THE CANCER LETTER

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ATTACKS ON NCI, CANCER PROGRAM PEAK FOLLOWING POST SERIES; DEFENDERS CITE INACCURACIES, MISCONCEPTIONS

The unprecedented series of attacks on NCI and the National Cancer Program peaked during the past two weeks with the *Washington Post* series, the "20/20" TV program and hearings by House and Senate

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In Brief

DEVITA ON LAETRILE HIT LIST; HAMMER REMOVAL AS PANEL HEAD SOUGHT BY LOVE CANAL ACTIVISTS

NCI DIRECTOR Vincent DeVita is now the target of the laetrile crowd. The official publication of the National Health Federation, a laetrile proponent, has for two consecutive issues printed a headline, "DeVita Must Go," followed by a form letter demanding his dismissal to be sent to Senators Orrin Hatch and Paula Hawkins. Laetrile pushers were enraged by the NCI study which showed conclusively that the substance is totally useless in the treatment of cancer. . . . **ARMAND HAMMER** threatened to call in police to remove from last week's meeting of the President's Cancer Panel representatives of an organization they said was called "Citizen's Committee Against Corporate Cancer." They appeared at the meeting to demand Hammer resign as chairman of the Panel because his Occidental Petroleum is now the parent company of Hooker Chemical, of Love Canal infamy. Hammer said Occidental didn't acquire Hooker until well after the dumping incidents, and when members of the group tried to argue with him, he asked for "the sergeant at arms to remove these people if they persist in interrupting the meeting." The protestors complied, and later agreed to meet with the head of Occidental's Washington division. They refused an offer to meet privately with Hammer, who has worked energetically to clean up the Hooker operation. . . . **JOHN ULTMANN**, director of the Univ. of Chicago Cancer Center, told the Panel that there are "17 layers of monitoring" in drug development. "We should be looking at how many of the 17 could be abolished to get the maximum number of effective drugs with the minimum amount of paper pushing". . . . **HAROLD AMOS**, member of the Panel, said, "The public has a much more balanced view of what's going on than some reporters and some congressmen". . . . **JOSEPH PERPICH**, NIH associate director for program planning and evaluation since 1976, will leave in December to become vice president for corporate planning and administration for Genex Corp., a recombinant DNA technology firm. . . . **FREDERICK HELM** has been appointed chief of the Dermatology Dept. at Roswell Park Memorial Institute. He has been a cancer research dermatologist there since 1963. **HEINZ KOHLER**, professor in the Dept. of Pathology and Biochemistry at the Univ. of Chicago, has been named director of the Immunology and Immunochemistry Research Dept. at RPMI.

WAXMAN, GORE ASK FOR BETTER INFORMED CONSENT IN CANCER CLINICAL TRIALS

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committees. The negative impact may have been countered to some degree by a superb article in the Nov. 2 issue of *Newsweek,* which described areas of progress in cancer research and present state of cancer therapy, including the stunning achievements in improved survival during the past 10 years.

The four part Post series (***The Cancer Letter,*** Oct. 23) dwelled on the theme that experimental anticancer drugs are toxic, and contended that investigators are frequently careless in prescribing and administering the drugs. Individual case studies were presented, with names of patients and sometimes those of their physicians, in which extreme toxicities were endured and with some ending in drug related death.

The thrust of the series: Anticancer drug development has been ineffective, poorly managed by NCI, and causes more harm than good.

The "20/20" segment over the ABC network was typical of that program. It opened with the statement by hosts Hugh Downs and Renaldo Hererra that "we are losing the war on cancer, and here is why." They blatantly used misrepresentations, untruths and unprincipled tape editing to support their premise. Comments by NCI Director Vincent DeVita and former Director Frank Rauscher were chopped up and cut short to make them look bad while critics such as Samuel Epstein came on like world statesmen.

No wonder "20/20" is looked upon by journalists as phony showbiz—and is hardly looked upon by the public at all, with a Nielsen rating at the bottom of the scale.

The hearing by the House Health Subcommittee and Investigations and Oversight Subcommittee was called specifically to look into the allegations in the Post articles. It was a fair hearing, far more so than the Hatch and Hawkins hearings in the Senate last spring.

Chairmen Henry Waxman of the Health Subcommittee and Albert Gore of the Investigations Subcommittee both expressed concern that physicians using investigative drugs may not be doing enough to thoroughly inform patients of toxicities and risks. Both also were concerned that public reaction from actions perceived as exploiting cancer patients could damage support for the National Cancer Program.

Reaction to the Post articles, from scientists and other Cancer Program advocates and from the public, appeared almost universally opposed to the points made by the writers.

Cancer center directors Stephen Carter and Charles Moertel, quoted in the articles in ways which made them appear to be agreeing that clinical research with drugs was fruitless, contended they were quoted out of context.

The Post filled its letters to the editors section for two days with comments from readers, most of them taking issue with the articles, and some, by professionals, pointing out a multitude of factual errors.

The Post itself in an editorial came down on the side of continuing the development of anticancer drugs, but without admitting violation of journalistic principles by the paper.

Although DeVita submitted three letters responding to the articles pointing out errors, the Post used only the first (which appeared Oct. 23 in ***The Cancer Letter***).

Excerpts from the others follow:

We remain concerned with misconceptions created daily in the series of articles on drug development by Neumann and Gup. These points we believe need emphasis:

One, the statement that too many patients are studied during the clinical testing of a cancer drug shows a lack of understanding of what is required for clinical tests of this sort. There are hundreds of tumor types that might respond to a drug. We can't study all types. NCI selects about eight common types of cancers from many. The tests are conducted in a minimum of 30 patients per type of cancer, usually at more than one dose level and schedule of administration. With only two doses and two schedules in 30 patients for each of eight tumor types, about 1,000 patients are required to complete a minimal test. The failure to do a complete test can be tragic if a useful drug is passed over. The authors claim the drug referred to as Methyl GAG is ineffective. Actually, our data suggest it will be of significant value in patients with lymphomas. MeGAG was almost discarded because it was initially tested in too few patients on too few schedules.

Two, the statement that over 600 patients died from drugs is a misinterpretation of the meaning of drug related deaths. Cancer patients usually die of infection or hemorrhage or both. Where drugs are being administered during these episodes our investigators quite correctly classify the deaths as "drug related" because in part the drugs prevent the patients' normal defense against these problems. The actual number of patients who die of unexpected adverse effects exclusively related to cancer drugs is small and the risk almost never exceeds that of the consequences of the cancer itself.

Three, the authors daily attack priorization of drugs, which is a management tool used by us and the industry to select the few drugs that can be tested in humans from the many that receive preclinical testing in rodents. "High priority drugs" have one of several characteristics: impressive activity against an array of rodent tumors; a unique structure or mechanism of action; or a dramatic effect in a rodent tumor of a type common to human patients.

It would be foolish to consume scarce resources on drugs that appear unimpressive in preclinical tests. Of all drugs tested only 1 in 5,000 reach clinical testing and only 1 in 50,000 are marketed, which is also an industry average. Setting priorities is the most difficult issue in cancer drug development because many people feel they have discovered useful drugs we should develop but cannot.

Four, the statement that anticancer drugs exacerbate tumor growth is an impression unsubstantiated by fact.

Five, the authors seem unaware that marketed anticancer drugs take on the average a dozen years to become commercially available. The authors seem to assume that mitoxantrone, MeGAG, high dose methotrexate, chlorozotosin, and deoxycoformycin are all toxic and ineffective. The same conclusions were once drawn by some about the usefulness of cisplatin. Actually, in our view, based on current data, the above mentioned drugs are virtually assured a place in the thera-

peutic armamentarium for one or another type of cancer. We will be pleased to supply the data.

Six, finally, we remain most concerned by the fear the articles may create in cancer patients now living and the anxiety provoked by interviews of families of those who have died.

DeVita's final letter to the Post summarized his objections to the series:

We have noted with interest the use of the phrase from the Hippocratic Oath, "first, do no harm," as a subtitle. Hippocrates, it should be noted, also said in his Aphorisms, "for extreme illnesses, extreme treatments are most fitting." Cancer is an extreme illness. A more humanistic credo for a cancer investigator who seeks better therapy is that he or she should accept no hazard for the group of patients under study, or, when identifiable, for an individual in the group, greater than the ordinary outcome of the disease itself when treated by standard means. For patients with advanced cancer on phase 1 studies, there are no standard means. The search or foray into the unknown cannot be totally risk free. Doing nothing because there is risk involved, it seems to us, is most toxic to the cancer patient. Rephrased, the most humanistic credo is "at least do some good."

Most of the cases cited by the authors do illustrate the risks, expected and unexpected, of early drug testing but do not as was often implied reflect a failure in the monitoring system. It is doubtful that unexpected side effects can be totally avoided by any monitoring system yet devised. Overregulating these early trials, on the other hand, could suppress the identification and development of new important leads in cancer therapy. . . . It is premature to draw negative conclusions, particularly by inexperienced people.

Actually, we think cancer therapy, including chemotherapy, is less toxic today than it was before 1970. In this vein, I would like to pose the following questions to Gup and Neumann:

1. Before 1970, patients with sarcomas (cancers of supporting structures of the body) died 60 to 80 percent of the time. They died without their limbs and they asphyxiated as their lungs filled with cancer. Now, over 90 percent of these patients live free of disease with their limbs. To accomplish this, however, they must go through a toxic drug protocol. Is the net toxicity to these patients more or less in 1980?

2. Before 1970, over 60 percent of women with breast cancer that had extended into the lymph glands under the arm died by five years. Now using adjuvant (but toxic) chemotherapy there is a 60 percent improvement in the survival of these patients. The advent of adjuvant chemotherapy has allowed surgeons and radiotherapists to use less radical approaches to the treatment of the primary disease. Is breast cancer treatment in the 1980s more or less toxic than prior to 1970?

3. Before 1970, patients with metastatic testicular cancer were cured only 10 percent of the time with toxic drugs. In the last five years, the cure rate has jumped dramatically to 70 percent—but, the new more effective drug programs are even more toxic than the old ones. Is the net effect of treatment for men with testes cancer more or less toxic in 1980?

4. Prior to 1970, few patients with advanced Hodgkin's disease were curable and most died within two years. Now 50 percent are curable using toxic drug programs. Actually, 70 percent of all patients with Hodgkin's disease are curable when drugs are combined with radiation. These treatments are not only acutely toxic, but we now know they include a seven percent risk of developing leukemia 10 years after treatment. Is living a normal tumor free life for 10 years with a small risk of developing leukemia less toxic than dying within two years of the time of diagnosis at the average age of 32?

5. Before effective chemotherapy, leukemic children all died miserable deaths. Now half are curable with toxic chemotherapy. Is the net effect more or less toxic in 1980 than in 1970?

6. Advanced diffuse histiocytic lymphoma (often called reticulum cell sarcoma), a common lymph node cancer of adults, was considered incurable prior to 1974. Now, over 50 percent of patients are curable with very toxic chemotherapy. Is this net effect to the patient more or less toxic than what was available prior to 1970?

Success in treating these diseases with toxic treatments accounts for the significant fall in national mortality in patients less than the age of 45.

It should be noted that the clinical studies that led to the success in the above programs are referred to as phase 3 and 4 clinical trials. To get there, the drugs in those programs had to go through phase 1 trials and each effective drug we have today did. When I was interviewed by Gup and Neumann they asked me why we didn't stop phase 1 clinical trials. This is truly a naive question. At the present time we know no way of evaluating any cancer treatment, new drugs or biologicals like interferon, different types of surgery, or new types of radiotherapy without some risks.

The sad thing is that even with good therapeutic programs not all patients respond well to treatment. At the present time, in all types of clinical studies, it is impossible to distinguish those patients who will respond and those who won't and it is heart rending to watch the patients who fail to respond suffer not only the consequences of a cancer that continues to grow, but the side effects of therapy. Making such distinctions has been an area of intense research in the National Cancer Program. The new promising petri dish assay system developed at the Univ. of Arizona by Dr. Sidney Salmon using human tumor tissue is one result.

A word about my "back of the envelope" statistics [referring to DeVita's estimate on numbers of patients cured by chemotherapy]. I have referred to them in this way not because they are casually derived, but because they are derived by hand through laborious searching of textbooks and literature for data not presently available on our computerized systems. To assess the impact of each type of treatment we needed to determine operability, how many patients present to their doctors with localized cancers, etc. When we first went through this exercise we used data from the year 1977 and came to the conclusion that the number of patients cured exclusively by drugs (not added to surgery or radiation) was about 11,000. This was the figure I used at the hearings because it was available to me at the time. By the time I spoke to Gup and Neumann, we had redone the calculations using 1980 incidence and mortality figures. Our estimates of the number cured exclusively by drugs for 1980 is 14,400. If one then adds in all the patients who derive additional benefit derived when drugs are added to surgery or radiation, such as the example of the sarcomas cited above, drug related cures for 1980 rise to 46,000. We have tried to be as conservative as possible in arriving at these conclusions. It is reasonable to assume that these estimates could be over or underestimated by as much as but not more than 10 percent.

After reading the series I was reminded of a quotation by Winston Churchill. He said, "I don't mind criticism even when for the sake of emphasis, it departs for a time with reality." Certainly, the authors, for the sake of emphasis, depart from reality. In the case of the Post series, I do mind, because their departure from reality can only cause anguish to the very people who don't need more: cancer patients. Gup and Neumann should follow the same doctrine of "first do no harm."

The Post did use letters to the editor pointing out factual errors in the series from Bruce Chabner, acting

director of NCI's Div. of Cancer Treatment; James Holland, Mount Sinai Medical Center; and Raymond Weiss, Walter Reed Army Hospital and former DCT staff member. Other letters objected to the biases in the articles and supported anticancer drug development.

One letter the Post did not use demonstrated clearly a lack of concern for journalistic ethics by reporters Ted Gup and Jonathan Neumann and their editors. This letter was written by Brigid Leventhal, director of the Div. of Pediatric Oncology at Johns Hopkins Oncology Center, to Neumann. It was dated a week before the series started.

Neumann had interviewed the parents of a child, one of Leventhal's patients, who had died a few months earlier. The series opened with an account of the death of another child, an 8 year old girl who had been treated with mitoxantrone, "an experimental drug derived from a dye used in ballpoint pen ink."

Levanthal's letter to Neumann follows in part:

The family agreed to an interview with you, thinking that it might be helpful in some way and they called you themselves. I am writing to you now because I am concerned about the way this interview was handled, not from a legal point of view but from a humane one. . . . at least as it was later recounted to me by the family. Remember now, that this is a family whose child has been dead for only a few months and who are trying to get the point across that their child's life and even his death had a meaning for them. I think this is the way we would all like to feel after we lose someone close to us.

One question was remembered like this: "How would you feel if I told you that this drug is closely related to the material that is used for ink in ball point pens?" Come now, Mr. Neumann. In the first place, that piece of information is in the protocol which the parents were given to read. . . but what were you hoping to achieve by that question asked in an angry tone of voice? Why shouldn't a material with a structure close to that of ball point pen ink cure cancer? After all, closely related materials can be used both for food and run automobile engines. Why not take the attitude of amazement at what a small change in chemical structure can result in an incredible difference in the effectiveness of a compound? For example, there are two drugs, daunomycin and adriamycin, with complex chemical structures which differ only in one small OH group but the one, daunomycin is active really only in leukemia while the other, adriamycin, is active in most of the solid tumors against which it has been tested. I hope you will include in your story some of the amazement we all feel and the thrill when a small change in a large molecule like that leads to a large change in efficacy.

The next question which I find vicariously upsetting was: "How would you feel if I told you that only six of 500 people tested with this drug have responded?" Again, shame on you, Mr. Neumann, for the implication that we knew this drug was inactive before it was tried. We spend a great deal of time trying to educate our families that each type of cancer is different. Drugs that work in leukemia usually do not work in cancer of the pancreas, for example, so the rate of response in patients, other than those with an identical tumor type is not particularly relevant. In addition, the response rate to the drug is higher than that quoted by you. We have seen at least five responses to this drug in our small pediatric research group alone.

None of your questions were in any sense illegal since they all began with "How would you feel if I told you that..." which means that if the statement later turns out to be untrue there is no defense against it. However, when the interview with you was finished the family was depressed. They had called you trying to get a point of view across. Don't forget they feel some responsibility for having their child participate in the trial, since they signed the consent form agreeing to it, and they wanted to tell you the positive reasons they had for making that difficult decision. They wanted to tell you something about maintaining hope in a bright child whose tumor is growing and hurting him. They wanted to tell you something about belonging to a "family" of people with a particular disease and trying to help those people coming along after their child by agreeing to a test of a new drug. They wanted to tell you something about working as a team with the physicians who were looking after their child and making decisions together while facing extremely difficult and, in the end, insurmountable odds. They wanted to tell you something about their child not having died in vain. And they had the impression that you were trying to get them to say something critical which would appear to diminish the value of the drug trial.

Mr. Neumann, I would characterize the way in which those questions were asked as at best insensitive and at worst sadistic. If I have been overly sensitive to the negative aspects of your questions then I apologize, but don't forget we are all pretty sad when it comes to the death of a child. It doesn't take much to hurt our feelings further or get us more depressed.

I have been in the practice of pediatric oncology for almost 20 years now. It is always thrilling to see an effective new drug come along and, fortunately for us in pediatrics, we have a number of such exciting events which have occurred during that period of time. Please include the positive point of view in your story. Don't just make it another description of bureaucratic mismanagement or callous physicians...that has been done. You have been working on your story for a year, and I respect you for that. That must give you some feel for how many little steps it takes before the big one occurs which is then hailed as a "breakthrough" or "discovery". Give us some of the thrill and the excitement we all feel when the years of hard work which started with an idea and a few mice pay off and you see the first patients actually improve with a new drug.

As it turned out, the series did none of the things asked by Leventhal and did turn out to be "just another description of bureaucratic mismanagement."

The fact that Leventhal's letter was written a week before the series began is damning, unless the Postal Service between Baltimore and Washington D.C. broke down completely. The article totally ignored the points made by Leventhal, the reporters refusing to allow facts to ruin an eye grabbing opening for their series.

At the Waxman-Gore hearing, DeVita challenged the Post's contention that there were 620 drug related deaths in a two year period covered by the investigation.

More than 1,400 patients have entered NCI supported phase 1 trials in the past 18 months, DeVita said, and there have been 43 drug related deaths—less than three percent. Responses were seen in nine percent.

Edward Brandt Jr., assistant secretary for health, defended NCI and the National Cancer Program

against the Post and other attacks.

"Because of the media attention given NCI research efforts and FDA enforcement of existing regulations, there has been a false perception created that we are callous toward the patients involved in clinical trials and that our system of monitoring and regulation is inadequate," Brandt said. "I repeat, this is a false perception. As we all know in medical science, particularly when on the frontiers of research on new treatment modes, there is a fine line between permitting freedom for innovation and monitoring by sponsors and regulation by government agencies. We are often accused of too much regulation and thus stifling research. Others accuse us of not enough regulation and thus endangering the patient. We realize that the fine line we must follow has a potential for overregulating or for allowing too much freedom for investigators. But, as a system, I believe that the monitoring and drug distribution efforts of the NCI and the regulatory monitoring functions of the FDA provide a framework for scientific research that both allows for innovation while protecting the patients engaged in those clinical trials. There is no pattern of abuse or mismanagement. When problems have arisen, they have been addressed and we will continue to seek ways to improve the system."

Richard Crout, director of FDA's Bureau of Drugs, denied claims by two FDA staff members that the agency does not adequately monitor or regulate NCI drug development. Gore asked Crout if the statement by Michael Hensley, an investigator in FDA's Clinical Investigations Unit, that "NCI is off limits to FDA" (as quoted in the Post), was true.

"No," Crout said.

"Is NCI treated more leniently, differently?" Gore asked.

"There is a special relationship because of the situation," Crout said. "It is not so from an investigation standpoint. We have investigated NCI when necessary."

Gore, Waxman and other committee members were interested in an admission by DeVita that some "leakage" occurs with drugs distributed for clinical trials or sent to physicians under the "Group C" procedure. "Leakage" occurs when the investigators or physicians do not use all of the quantity supplied and give it to other physicians for use with patients not enrolled in trials. DeVita promised to tighten up distribution and insist on return of unused drugs.

Emil Freireich, M.D. Anderson, has long been an outspoken critic of FDA regulations and the IND process. He told the committee:

"Continued progress in developing cancer treatment is increasingly impeded by what are certainly oppressive regulations designed in theory to provide protection for patients with cancer. It is truly ironic that the mechanisms designed for protection create serious harm to thousands of individuals with cancer without any potential for benefit. I have worked full time as a clinical investigator caring for patients with malignancy and having a total commitment to developing new information which would lead to new treatments effective against malignancies. This full time commitment has been carried out over the last quarter of a century as a full time employee of the federal government for a decade and for the government of the State of Texas over the last 17 years.

"Throughout that period of time, I have experienced first hand progressively increasing difficulty with performing my professional activities resulting from the continued introduction of new regulatory activities designed to protect patients. Throughout my entire career, I have yet to have a patient inquire about the potential for harm that might come from my activities. Virtually everyone who seeks attention is concerned about 1) getting the very best professional medical care and 2) about being offered hope when his community physician has told him there is no known treatment for his illness.

"I have found myself in recent years confronted with patients for whom developmental therapies are present in the institution, with all of the financial, fiscal and physical needs present and prepared for clinical trials. Yet I am forced to tell my patients that I am unable to offer these treatments to them because regulatory agencies, particularly the Food & Drug Administration, have failed to approve my application for permission to conduct these studies. I also must tell my patients that the objections to research are such that I cannot understand them and therefore I am unable to comply with them. I have repeatedly had patients who die before the opportunity for offering a potentially effective treatment has received the appropriate approvals.

"Speaking as a physician scientist whose full time activities are related to caring for cancer patients who come to our institution for the latest, most up-to-date and hopefully the best opportunity to have effective treatment, I can say that there is continuous frustration resulting from excessive regulation. The real tragedy is that these regulations are in fact harming the very patients they are designed to protect."

Holland's testimony pointed out that there has been a significant decline in cancer mortality since 1970 for all patients up to age 45. "Indeed the trend shows that up to the age of 55 cancer mortality is decreasing, largely because of the more intelligent and effective use of chemotherapeutic agents in the past 10 years. These drugs represent the pay off of the earlier phase 1 and phase 2 trials which are the sine qua non for developing effective chemotherapy.

"Human error may occur in this, as in any other human endeavor, but the clinical investigators involved are neither callous nor heartless men and women. All patients are volunteers, and all are beyond

cure by surgery, radiotherapy or conventional chemotherapy. In our own experience at Mount Sinai Medical Center since 1974, 998 patients have entered phase 1 and early phase 2 trials, of whom 15, or 1.5 percent, have died in some way related to the drug. All the patients involved have had a chance that therapeutic benefit might ensue."

John Ultmann, director of the Univ. of Chicago Cancer Research Center, was especially critical of the Post articles and agreed with Freireich on results of FDA restrictions:

Gup and Neumann . . . summarized one year's investigative work of on the record interviews with over 600 doctors, patients, relatives, nurses and researchers. Hundreds of files were examined. And what was the result of all this laborious investigation? A very inaccurate, imbalanced recitation of partially verified stories, taken out of context, emphasizing only the negative aspects of the phase 1/2 trials of over 20 drugs, and written with singular insensitivity to the feelings of the people involved. The harm done to the patients and relatives who were interviewed is hard to assess, but surely the allusions to "ball point pen ink", "urine and serum turning green" and similar statements, added little light or comfort to the patients or relatives interviewed. Nor, I am certain, did these statements encourage current and future patients in undertaking needed chemotherapy with the over 40 approved agents which do have a variety of toxic complications. We should remember that is is small modifications, be they of ball point pen ink or bread mold that lead to useful cancer chemotherapeutic agents or lifesaving penicillin. Further, urine and serum turning green is no worse than urine and serum turning red, the latter a side effect of the drug adriamycin, which is one of the most effective chemotherapeutic agents of the 1980s, useful against many cancers.

What was missing in the Washington Post series was a proper, accurate introductory review of the problem of advanced cancer, with its high mortality and morbidity rate; the positive benefits of chemotherapy in a combined modality setting or as the only treatment; the nature of drug procurement, screening, toxicology, phase 1/2 trials; and the very extensive overview/control mechanisms in place to monitor the drug testing program. None of this was covered. In fact, some of the general background that was given, was inaccurate. . . .

Candidate compounds are evaluated in an animal screening panel which is designed so that it can pick up over 35 of the 40 currently used agents were they presented as unknowns. It's an imperfect system, but it is the only one that is economically and practically feasible. Some 40,000 compounds annually in past years, more recently about 15,000 compounds annually, receive careful scrutiny based on chemical and biological rationales. About 500 to 1,000 compounds pass then to a more detailed tumor panel screen and from this are selected the most promising candidates for animal toxicology and finally for human trials. The ultimate aim of course is to discover compounds that have benefit to humans with cancer and have tolerable toxicity. . . .

There is no doubt that some problems will occur in the administration of 40-50 compounds to 40,000 patients by 2,000 investigators each year. However, the process is an open one with multiple control mechanisms at the local and national level and rapid communication to insure maximal exchange of information—particularly of the information as it is related to untoward drug reactions.

In regard to the question of informed consent, I would like to review only a few points. A cancer patient seeking help recognizes the mortal danger he is in and knows all too well the hazards of any treatment. The physician and the patient together must undertake appropriate therapy, despite variable degrees of risk, to insure cure if possible, or at least meaningful palliation with prolongation of useful life.

Legitimate concerns for patient safety and validity of informed consent, have led to the significant improvement over the past three to five years of the process of monitoring the quality of research programs. . . .

At the present time, I believe, the system is overloaded and impeded by control mechanisms of a nature which is unnecessary and cumbersome. The regulatory process actually reduces the number of all types of potentially useful drugs, including cancer drugs, so that the U.S. now lags behind Japan and many European countries in our ability to develop new compounds. Institutional review boards, pharmacy committees, local health authorities, NCI/DCT IRB committees, FDA IRB committees, all concern themselves with form and nature of consent. The number of forms, the bureaucratic machinery, the whole process is hopelessly bogged down. Rather than more control, it needs less. The effort should be directed to the mission at hand: production of new drugs to cure cancer and not the restraint of ethical drug investigators dedicated to that task.

Let me picture for you the possible consequences of the recent articles in the Washington Post and the recent ABC 20/20 program:

1) Fewer patients will accept *current* life saving treatments and many will die unnecessarily.

2) Fewer patients with advanced disease will consent to participate in drug investigation programs from which they, or others later, will benefit.

3) Patients will turn to alternative, unorthodox modes of treatment with diets, injections, enemas, etc. known to be worthless, falsely lifting their hopes, draining their resources uselessly, and risking their very lives unnecessarily.

4) Fewer young investigators will enter clinical research in this field, leading later to a serious delay in the development of new discoveries.

Hensley and Robert S.K. Young of FDA were the committee's final witnesses. Hensley seemed to back away somewhat from his adamant statements qo quoted in the Post.

"I honestly can't say I disagree with Dr. Freireich and Dr. Ultmann," Hensley said. "But we are stuck with the provisions of the Food, Drug & Cosmetics Act." He said he was "uncomfortable" listening to other testimony, noting that FDA regards phase 1 trials as not having therapeutic intent while "with NCI, phase 1 means initial clinical trials."

Hensley suggested that NCI is lax in enforcing informed consent rules. "NCI has never put anyone out of business for failing to get informed consent. We brought several cases to their attention, but they were never put forward."

The congressional committees "should sit back and look at NCI," Hensley said. "It is a billion dollar a year pharmaceutical firm, run by a combination of government and academia. It does not work."

Pressed by Gore to explain his statement that NCI is "off limits" to FDA investigators, Hensley said only that "there are very few audits of NCI trials. This evolved out of the special arrangements with NCI. Our division clearly would like to regulate NCI more closely." He did agree that "some things have

changed. We do seem to be getting better cooperation from NCI."

Gore questioned Hensley about the methyl CCNU kidney toxicity issue, in which NCI delayed relaying reports of the complication until they could be verified, a delay of several months. DeVita told the committee that that was the result of a misunderstanding and that henceforth toxicity reports from investigators will be passed on to FDA as soon as they are received.

Hensley's comment that Bristol, sponsor of Me-CCNU, had withdrawn its own IND when the first reports of renal toxicity came in excited Gore. "Wait a minute," he said. "Here we have the company that manufactures the drug withdrawing the IND the same day it finds out there is kidney damage. The only conclusion I can draw is, the company hopes the drug will go through NCI tests and the kidney damage will not be picked up."

"That's right," Hensley said. "That's one of the loose ends not cleaned up."

Young praised the Post series which he said revealed "what people always wanted to know about cancer research but were afraid to ask. Thank goodness we have a free press."

The series developed two central issues, Young said—informed consent and the scope of consent. "Several patients quoted in the series did not understand the remoteness of therapeutic benefit [from the drug studies in which they consented to participate] and the certainty of toxicity."

Asked by Gore what should be done, Young said, "I kind of like the law the way it's written. It's not too long, only a few pages. If we enforce the regulations even handedly, I think we can protect patients. We need a central repository for information coming in. If something happens, someone can look at it and say, something's going on, let's cut our losses. I would not say there is mismanagement. Maybe it's non management, with thousands of investigations. Somebody has got to take responsibility."

Gore closed the hearing by saying he intended to submit recommendations to HHS Secretary Richard Schweiker on "how better to handle informed consent and on relationships between NCI and FDA."

NCI CONTRACT AWARDS

Title: Carcinogen bioassay of 1,2,3-trichloropropane
Contractor: Hazleton Laboratories, $183,337.

Title: Carcinogen bioassay of acetonitrile
Contractor: Hazleton Laboratories, $172,266.

Title: Carcinogen bioassay of tricresyl phosphate and o-benzyl-p-chlorophenol
Contractor: Battelle Columbus, $376,668.

Title: Support services for extramural clinical trials
Contractor: EMMES Corp., $1,635,153.

Title: Intraoperative radiotherapy
Contractor: Massachusetts General Hospital, $231,424.

Title: Modification of the salmonella test for chemicals that may be metabolized to mugagens under reductive conditions
Contractor: Michigan Cancer Foundation, $154,099.

Title: Collection, storage and quality assurance and distribution of biological response modifiers, Task A
Contractor: Meloy Laboratories, $320,395.

Title: Carcinogen bioassay of promethazine and methdilazine
Contractor: Litton Bionetics, $392,962.

Title: Prechronic studies of tetrahydrofuran
Contractor: Gulf South Research Institute, Baton Rouge, La., $63,053.

Title: Carcinogen bioassay of C.I. Acid Red 114, 3,3' dimethylbenzidine, C.I. Direct Blue 15 and 3,3' dimethoxybenzidine
Contractor: Hazleton Laboratories, $1,833,988.

Title: Carcinogen bioassay of manganese sulfate
Contractor: Gulf South Research Institute, $72,920.

Title: Chromosome damage testing in Chinese hamster ovary cells
Contractor: Small Business Administration, Columbus, Ohio, $216,756.

Title: Bioassay of P-nitroaniline and O-nitroanisole
Contractor: Raltech Scientific Services, Madison, Wis., $145,984.

Title: Carcinogen bioassay of one chemical, C.I. direct blue
Contractor: International Research & Development Corp., Mattawan, Mich., $68,645.

Title: Use of screening techniques for blood in the stool as a means of detecting early cancer of the bowel, continuation
Contractor: Univ. of Minnesota, $666,280.

Title: Therapy of patients with large bowel carcinoma, continuation
Contractor: Albany Medical College, $3,750.

Title: Bioassay of methylphenidate and seneciphylline
Contractor: Raltech Scientific Services, $554,868.

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, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute,

8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

RFA NIH-NCI-BRMP-81-5

Title: *Monoclonal antibody in cancer therapy*
Deadline: *Dec. 15*

The Div. of Cancer Treatment of NCI invites grant applications from interested investigators for basic and applied studies to evaluate the therapeutic effectiveness of monoclonal antibody administration in man.

Biological response modifiers refers to agents or approaches that alter the relationship between tumor and host by modifying the host's biological response to tumor cells, with a resultant therapeutic benefit. The application of these agents with a primary intent of therapy is the major focus of the Biological Response Modifiers Program.

Components of the BRM program include immunoaugmenting agents, immunomodulating treatments, immunorestorative agents, interferon inducers; interferon and cytokine factors; thymic hormones and factors; tumor antigens and cell surface modifiers, antitumor antibodies, antitumor immune cells; maturation and differentiation factors.

This RFA addresses the component antitumor antibodies and specifically hybridoma derived monoclonal antibodies. Experimental studies have been carried out on the therapeutic effects of antitumor antibodies in animal models and, to a lesser extent, in man. Such studies have been hampered in animals by the lack of potent antibody and in man by the lack of solid evidence for the presence of tumor specific antigens and therefore for the antitumor specificity of the antibody employed. The recent utilization of hybridomas for the production of monoclonal antibodies should help in identifying human tumor antigens. It may also provide large quantities of highly specific high-titered antitumor antibody for possible therapeutic testing. Monoclonal antibodies provide a chemically and immunologically homogeneous reagent of defined specificity. They can be obtained in quantities necessary for therapeutic evaluation in man either as a means of selectively eliminating tumor populations directly or indirectly by eliminating or inactivating suppressor cellular components of the immune system.

Studies to be proposed should evaluate the therapeutic effectiveness of monoclonal antibody administration in man. Monoclonal antibodies directed against specific antigens expressed on human tumor cells or on lymphoid cells suppressing an effective antitumor immune response may be evaluated alone or coupled with drugs, toxins, or radioisotopes to determine the pharmacokinetics, clinical toxicity, potential efficacy as anticancer agents and maximum tolerated dose that can be administered parenterally. Parameters to be monitored following administration of monoclonal antibody preparations as therapeutic agents could include degree and specificity of binding to target cells, fate of antibody bound tumor cells, modulation of target antigen and alterations in circulating tumor cells and tumor antigen.

This RFA will use the NIH grant in aid. Responsibility for the planning, direction, and execution of the proposed research will be solely that of the applicant. The total project period for applications submitted in response to the present RFA should not exceel three years. Intent is to fund several projects, with total costs amounting to approximately $1.323 million for the first year. This funding level is dependent on receipt of a sufficient number of applications of high scientific merit. Also, although this program is provided for in the financial plans of NCI, the award of grants pursuant to this RFA is contingent upon availability of funds for this purpose.

Each application submitted in response to the RFA will be reviewed by (1) an appropriate review panel of the Div. of Research Grants, NIH, and (2) the National Cancer Advisory Board. All applications will be evaluated by a single review group in competition with each other.

Future renewal applications will not compete for earmarked funds. Instead, all renewal applications will be considered as unsolicited grant applications which will compete with all other unsolicited applications received by NIH.

Applications must be responsive to this RFA, in the sense of being directed towards the attainment of the stated programmatic goals. If the application is judged by NCI not to be responsive, the applicant will have the opportunity of having the application considered along with other unsolicited applications received by NIH.

Applications must be submitted on form PHS 398 (revised 5/80), the application form for research project grants. Application kits are available at most institutional business offices, or may be obtained from DRG, NIH. The conventional presentation in format and detail applicable to regular research grant applications should be followed. The words "Proposal in Response to RFA: NIH-NCI-DCT-BRMP-81-5 Monoclonal Antibody in Cancer Therapy" should be typed in bold letters across the top of the face page of the application.

The completed original application and six copies should be sent or delivered to: Div. of Research Grants, NIH, Rm. 240, Westwood Bldg., 5333 Westbard Ave., Bethesda, Md. 20205.

A copy of the application should also be sent, and inquiries directed to: Dr. Cedric Long, Biological Resources Branch, BRMP, Div. of Cancer Treatment, NCI, Landow Bldg., Rm. 8C03, Bethesda, Md. 20205. Phone 301-496-9664.

RFA NIH-NCI-DCT-BRMP-81-6

Title: *Monoclonal antibodies in animal tumor models*

Deadline: *Dec. 15*

The Div. of Cancer Treatment of NCI invites grant applications from interested investigators for basic and applied studies to evaluate the therapeutic efficacy of monoclonal antibody administration in animal tumor models.

Studies to be proposed should evaluate the therapeutic efficacy of monoclonal antibody administration in animal tumor models. Currently available monoclonal antibodies directed against specific antigens expressed on tumor cells or on lymphoid cells suppressing an effective antitumor immune response may be evaluated either alone or coupled with drugs, toxins, or isotopes for in vivo antitumor properties. Therapeutic potential of these antibodies may be evaluated in the treatment of transplanted, induced or spontaneous animal tumors or human tumor xenographs in nude athymic mice. Studies may examine such parameters as: effects of passive administration of antibody or antibody conjugates on survivial and cure rate; differences in ability of antibody of different isotype to mediate and to modulate antitumor effects; antibody halflife and tissue distribution, degree and specificity of antibody binding to tumor cells, in vivo and in vitro fate of tumor cells, modulation of tumor cell antigens, optimal dose schedule and short and long-term toxicity.

This RFA will use the National Institutes of Health grant in aid, as in the RFA above. Direct applications and inquiries to the addresses shown in that RFA, citing the title of this RFA.

RFA NIH-NCI-DCT-BRMP-81-8

Title: *Animal tumor models for antipeptide growth factor and maturation factor therapy*

Deadline: *Dec. 15*

The Div. of Cancer Treatment of NCI invites grant applications from interested investigators for basic and applied studies in which a transplanted or spontaneous animal tumor will be developed to determine the therapeutic efficacy of anticancer agents which act by specifically blocking the actions of specific peptide growth factors.

This RFA addresses maturation and differentiation factors. The continuing progress being made in clarifying the mechanisms of regulation of bone marrow differentiation and the recognition of the existence of stemm cell like cells in the tumor directs attention to the possibility that tumor cell differentiation may be achieved through therapeutic means. In other words, the possibility is theoritically considered that some agents may be developed which will not kill the tumor cells but will actually cause their further differentiation from the malignant state.

Low molecular weight peptide growth factors which promote cell division and anchorage-independent growth of normal and transformed human cells in vitro and which may be required for tumor growth in vivo have been recently identified and characterized. In order to assess the potential therapeutic efficacy of agents which specifically block these growth factors, suitable animal models need to be developed. In addition, other peptide growth factors and certain other substances have been shown to induce maturation (terminal differentiation) of tumor cells in vitro. Animal tumor models are also required to assess these substances as potential anticancer agents.

Studies are encouraged to develop a transplanted or spontaneous animal tumor to determine the therapeutic efficacy of anticancer agents which act by specifically blocking the actions of specific peptide growth factors.

These factors might include both normal and tumor cell products. Of particular interest are animal tumors shown to be response in vitro to a peptide growth factor (for example epidermal growth factor) and agents shown to specifically block this same factor. In similar fashion an animal tumor model may be developed which can demonstrate the anticancer activity of maturation factors which are capable of inducing terminal differentiation of various transformed cell lines in vitro. Examples of cell lines previously shown to be responsive to such agents include PC-12 pheochromocytoma cells and HL-60, Kg-1, and K 562 myeloid leukemia cells. Transplantable tumors of these or similar cell lines might form the basis of a suitable animal tumor model.

This RFA will use the National Institutes of Health grant in aid, as in the RFAs above. Direct applications and inquiries to the addresses shown in the first RFA above, citing the title of this RFA.

RFA NIH-NCI-DCT-BRMP-81-9

Title: *Therapeutic use of lymphokines in cancer*

Deadline: *Dec. 15*

The Div. of Cancer Treatment of NCI invites grant applications from interested investigators for basic and applied studies to evaluate the therapeutic value of defined lymphokines in antitumor immunity.

This RFA addresses cytokines (lymphokines). These factors are glycoproteins in the 5,000 to 100,000 molecular weight range. The cytokines obtained from lymphoid tissues or supernatants of mononuclear cell cultures are called lymphokines. Some have been shown to have direct cytocidal or antiproliferative activity, some to modulate and exert selective regulatory effects on various components of immune responses and others to affect bone marrow proliferation, or ossification or vessel proliferation. Production and purification of lymphokines have been a problem in the past. More recently, means have been developed to obtain lymphokines from lymphoid

lines in culture thus helping to resolve the problem. Administration of lymphokines that can selectively activate or suppress certain components of the immune system may produce a beneficial antitumor effect in vivo.

Studies to be proposed should evaluate the therapeutic value of defined lymphokines in antitumor immunity. Currently available lymphokines, purified to near homogeneity, may be used in both in vivo and in vitro studies to evaluate and monitor specific effects on the various cellular components of the antitumor response. A further stage of analysis could involve testing the therapeutic efficacy of various lymphokine preparations in transplantable and spontaneous animal tumor models. Investigators may restrict their study to a single lymphokine or may wish to perform comparative studies on various lymphokines. A goal of the studies should be to provide information relevant to the choice of a lymphokine(s) for preliminary clinical testing and the type(s) of tumor host relationship most amenable to effective biological modification using lymphokines.

This RFA will use the NIH grant in aid, as in the RFAs above. Direct applications and inquiries to the addresses shown in the first RFA above, citing the title of this RFA.

RFP N01-CP-15817-56

Title: *Information resources master agreement*
Deadline: *Dec. 9*

The National Toxicology Program is interested in receiving proposals that will provide computer and manual searching on compounds and concepts, to duplicate various experimental design packages or other documents. NTP estimates that this project will be for a two year period.

This is a 100 percent set-aside for small business.

Contract Specialist: Molly Eng
RCB, Blair Bldg., Rm. 2A01
301-427-8774

RFP NCI-CM-27533-29

Title: *Operation of an animal virological diagnostic laboratory*
Deadline: *Jan. 8*

NCI is interested in contracting with an organization having capabilities for operation of an animal virological diagnostic laboratory. The project will be utilized to monitor the viral health status of laboratory animals from genetic centers, rodent production centers, hybrid production and various testing laboratories.

The successful offeror will supply services, qualified personnel, material, equipment and facilities not otherwise provided by the government, under the terms of the contract, to carry out the following procedures: (1) operate and maintain a virus serum diagnostic laboratory. Serum samples will be submitted from contract animal suppliers and testing laboratories. The profile will include from four to nine viruses depending upon the animal being tested. About 90,000 virus tests will be performed annually. (2) Test experimental tumors for viral contaminants. Tumor samples will be monitored for 12 viruses. 1,000 tumor samples are to be tested annually. (3) Perform up to 6,000 ELISA tests annually for the detection of murine corona virus antibodies to mouse hepatitis virus (MHV) and (4) Capability to produce 100,000 units of ectromelia vaccine annually.

It is anticipated that the award will be for five years, funded by yearly increments.

Contracting Officer: Clyde Williams
RCB, Blair Bldg. Rm. 232
301-427-8737

Subcontract Under Contract N01-CO-95447

Title: *Qualitative research on public knowledge, attitudes and practices related to cancer*
Deadline: *Nov. 30*

This proposed procurement will be made from Porter, Novelli & Associates, Washington D.C. This procurement is for phase I, exploratory and qualitative research leading to a national survey of public knowledge, attitudes and behavior related to cancer. The full scale survey will be procured by separate action following completion of this phase.

The work will take approximately 10 weeks and will include: 1) conducting a literature review synthesizing extant knowledge; 2) identifying appropriate topics of inquiry, subpopulations, sample questions, and methodological problems and solutions; 3) conducting and analyzing exploratory group (i.e. focus group) interviews of representative populations; and 4) identifying primary areas of inquiry and hypotheses for a final quantitative survey. The contractor must provide highly competent personnel experienced in conducting computerized literature searches, and qualitative research on health related areas.

Requests for copies of this RFP must be submitted in writing to:

Dr. Jeffrey Milstein
Porter, Novelli & Associates
3240 Prospect St. N.W.
Washington D.C. 20007
202-342-7000

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