18-month extension, $434,179; Iowa Lutheran Hospital, 18-month extension, $385,067; Univ. of Michigan, 18-month extension, $386,841; Emory Univ., nine-month phaseout, $82,337; Univ. of Southern California, one-year renewal, $272,146.

Title: Environmental health data base for New Jersey
Contractor: New Jersey Dept. of Environmental Protection, $494,370.

Title: Oncogenesis and other late effects of cancer therapy
Contractor: Children's Hospital of Philadelphia, $478,746.

Title: Support for the Diet, Nutrition & Cancer Program
Contractor: Capital Systems Group, $2,443,263.

Title: Resource for microscopic and autoradiographic technology, basic ordering agreement
Contractors: Meloy Laboratories, and Experimental Pathology Laboratories.

Title: Gather and analyze information relevant to the production, distribution and use of chemicals for nomination for overall evaluation of carcinogenicity and supply information to International Agency for Research on Cancer
Contractor: SRI International, $5,151,841.

Title: Development of detailed methods and protocols for carcinogenesis screening using cell culture assays-hamster host mediated system
Contractor: SRI International, $257,364.

Title: Influence of repeated low dose irradiation on mammary gland carcinogenesis in estrogenized rats, modification
Contractor: Alton Ochsner Medical Foundation, $129,564.

Title: Pathology support for Carcinogenesis Testing Program
Contractors: Task I (Diagnostic pathology support): Experimental Pathology Labs, Herndon, Va., $1,665,690; Clements Associates, $2,075,925. Task II (quality assurance report production): Experimental Pathology Labs, $1,790,987. Task III (pathology repository & archives): Tracor Jitco, $711,265.

Title: Rodent production colonies
Contractors: Charles River Breeding Labs, $1,374,767; and $1,419,383; Harlan Industries, $1,376,360; and Simonsen Laboratories, $1,258,405.

Title: San Francisco Bay Area Resource for Cancer Epidemiology, continuation
Contractor: California Dept. of Health, $127,054.

Title: Study of ovarian cancer in Greater Washington D.C., continuation
Contractor: George Washington Univ., $182,995.

The Cancer Letter _Editor Jerry D. Boyd
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