THE CANCER LETTER

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CCRAC APPROVES NEW GRANT PROGRAM FOR STUDIES OF CANCER PATIENT COMPLIANCE; RFA TO BE ISSUED

NCI's Cancer Control Program not only suffered a major cut in its proposed 1981 fiscal year budget, but it soon will be incorporated in a new division which will contain other important elements. Although some may feel that cancer control is being deemphasized, staff and advisors to the existing Div. of Cancer Control & Rehabilitation are proceeding with plans for new programs.

The Cancer Control & Rehabilitation Advisory Committee, in what

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In Brief

MEDICAL SCHOOL DEANS BIGGEST ENEMY OF CANCER PROGRAM, SAUNDERS SAYS; HOUSE OKs LINE ITEM

"MEDICAL SCHOOL deans emerged as the single most refractory group with which we dealt," Palmer Saunders, former director of NCI's Div. of Cancer Research Resources & Centers, said in relating a history of the Cancer Centers Program. Saunders, now at the Univ. of Texas Medical Branch Clinical Cancer Center, said, "Deans became the biggest enemy of the Cancer Program, with some notable exceptions. They felt we were encroaching on their prerogatives, interfering with their relationships with their departments. Many were not qualified to appreciate the cancer problem." Saunders spoke at the recent meeting of the Assn. of American Cancer Institutes. . . . **THE CONTENTION** that cancer center core grants "steal money from R01 (traditional individual grants) is a myth," Timothy Talbot, Fox Chase Cancer Center, told AACI members. "In truth, 98 percent of our money supports R01 grants." Other myths cited by Talbot: That peer review of investigators at centers is less stringent than elsewhere, and that the quality of research in centers is not up to that at other institutions. . . . **HOUSE COMMERCE** Committee went along with the request of Health Subcommittee Chairman Henry Waxman to insert authorization figures as a line item for cancer center core grants in the biomedical research authorization bill. The amount for fiscal 1981 is $90 million, 1982 $108 million, and 1983 $130 million. NCI, like other Executive Branch agencies, does not like line items, preferring to keep all its appropriations "flexible." AACI members felt NCI has been too flexible with the centers budget and sold Waxman on their case. They were not successful with Sen. Kennedy, and his bill has no authorization figures. That will be a major difference that will have to be settled in conference, barring amendments on the floor. . . . **JOHN POTTER**, director of the Vincent Lombardi Cancer Research Center at Georgetown Univ., has been designated official observer at meetings of the National Cancer Advisory Board by both the American College of Surgeons Commission on Cancer and the Society of Surgical Oncology.

CCRAC OKAYS NEW RFA FOR COMPLIANCE STUDIES, CBCCP EVALUATION CONTRACT

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probably was its last meeting before being reconstituted as the Board of Scientific Counselors for the new Div. of Centers, Community Activities & Resources, last week approved the concept of a new grant program for research in patient compliance. The committee also approved the concept of a contract with a group of individuals who participated in the merit review of the Community Based Cancer Control Program for an evaluation study of the program.

The patient compliance study will be developed into an RFA (request for applications) soliciting grant applications. At that time, a definite amount of money will be earmarked to fund the grants, although NCI will not be obligated to use it all for that purpose. Details on the nature of proposals sought will be included in the RFA.

Sandra Levy of the DCCR staff presented a supporting statement to CCRAC, much of which probably will be written into the RFA. The statement, with some editing:

In general, lack of patient cooperation with diagnostic, treatment, and rehabilitation efforts across chronic disease states is a major and growing concern for health care providers. Although there is no reason to assume that the problem is less acute in the cancer patient population, to date only one careful investigation of cancer patient compliance with treatment requirements has been carried out.

Aims of this RFA Research Support

A. A major reason why there is such inconsistency and noncomparability of studies in the general compliance literature is that there are few good measures of compliance response. One aim will be to facilitate research that will provide valid and reliable measures of compliance. For example, there has been preliminary research at the Johns Hopkins Medical School on the feasibility of measuring levels of urinary cytoxan metabolites as a quantitative measurement of patient medication compliance. Much more work on measurement development needs to be done. This latter would include direct measures, including laboratory tests and also less direct, but valid means of patient self-report of cooperative behavior.

B. The major aim of this RFA will be to foster systematic research into the nature of cancer patient compliance which will lead to greater understanding of the sources of individual and group variation in compliance behavior. Such knowledge also will allow for prediction of noncompliant behavior in order to intervene with those at high risk for noncompliance.

C. The ultimate aim of research in this area will be to improve staff training in regard to fostering cooperation in patients for their own self-care. Following upon a greater understanding of who is noncompliant and why, care givers can be trained to intervene with high risk patients and can learn intervention techniques that will optimize cooperation in these patient groups.

Nature of Compliance Issues for Cancer Patients

The necessity for patient cooperation in health care delivery extends from prevention of disease (such as the willingness to alter smoking behavior) and detection of cancer (the willingness to engage in regular breast self-examination), through cooperative alliance in treatment, rehabilitation, and continuing care efforts.

Diagnosis and treatment. Compliance for diagnostic purposes requires obtaining a full medical workup when suspicious signs are detected. Many persons experience these signs, know that they may indicate cancer, and still delay or refuse examination. In some instances, persons may initiate a series of medical examinations but do not follow through to their completion. This pattern of behavior may be related to a general life style in which other concerns, such as work or family responsibilities, have higher priority, rather than to anxiety concerning diagnostic outcome. This pattern is especially common among poor and minority persons.

Compliance with pretreatment evaluation includes not only obtaining full information on the kinds of treatments necessary for a given malignancy, but also avoiding unproven methods. Cooperation with treatment regimens involves following recommendations for a full course of treatment—suggested surgery, chemotherapy, radiation therapy, and when demonstrated effective, newer forms of treatment such as immunotherapy. Compliance also means following nutritional directions and discontinuing exposure to various carcinogens. Noncompliance to these recommendations appears most frequently when personal suffering is experienced as a result of cancer treatment; when surgery is markedly disfiguring; when limbs, breast, speech, or hair is lost; or when sexual or earning abilities are reduced markedly.

Rehabilitation and continuing care. Rehabilitation compliance involves accepting relevant rehabilitation therapies, such as occupational, physical, vocational, inhalation, and speech therapy. Training in the use and care of prosthetic devices, laryngeal speech training, or the following of special diets may also be indicated.

Cooperation in continuing care generally means returning for checkups and complying with new treatment courses as necessary. For some patients, compliance means repetitions of previously painful and unpleasant experiences which may become increasingly undesirable. Patients may then be noncompliant, despite knowing that their lives are at stake. The resultant quality of life is so diminished, that they prefer living as well as they can for as long as they can, even if that means dying sooner. Noteworthy is the heightened tendency of many patients to seek nontraditional treatments during this time, especially when cure is not possible. Rejection of rehabilitation recommendations and continuance of proscribed activities are also common at this time.

Noncompliance in cancer patients. As indicated above, the question of patient compliance is a very complex one. Some cancer patients may be extremely cooperative during the early phases of treatment, readily accepting operations, radiotherapy, and even chemotherapy. Later, especially when a cure is less feasible, they may become quite noncompliant. Or earlier noncompliant patients may become more compliant during the course of treatment. Here, to be considered as noncompliance, lack of cooperation with health care recommendations must impair or interfere with treatment influence. Thus when a terminal patient rejects a palliative treatment which is unlikely to change the course of his or her cancer, this refusal for all practical purposes is not noncompliance.

Despite the complexity of patient response in the therapeutic "alliance" across the whole gamut of cancer control activity, research directed towards understanding intraindividual and interindividual variation in cooperation clearly should be carried out. Leaving aside the issues surrounding feasibility and worthwhileness of some prevention and detection activities—and leaving aside the question of compliance in metastatic and terminal patients—there is a wide range of effort in cancer control that requires patient initiative and cooperation, and there is little dispute about the efficacy of compliance in these cases. It is this wide range of concern in the areas of diagnosis, treatment, rehabilitation, and post-primary treatment

continuing care that will be addressed through this RFA research initiative.

Extent of the Compliance Problem in the Cancer Patient Population

As was indicated above, almost no systematic research on compliance has been carried out with cancer patients. Most of the evidence then for the existence of the problem is clinically based. An oncologist in the department of surgery in a fairly new hospital in Los Angeles (with a patient population comprised of 50 percent blacks and chicanos), conducted a survey of patient outcome over the first five years of the hospital's operation. One-third, or over 300 patients, simply disappeared from treatment immediately, and it is very unlikely that these patients went elsewhere for treatment. In that same facility, the majority of patients who came into the facility were reportedly already in advanced stages of the disease when they were first seen, and relatively few came into that hospital in the early stages of disease when treatment might have been more feasible.

Ulmer (1980) also stressed that noncompliance is a major problem for cancer patients, particularly for low socioeconomic status patients, and that this latter demographic association may account for some disagreement regarding the extent of the problem. Noncompliance may be a differential problem depending on context. It may be that low rates of noncompliance are reported at a research facility such as the Clinical Center at NIH because the kinds of patients referred there represent a biased, and hence unrepresentative sample. They may have very high expectations because of the context and may be very motivated to cooperate, etc. Apparently, the experience is very different in less prestigious facilities.

One exception to the dearth of studies on cancer patient compliance is a project that was carried out at the Univ. of Kansas Medical Center (Smith, Rosen, Trueworthy & Lowman, 1979). These investigators studied prednisone compliance is a group of adolescent outpatients diagnosed as having some form of malignancy (acute lymphoblastic leukemia, acute myeloblastic leukemia, and non-Hodgkin's lymphoma). Measuring compliance to treatment regimen by quantifying urinary 17-ketogenic steroids from urine samples taken at random, these urine levels in outpatients were compared to those from inpatients receiving the same medication, as well as outpatients who were currently off prednisone at the time of testing. These investigators found that 33 percent of the outpatients who by protocol and instruction were supposed to be receiving prednisone were not complying. Separate analysis of older patients in the study revealed an even more alarming 59 percent noncompliance rate. "This striking level of noncompliance strongly suggests that the survival of patients may be threatened by noncompliance," the investigators said.

These researchers pointed out that not only do these data raise the important question of whether the "known poor prognosis of adolescents with acute leukemia" is potentially caused by their poor drug compliance, but also they raised the question of the role of compliance in clinical trials.

As the prognosis and length of survival improves in childhood malignancies, one question that has become of great interest and importance is why children with the same disease on the same therapy show such a wide variation in response. Many investigators have been frustrated by the lack of reproducibility of studies in acute leukemia. Data collected at one institution is not always reproducible when attempted by a cooperative group. One drug regime (POMP) for childhood acute lymphoblastic leukemia produced a 92 percent complete remission rate at one institution but only a 56 percent complete remission rate when studied by the pediatric division of the Southwest Oncology Group. Sequential protocols conducted within the same institution have not always produced the statistically predicted results.

At St. Jude Hospital, in four sequential acute lymphoblastic leukemia protocols, the proportion of patients in complete remission after 24 months of therapy showed an unexpected decline. These studies used essentially the same drug regimes, and these results have been difficult to explain. One of the factors that may influence some of these conflicting results is poor patient drug compliance.

Goldsmith (1976) and Feinstein (1976) also address the problem of "compliance bias" in the interpretation of therapeutic trials, and Haynes (1980) recently differentiated effectiveness from efficacy in chemotherapy treatment. A treatment is considered effective when it does more good than harm to those to whom it is offered (in an ideal, randomized trial condiction); a treatment is efficacious when it does more good than harm in those who actually take it. Any difference in the two response rates is obviously due, at least in large part, to noncompliance behavior. The implications for noncompliance is that the therapeutic benefit is jeopardized in those who do not cooperate with treatment recommendations.

The point is that at least for some significant subgroups of cancer patients, it appears that noncompliance is a major issue. While the clinical experience of oncologists in the field suggests that noncompliance is a major problem, the extent of the problem has not been documented precisely. Who is noncompliant, and what the associated demographic and socio-psychological variables are are questions that need to be assessed more systematically. The professionals who were consulted in order to supply background information for this RFA concept asserted that the problem was sizable, but the exact percentage of noncompliant patients is unknown at this time. Therefore, researchers in various facilities would need to document the incidence, prevalence, and types of noncompliance for the study population with which they are concerned, in order to suggest the direction for future research endeavors should significant predictors of noncompliance be found in the sample under study.

Turning to specific variables that might predict noncompliance, elements of the Health Belief Model (Becker & Maimon, 1975; Rosenstock, 1966), although not labeled such by these consultants, seemed to emerge. A practicing oncologist at the Scripps Cancer Center insisted that the patient's belief in the source of healing was an important factor in terms of electing treatment modes; Ulmer in his work involving diagnosis of compliance risks, has isolated attitudes toward medical personnel and belief in personal vulnerability as important predictors of actual compliant behavior in cancer patients. These cognitive variables are central to the Health Belief Model, and while not scientifically assessed in cancer patients, appear to be as operative here as in other patient groups.

General Background of the Problem Area

Howard (1978) refers to "patient-centric technologies," or health care delivery efforts aimed at utilizing and facilitating skills and capacities that only the patient possesses. Such behaviors as self monitoring for symptoms, initiation of care provider contact, life style change, and cooperation with long-term medical and rehabilitation regimens lie within the patient's special province. These skills and capacities are directly relevant to the whole issue of patient compliance, and while the latter term implies passivity on the part of the patient, in actuality, the patient is an active partner in the entire health delivery enterprise. If voluntary initiation and cooperation are not forthcoming—if the patient resists active partnership and withholds his/her necessary initiatory skills—then no amount of scientific treatment or rehabilitation progress will benefit such a patient.

The seriousness of the problem of noncompliance is readily seen by a review of related studies. Ball (1974) in an examination of 140 papers on the topic, concluded that compliance with preventive medical regimens appeared to be about 80 percent for short term, but only 40 percent for long term pro-

phylaxis. In addition, a marginal 50 percent compliance to medication regimens was found; with 1/3 of the patients always complying, 1/3 sometimes, and 1/3 never. Davis (1967) reports that at least a third of patients in most studies failed to comply with doctor's orders, and that one third of the studies reviewed reported a noncompliance rate of 50 percent or more.

Compliance is not a unidimensional variable. Its components can change over time and from situation to situation. It has been found that the greater the behavioral change required, the poorer the compliance. Other studies have shown that mere knowledge about the disorder did not lead to desired change in health behavior. The necessity of changing culturally ingrained habits has also been found to be negatively related to following such orders as dietary prescriptions.

Measurement of compliance. Investigators differ in their operational definition of compliance. Neither faithfulness in appointment keeping nor objective course of the disorder can be used as reflections of compliance, because patients tend to keep appointments for a variety of reasons not necessarily associated with a desire to cooperate with aspects of their regimens, and patients can get worse whether they cooperate or not. Patient compliance has been measured by clinical tests for presence of medication in the urine or blood, pill bottle counts, weight changes, direct observations, patient self reports, and blood pressure readings. The literature on compliant behavior is both mixed and contradictory. Many individual studies have been performed without adequate means of measurement or standardized methods of data collection or evaluation. Heterogeneous settings and patient populations have been used, affording little comparability among studies concerned with this issue.

Sources of compliance. Some studies have examined the correlations between compliance and demographic variables. Some have shown that noncompliance occurs most often at age extremes. One fairly consistent finding is that patients who live alone are less likely to comply than those who live with a spouse. Other demographic variables such as sex, socio-economic status, education, religion, and race, when examined apart from other variables, have rarely been predictive of compliance with medical recommendations.

As Marston points out in her review of studies with compliant behavior, there have been few attempts to explore the relationship between the results of psychological tests and the prediction of noncompliance. When studies utilizing psychological measures have been conducted on medical patients, frequently no attempt is then made to actually measure behavioral compliance outcome. Aside from this obvious limitation, few clearcut relationships have appeared between psychological variables—such as internal-external locus-of-control or risk taking—and active cooperation with medical advice.

There does seem to be a positive relationship between compliance and the quality of the patient's interaction with medical caretakers. Studies that have attempted to relate such interaction patterns with compliance have considered deviations from the normative doctor-patient relationship, the negotiation between doctor and patient, seriousness of illness and complexity of instructions, and length of interview.

Increasing attention is also being given to satisfaction with with provider and treatment, as indicated by patients' subjective perceptions of care, patient feelings of reassurance, relationship of satisfaction to psychological health and speed of recovery, and influence of satisfaction or dissatisfaction on patient behavior. One difficulty in the satisfaction literature is the nebulous definition of the concept. Attempts to divide satisfaction into more specific elements have been made recently, with the general conclusion that the patient-provider relationship is the most important element influencing patient satisfaction.

Cancer treatment plans often cover several years. As the number of patient-provider interactions increases, it is likely that the potential for the quality of interactions to influence behaviors that affect medical outcomes of therapy also increases. The evidence indicates that the patient-provider interaction is worthy of further study, especially in a cancer control setting.

Limits of previous research. In general, the literature on compliance suffers from some major gaps that are only recently being recognized and addressed. First, it is difficult to compare many studies (especially those dealing with compliance with medication regimens) because measures of compliance vary substantially from study to study. Second, most investigators have not assessed the relationship between compliance and actual medical or health outcomes; nor have they recognized that patient noncompliance may be the result of a decision on the patient's part based on his or her own assessment of benefits, risks, and personal goals. Third, most early investigators failed to recognize the complexity of the determinants of compliance, and concentrated on studying small numbers of variables to try to identify noncompliant patient types.

A major limit that is being addressed here is that very little good research has been done on compliance in cancer patients. In Sacket and Haynes (1976) book, "Compliance with Therapeutic Regimens," out of approximately 246 studies reviewed by these authors, two were relevant to cancer patients: 1) a 1964 descriptive study of why women delay in seeking diagnosis of breast changes, and 2) an interview study reported in 1950 concerning reasons given for delay in seeking care. There has been other work done since, but with the exception of the study by Smith, et al. on prednisone compliance in adolescent cancer patients, most has been of a clinical, descriptive, unsystematic, and uncontrolled nature. Clearly, this investigative lack leaves unexamined a critical component of the treatment and continuing care of the cancer patient.

Relevance of this Research Area for NCI

The need for compliance in cancer control is likely to increase markedly in the future. This is true not only in terms of preventive activities related to avoidance of carcinogenic substances but also treatment and rehabilitation compliance. Compliance behavior also tends to be negatively correlated with chronological age. As patients live longer because of improved diagnostic and treatment techniques, continuing compliance may become increasingly significant and difficult to obtain. This latter is true because the longer a person has a chronic disease, the more likely he or she is to be noncompliant to the extent of even dropping out of treatment entirely.

In addition to research implications related to therapeutic trials and the development of more effective treatments, implications for future clinical applications of treatment and continuing care are present. No matter how effective the intervention, if patients do not cooperate, negative outcome can be expected. Treatment and rehabilitation responses are not isomorphic with technical advance, and noncompliance would seem to be a major moderating factor in outcome.

Noncompliance with rehabilitation and treatment regimens is an undocumented area with definite relevance to cancer control and the mission of NCI. At the very least the clinical and research evidence would warrant a careful examination of psychosocial mediators of medical, as well as rehabilitation, compliance in the cancer patient.

Committee member Anthony Miller suggested that "compliance should be an inherent part of what anyone would do with research involving cancer patients or screening. We know there is a problem and no research project should be approved without it."

"People who design clinical trials are not necessarily those with insight into compliance problems," said William Terry, acting DCCR director.

"Many regimens are not self administered," Miller said.

"That is true," Terry answered, "but they are becoming more so. It is a product of our success. As treatment becomes more effective, there are more options."

"The whole concept of compliance is ambiguous," said committee member Harold Mendelsohn. "People don't seem to want to do what other people tell them what's good for them. Everything in our society is training people not to comply, to doubt, to be incredulous. Then we tell them they must comply to these regimens."

Levy responded that the concepts in the proposed grant program are that investigators will have to spell out approaches and address specific problems.

"I like the concept," said committee member Gale Katterhagen. He asked if the terminally ill and their families would be excluded from the study.

"Yes," Levy answered. "With the terminally ill, we are not sure what is compliance and what isn't. Ethical issues are paramount."

"But 50 percent still die," Katterhagen said. "There is a great deal to be done, and noncompliance is still a problem. Are they taking their narcotics at home? The practitioner needs help to identify those not complying, and why."

Committee consultant Anthony Mazzochi said that "assuming social class has a lot to do with compliance, and that poverty and alienation also have something to do with it, it is my guess that the investigators will conclude that segment will not comply anyway and therefore concentrate on the upper classes. Behavior modification means lecturing people on lifestyle."

"Behavior modification is a term not used in this context," Levy said. "We prefer behavior intervention. We do not intend to coerce anyone."

"There is a third alternative," Terry said. "While we may not address poverty or alienation, we may identify support mechanisms, which can operate in the context of poverty and alienation."

"The average worker in the cancer field is not aware of the problem or the extent," said committee member Glenn Sheline. "It might be better to take off in an area which can be defined. I'm seeing more patients, potentially curative, who refuse therapy. People are scared by radiation, perhaps."

Committee member Willie Dell said she had mixed feelings about the concept. "When someone doesn't do something we want them to do, we think they don't understand. I think maybe the patient does understand but chooses not to accept that option. The assumption is that what we recommend is best, but a person has the right not to accept that. People have different values. There is the question of the quality of life, disfiguration."

"I suggest aiming this at early stages of treatment," said committee member Kenneth Casebeer. "There is a problem with compliance by terminal patients, but this borders on intrusion. We can find reasons for noncompliance in later stages, perhaps, in studies with earlier stages. Compliance measurement depends to some extent on physical intrusion, such as collecting blood samples."

"Many millions of dollars could be spent on compliance," said George Omura, a review committee liaison representative to CCRAC. "What we would like to get out of it is not only a definition of the magnitude of the problem, but go to the next step, finding out what we can do about it. Prednisone was not effective against AML. Maybe the patients were smarter than we were. These studies need a sound basis from the standpoint of the effectiveness of the treatment offered."

Terry said that while the dollars to support the studies could not be determined now, "we consider this high priority. We think it is important, and no one else is addressing the problem."

The motion by committee member Harold Rusch to approve the concept, "taking into consideration the comments made here," was approved unanimously.

The committee also approved the CBCCP evaluation study without objection. It will be a noncompetitive contract with the group of individuals who participated in the merit review. It will be a three year award to assess the concepts, strategies and outcomes of the six CBCCP contracts.

AACI SUMMARIZES POSITIONS ON NEW CORE GRANT GUIDELINE PROPOSALS

A summary of the positions expressed by members of the Assn. of American Cancer Institutes on the proposed new guidelines for center core grants has been prepared by Alvin Mauer, AACI president.

Members of the association met recently to consider the proposals and develop counterproposals (*The Cancer Letter*, May 2). Mauer's report states the AACI's recommendations on each of the proposed changes:

Developmental

"1. The notion contained in the 1976 guidelines concerning the application of developmental funds to new programs should be retained. Developmental funds should not be used only as a recruiting device for new investigators.

"2. Decisions concerning the use of developmental funds should be in the hands of the center director, not NCI staff.

"3. There should be no cap on the total amount of developmental funds.

"4. The $60,000 limit for each supported investigator should be removed to allow for recruitment of more senior staff for the strengthening or development of new programs.

"5. Reallocation or rebudgeting should be done at the discretion of the cancer center director for use in developmental programs.

Administration

"The definition and purpose of the Cancer Center Program should be returned to that used in the 1976 guidelines with the exception that prevention replace detection as one of the aims. It was also noted that the classification of cancer centers in the proposed guidelines is inadequate.

"1. Consensus was reached that there should be no lower limit of NCI funding set for application. The cancer center should be defined by program not by size.

"2. The letter of intent should be used for information exchange only and not to apply for submission to submit a research application. The veto power over submitting a grant application should not rest with NCI staff.

"3. The requirement for six months notification by letter of intent before a supplemental grant application is submitted should be removed.

"4. The CVs of members included in the grant application only should be part of the application, not all members of the center.

Shared Resources

"It was acknowledged that there should be some chargeback provision but also that evidence of cost sharing should also be considered as part of institutional support.

"It was acknowledged as a positive attribute that the section on shared resources was vague and nonspecific, leaving room for considerable flexibility.

"To the sentence on hospital costs should be added 'when those are available'.

"Shared resources and facilities should be available to all investigators of the cancer center regardless of how these investigators are funded. These resources should not be available only to individuals having NCI grants.

"The charge back system should be phased in for these shared resources in parallel to the systems used for other funding sources.

"It was stressed that in some circumstances the increased cost of accounting for the charge back system defeated the purpose of the system with respect to supporting the shared resources. In those circumstances this system should not be used.

Staffing and Personnel

"There should be no ceiling of 25 percent of the total budget as the amount which could be used for staffing and personnel. It was pointed out that this limit is vague and does not indicate whether it reflects the proportion of total budget requested or proportion of total budget awarded.

"The limitation on support of senior leadership to three fulltime equivalents was deemed generally acceptable. The term 'large' center should not be used as it is too indefinite. Senior leadership definition should be extended to include such associate directors as cancer control and education.

"There should be no cap on the salary of major program leaders. There should also be no stipulation that major program leaders must qualify as center investigators.

"Center investigators should be identified as those possessing funded grants without specifying the amount of the grant. Site visitors should be able to determine if an investigator qualifies without regard to the research funding amount.

"Center investigators should be named in the grant application.

"If the center investigator loses grant support, salary may be paid from the core grant for a grace period of one and one half years.

"If a position becomes open for support of a center investigator from the core grant, it may be filled at the discretion of the center director without prior approval from NCI.

"There should be no specification with respect to the site at which a center investigator conducts his research."

REGULATION THREATENS CLINICAL TRIALS, GEORGE HIGGINS SAYS IN JAMES LECTURE

"With clinical investigators being pressed on all sides into uncomfortable positions, there is genuine and sincere concern that regulatory obstacles threaten to strangle significant clinical research so important to the ultimate goal of cancer control."

George Higgins, chief of surgical service at the Veterans Administration Medical Center in Washington D.C. and chairman of the VA Surgical Oncology Group, described how clinical investigators are "submerged in administration and regulatory details" in the Lucy Wortham James Clinical Research Award lecture presented at the annual meeting of the Society of Surgical Oncology annual meeting this week.

Higgins' lecture was titled, "Problems in Clinical Trials: Lessons from the 'Tuck-Uppers'." The term "tuck-uppers" was a frontier name for practitioners who were not degreed MDs, "they just tuck up medicine," frontiersmen said. Higgins noted that Ephraim McDowell, who in 1809 performed the first successful abdominal surgery, and William Beaumont, who made extensive observations and experiments in digestion and gastric secretion starting in 1822, were both "tuck-uppers. . . . They made momentous contributions to medical science without benefit of a single committee," Higgins said.

Higgins acknowledged the need for institutional review and regulations when human subjects are used in research. "In past times and still too often today, medical therapies have emerged in a trial and error, haphazard fashion, often to a glittering and enthusiastic prominence, only to sink back into the ooze of

obscurity when evaluated by the uncompromising eye of time. . . .

"As randomized trials have proliferated," Higgins continued, "many practical and philosophic problems have emerged, leading some to advocate that such trials be abandoned and that innovative new methodologies and observational studies more consistent with the traditional doctor-patient relationship be developed. Controlled trials as well as all other health matters have been swept up in the regulatory frenzy of government agencies so that strict adherence to regulatory guidelines has made it increasingly difficult to enter patients into therapeutic trials.

Referring to the Helsinki Declaration of 1964 and principles established by the National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research, Higgins said:

"While on the surface these guidelines seem most reasonable, their strict application may not be so simple. It is quite conceivable that overzealous application of the consent ritual may in itself result in harm to the subject by producing undue fear and anxiety. . . . To the patient considering entry into a study protocol, detailed explanation of all the possible toxic effects of the proposed therapy, often including 'those yet unknown' and 'death' may have serious emotional and even physical consequences. There is an increasing body of evidence to show that the administration of a placebo following a long recitation and explanation of a multitude of undesirable side effects may result in some of these manifestations even though the medicine itself is never administered. . . .

"There is considerable disagreement existing as to just what informed consent means, and there are many who maintain that the concept in its full ramifications is illusionary at best. No one can seriously question the basic precepts of this humanistic concept; however, overzealous application of these principles can seriously impede the effectiveness of an important clinical investigational tool."

Higgins pointed out that regulations which guide approprate human study committees are generally applied to large academic institutions which already have extensive internal review mechanisms "sufficient to ensure seriousness of purpose and to avoid capricious or meaningless experiments. In addition the results of these investigations are widely presented and published.

"Conversely there is absolutely no restraint on the individual practitioner in trying the latest type of therapy about which he has read in the literature or heard at a recent meeting without any discussion with the patient concerning the treatment or possible harmful effects of the method.

"In other words, the closest controls and strictest regulations are applied where abuse is least likely to occur. . . . The need for alternative methods which are ethically more acceptable but still permit valid comparison of treatment methods is widely voiced. For the most part historical controls do not meet these requirements but perhaps alternatives such as a 'prerandomization' technique as suggested by [Marvin] Zelen in which only those patients randomized to receive experimental treatment would sign the informed consent, may lessen the obstacles in entering patients into trials.

"Likewise, there is great need for more discriminatory statistical methods that will detect a smaller treatment effect in surgical adjuvant trials. When observed survival following surgical resection is 50 percent at five years, at least half of the patients randomized to receive an adjuvant therapy have no possibility of survival benefit. A technique termed 'longevity increase from treatment' which takes into account the number of patients who have no chance of benefit as well as the expected attrition rate normally expected in patients in the age group being studied has been suggested but not widely accepted. These technical aspects of clinical research are currently under serious study by those involved in protocol design and statistical analysis. . . .

"In surgical adjuvant trials. . . the patient must be told that insofar as the surgeon can determine, all apparent disease has been removed. If this is the case, the suggested adjuvant therapy will have no chance of producing any benefit. When presented with this situation and a long document outlining in minute detail every conceivable toxic effect which may result from drug administration, many patients decline to participate. Those who do begin to find all manner of excuse for not returning for future course of therapy particularly if those already taken have resulted in significant toxicity. . . .

"Assuredly we cannot turn back the sands of time nor even slow the clock one second but we can ponder the vast hiatus between the self sufficient individualist and the present clinical trials investigator who finds himself hopelessly submerged in administrative and regulatory details through which the experimental objectives appear only as hazy and luminous shadows."

CCI MEMBERS TO DEVELOP POSITIONS ON REIMBURSEMENT OF PATIENT COSTS

Representatives from various organizations attending the meeting last week of the Coalition on Cancer Issues agreed to take on the issue of cancer care reimbursement.

Noting that current practice is not consistent, with ad hoc decisions resulting in insufficient and arbitrary reimbursement practices, the CCI members decided to develop a coordinated approach. First step will be for each member organization to submit a paper on its view of the problems involved. Difficulties en-

countered with reimbursement for all kinds of cancer care will be reported, including home, hospice, ambulatory, chemotherapy and some radiotherapy.

CCI will assemble the reports into a package, with further consideration probably leading to suggestions for remedies needed, including legislation.

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. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the contract officer or contract specialist named, NCI Research Contracts Branch, the appropriate section, as follows:
Biology & Diagnosis Section and Biological Carcinogenesis & Field Studies Section—Landow Building, Bethesda, Md. 20205; Control & Rehabilitation Section, Chemical & Physical Carcinogenesis Section, Treatment Section, Office of the Director Section—Blair Building, Silver Spring, Md. 20910. Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CM-17374

Title: *Preparation of bulk chemicals and drugs*
Deadline: *Approximately June 20*

The Pharmaceutical Resources Branch, Div. of Cancer Treatment, NCI, is seeking organizations having capabilities, resources and facilities for the preparation of bulk chemicals and drugs. The objective of this project is the preparation by synthesis of quantities of bulk chemicals and drugs for use as potential anticancer agents. The major emphasis will be on process development and will involve resynthesis and scaleup from the chemical literature.

Methods will be available for small scale runs in many but not all instances. The facilities must have the capacity for performing all types of chemical synthesis and must be able to demonstrate organizational experience in this area. A variety of large scale and pilot plant facilities will be needed. The size of the chemical reactors needed will vary with the contract.

The minimum requirement for all contracts is one small (20, 30 or 50 gallons) and one large (100 gallons or larger) glasslined reactor and necessary supporting equipment and facilities. The requirements go up to a well equipped pilot plant with equipment up to and including a 500 gallon glasslined reactor and necessary supporting equipment and facilities. All products must be completely assayed as to identity and purity. A well instrumented analysis laboratory including an in-house HPLC and adequate library facilities must be available.

All contractors must be registered with the FDA as bulk drug manufacturers, have been inspected by the FDA as bulk drug manufacturers, have been inspected by the FDA or state equivalent within the past three years, and be in compliance with current Good Manufacturing Practices regulations.

The principal investigator must be trained in organic or medicinal chemistry, preferably at the PhD level or equivalent, from an accredited school with extensive experience in chemical synthesis and process development. The principal investigator must be named and all technical personnel must be assigned to the project a minimum of 50 percent of the time, preferably 100 percent of the time.

It is anticipated that the project will require a total of 32 technical staff-years of effort per year. The effort will be undertaken in six contracts with the effort of the various contracts varying from four to 10 technical staff-years of effort per year. The proposal may be submitted for any one contract or for more than one contract and should clearly indicate the contract(s) for which it is being submitted.

Three of the six contracts to be awarded shall be totally set aside for award to small business concerns. A small business concern for the purposes of this procurement is one that employs 750 employees or less.

Contracting Officer: John Palmieri
Cancer Treatment
301-427-8737

NCI CONTRACT AWARDS

Title: Large scale production of oncogenic or potentially oncogenic viruses, continuation
Contractor: Electro-Nucleonics Laboratories Inc., $971,526.

Title: Cancer end results, continuation
Contractor: Connecticut State Dept. of Public Health, $59,841.

Title: Population based cancer epidemiology research center in Iowa, continuation
Contractor: Univ. of Iowa, $93,820.

Title: Production, purification and concentration of potentially oncogenic DNA viruses, continuation
Contractor: Life Sciences Inc., $339,446.

Title: Suppression of endocrine function by systemic agents as treatment of human breast cancer, continuation
Contractor: Milton S. Hershey Medical Center, $120,900.

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