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NEW GROUP REVIEWS FIRST NTP REPORTS, GETS JOB ON PERMANENT BASIS, WRANGLES OVER EXTRAPOLATION

The new group established by the National Toxicology Program to perform the function of the departed Clearinghouse Data Evaluation/-Risk Assessment Subgroup has completed its first review of program bioassay reports and has been given the job on a more or less permanent basis.

(Continued to page 2)

In Brief

PRETREATMENT CRITICAL IN ANTIEMETIC THERAPY, SALLAN SAYS; AGING/CANCER SYMPOSIUM PLANNED

STEPHEN SALLAN, Sidney Farber Cancer Institute investigator whose studies with THC as an antiemetic agent encouraged NCI to seek FDA approval for wider distribution of the substance through the Group C mechanism (*The Cancer Letter*, July 4): "We insisted that patients be pretreated (with the antiemetic) well in advance of chemotherapy. Most oncologists don't pay a great deal of heed to pretreatment. Some patients reported as refractory probably were not pretreated. A majority of compazine responders also respond to THC. About one fourth of the patients responded to THC only, one fourth to THC and compazine, and half did not respond." . . . "RESEARCH FRONTIERS in Aging and Cancer" is the theme of the International Symposium on Aging and Cancer Sept. 21-26 in Washington D.C. Discussions are planned on "the new anatomy;" organization of genetic material; regulation of gene activity; cell growth, movement and differentiation; viruses in aging and cancer; immunobiology; "cancer as a failure of normal differentiation;" and aging and cancer as genetic phenomena. Registration is required for the symposium, which will be at the Shoreham Hotel. Lewis Thomas is general chairman, John Ultmann vice chairman and Claude Pepper honorary chairman. Contact ISAC, 4635 W. Lawrence Ave., Chicago 60630. . . . 13TH ANNUAL Malignant Disease Symposium on "The Cooperative Approach for the Multidisciplinary Management of Patients with Cancer of the Lung, Head and Neck and Prostate and Bladder" will be held at the Univ. of North Carolina Oct. 31-Nov. 1. Contact Symposium, Cancer Research Center, Box 30, MacNider Bldg., Chapel Hill 27514. . . . "PROGRESS IN CANCER Control," a symposium scheduled Sept. 29-30 at Roswell Park Memorial Institute, will examine the state of the art and the impact of cancer control programs in communities. Topics will include professional and public education, prevention, early detection, rehabilitation and continuing care. Contact Curtis Mettlin, Program Coordinator, Cancer Control & Epidemiology, RPMI, 666 Elm St., Buffalo 14263, phone 716-845-4406.

NTP BOARD RECOMMENDS NCI/SRI TYPE DATA FOR ALL CHEMICAL TEST NOMINEES

(Continued from page 1)

Margaret Hitchcock of Yale, chairwoman of the Technical Report Review Committee of the NTP Board of Scientific Counselors, and the committee were commended by Board Chairman Norton Nelson for their initial efforts. Nelson recommended to the Board that the committee and the process be continued indefinitely "on the basis it has worked well." The Board unanimously accepted the recommendation.

"The procedure for report review will be subject to examination from time to time," Nelson said. Hitchcock will continue as chairwoman.

The committee, as did the Clearinghouse, provides peer review of program reports on the carcinogenesis bioassays with the objective of determining if the data support the program conclusions on test results. The reports and the peer review form much of the basis for regulatory decisions on the tested compounds.

The committee sailed through the 10 reports presented at the first review session, agreeing with program conclusions on eight and returning two for revisions and rewriting.

Two of the tests involved the herbicide 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the key ingredient in the infamous "Agent Orange" which was used as a defoliant in Vietnam. Both the skin painting and gavage tests were carcinogenic in test animals, the report concluded, and the committee agreed. However, Charles Irving, the primary reviewer, criticized the test design, said some of the data were not acceptable because of those deficiencies, and suggested that certain results related to the deficiencies be deleted from the report.

"We can't," answered NTP Director David Rall. "This program has been severely criticized in the past for not reporting results."

"We were told that we should review the reports as if we were reviewing an article for a journal," Irving said. "By god, if this were an article, I would delete those portions."

"It's not the same," Rall said. "We have legal obligations."

Nelson suggested that the committee's action could include a statement that the experiment was inadequate.

"If I made a motion that the entire report is not valid. . . ." Irving started.

"We would rewrite it," Rall said. "But we can't leave data out."

Irving moved that the report be accepted, "as long as it is clear that those experiments were horrible." The motion was approved unanimously.

Hitchcock, reviewing the caprolactam report, agreed with the conclusion that it was not carcinogenic under the conditions of the test. "It does not appear to pose a risk to humans," she said. The compound is used in plastics and food packaging materials.

Norman Breslow agreed that the study was valid "within the limits of the experimental design." But he objected to the statement that it was not a carcinogenic threat to humans. "There is no adequate scientific basis for interpreting human risk from animal data," Breslow said.

Breslow reviewed the report on cytembena, which concluded it was carcinogenic in rats but not mice. "In spite of the test limits, there is clear evidence of carcinogenicity."

Repeating his view that there is no scientific evidence to extrapolate human risk from animal data, Breslow said, "Nevertheless, when a test in animals is positive, prudent policy dictates that human exposure should be limited unless such exposure has substantial benefits."

Committee member Gary Williams disagreed with Breslow's premise. "Extrapolation to humans from animal data is eminently doable," he said. "There is sound basis for it." Citing a study by the National Institute of Environmental Health Sciences on species to species extrapolation, he said animal results "extrapolate very well to humans. . . . We ought to be able to make a qualitative human extrapolation."

"I agree," Breslow said. "But I object to ruling out human risks for negative results."

Breslow insisted the cytembena report be returned for revisions, and the committee agreed.

The committee also deferred action on the report on C.I. Acid Orange 10, a dye used in wood, biological materials, inks and other products. Various inconsistencies appeared in the report, the committee noted. Some of the tables did not agree with the narrative, and the report was returned to staff for revisions.

The committee accepted the reports on:

—Dibromochloropropane (DBCP), a herbicide now limited to use on pineapple fields in Hawaii, carcinogenic in inhalation tests in both sexes of mice and rats.

—1,2 dibromoethane (EDB), a gasoline additive and a pesticide ingredient, carcinogenic in mice and rats.

—Butybenzyl phthalate (DEPH), a widely used plasticizer, carcinogenic in female rats but not in mice of either sex. Because of compound related toxicity, it was not adequately tested in male rats.

—Di(2-ethylhexyl)adipate, a plasticizer approved by FDA for contact with foods, not carcinogenic in rats but carcinogenic in female mice and possibly in male mice.

—FD and C yellow No. 6, a water soluble dye used in lemon jello, carbonated beverages, pickles, and

toothpaste, not carcinogenic.

Hitchcock submitted three recommendations to the Board of Scientific Counselors for improving the reports and the review.

* State of the art methodology be used for data analysis.

* Provide for the occasions when contract and NTP pathologists disagree. "In these cases, a full disclosure of differences should be in the document with tables, etc., when it would affect the outcome of the bioassay."

* Regarding the committee's concern about making some estimate of human risk, "there are no clear guidelines. We have to develop guidelines for statements which have to be made on the basis of bioassay findings."

"I was content with the statement in the standard introduction (in each report)," Nelson said.

"That doesn't take into consideration the weight of the evidence," Hitchcock said.

In a discussion on selection of chemicals for testing, Nelson noted that NCI had contracted with SRI to provide data on production, use and exposure to help in determining priorities for carcinogenesis studies. "This is lacking with other NTP chemical nominees," Nelson said. "I suggest that NTP either get abord the SRI contract or find some other alternative. We will need those data for teratology and other studies as much as for carcinogenesis."

Committee and Board member Alice Whittemore suggested that the Board go on record asking NTP to seek outside support in developing information on chemicals proposed for study of other toxic effects, "to produce the same data as NCI gets for chemicals nominated for carcinogenesis studies." Board and committee member Thomas Shepard suggested that an NIH unit might be available to do that type of work.

"Whether it's inside or outside, the motion is to upgrade summaries including full data related to all compounds nominated for testing," Nelson said. It was approved unanimously.

Jack Moore, Rall's deputy, pointed out that compounds selected for short term tests need not have the complete workup until a decision was made to consider them for the animal tests, and Nelson agreed.

Board member Marjorie Horning suggested that an independent public advisory group be established to advise the NTP Chemical Selection Working Group. Her motion asking NTP staff to prepare a proposal for the Board to consider was approved.

FDA'S YOUNG QUITS JOB TO PROTEST APPROVAL OF TOXICOLOGY GUIDELINES

Robert S.K. Young, who as group leader in FDA's Div. of Oncologic Drugs has been the central figure in the difficulties between NCI and FDA over the last four years, has resigned from that position.

Young resigned in protest over the decision by Richard Crout, director of the Bureau of Drugs, to approve NCI's proposal for reducing the extent, time and expense of preclinical toxicology testing. He remains with the agency as a medical officer.

Young told the Oncologic Drugs Advisory Committee that he was not "forced out" but gave up his position because of "continuing differences with Dr. Crout."

Ill feeling between Young and his superiors has been building for years. Crout, chief of scientific evaluation Marion Finkel, and Oncologic Drugs Div. head William Gyarfas, have cooperated with NCI's Div. of Cancer Treatment in working out the problems in drug distribution, monitoring clinical tests, approval of INDs, and other matters. They became increasingly exasperated with Young's reluctance to accept the reasonable compromises worked out with NCI.

Young especially objected to the new toxicology guidelines, the major features of which eliminated the requirement for tests in monkeys and requires pathology review only after it becomes apparent that a drug will go into phase 2 studies. He contended that this violates FDA regulations. When Crout approved the new guidelines, Young resigned as group leader and filed a "citizen's petition" with the FDA commissioner asking him to overturn Crout's decision.

A hint of bitterness surfaced when Young appeared before the Oncologic Drugs Advisory Committee to state his objections to the new guidelines "as a private citizen, and my remarks do not represent the views of FDA." Ann Greenstein, executive

CROUT QUITS AS DRUGS BUREAU DIRECTOR

Richard Crout, director of FDA's Bureau of Drugs for the past eight years, announced to his staff last week that he has submitted his resignation from that position. He said the decision was prompted by his desire to return to scientific work. Crout said he hoped to remain in the Public Health Service.

According to NCI executives, it was largely Crout's leadership which brought about a more reasonable attitude at FDA toward cancer clinical investigations and anticancer drug development. Relations between the Bureau of Drugs and NCI over the last two years have been relatively smooth, in sharp contrast to the acrimony which existed before Crout intervened in disputes between his Oncologic Drugs Div. and NCI's Div. of Cancer Treatment.

Crout left immediately on vacation after making his announcement and was not available for comment.

secretary of the committee, carefully announced that Young was appearing on his "lunch hour" and not on government time. If he subsequently took time off for lunch that day, the time required to make his presentation would be deducted from his annual leave.

Young sarcastically referred to the new guidelines as "token, quote, toxicology guidelines" in his presentation to the committee and in his petition.

The petition cites the legislative authority for regulations requiring preclinical testing (FD&C Act, section 505i). The regulation requires the sponsor of a drug to submit:

"A statement covering all information available to sponsor derived from preclinical investigations and, any clinical studies and experience with the drug as follows:

"a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug; Such information should include. . . enough details to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing."

Young's petition states:

Regulatory grounds (21 CFR 312.1(d) for terminating an exemption include the finding that 'The results of prior investigations made with the drug are inadequate to support a conclusion that it is reasonably safe to initiate or continue the intended clinical investigation with the drug.' The statute and its implementing regulations clearly require preclinical tests in animals to justify proposed clinical tests. The fact that preclinical tests must be in proportion to the proposed clinical trial is specifically emphasized.

The policy of the agency with regard to defining the toxic effect of drugs in animals before they are given to humans has been publically discussed and published in articles such as, "Current Views on Safety Evaluation of Drugs" by Edwin I. Goldenthal, Phd, deputy director, Office of New Drugs ("FDA Papers"). When the proposed human administration of an investigational drug is expected to be six months or more, for a phase 1 or 2 study, preclinical testing of the drug for its toxic effects by administration of the experimental drug to two species of animals for at least three months is generally required. For phase 3 studies, tests are run in at least two species of animals for at least six months. A battery of observations and measurements are made including clinical examination of the animals, clinical chemistries, hematologic profile, and gross and microscopic examination of tissues. The FDA, with modification where appropriate, continues to require this preclinical test across the board, i.e., for all classes of drugs. Most drug sponsors voluntarily provide data in excess of the guidelines.

The legal requirement of preclinical definition of the adverse effects drug is soundly based scientifically. Even though the definitive study of man is man himself, man is not wholly distinct from other animals. Much that has been learned in animals, and even plants, can be usefully transferred to an understanding of how man functions and how he interrelates with other objects in his external environment. From the submicroscopic-molecular level up, man shares many systems in common with plants and animals. Inferences and predictions made from studies of lower forms of life generally hold true in man. It is within this framework that preclinical toxicology finds its place.

The purposeful study of the toxic effects of drugs in animals has several advantages to only a study of drugs in humans:

1. The dose can be escalated to certain toxicity and death. Whereas it is never justified to administer a dose to humans that certainly will kill, or maime, one can justifiably administer such doses to animals, in order to determine what exactly those doses are and what damage they do to tissue and organs. The dose need not be a single large dose, but might be a maximum (large) cumulative dose administered over weeks or months.

2. The microscopic effects of drugs on tissues and organs can be determined. Whereas it is never justified to kill a human being so that his organs can be examined to determine the effects of a drug, one can justifiably sacrifice an animal in order to determine what kinds of microscopic effects a drug has on the various organs of the body.

Preclinical tests biologically characterize a drug before it is given to humans so that investigators are adequately forewarned as to what the pathologic effects of the drug are on living tissues, on an intact anf functioning animal. Characterization takes the form of the usual pharmacologic-pharmacodynamic data. What dose causes particular adverse effects? What is the mechanism of the action that produces the effect? At what time after dosing does the effect occur? Is the effect reversible? If it is reversible, when and how much damaged function is regained? Can countermeasures be taken to mitigate against the severity of the toxic effect? What is the maximum dose that can be given before the effect occurs irreversibly? And so on.

The tradition in medicine that advocates discovering in humans only what cannot be learned in other animals is summed up in the oft quoted phrase, "primum non nocere." The bioethical tradition is more specifically delineated in the Nuremberg Code, which states, "Experiments should be such as to yield fruitful results. . . unprocurable by other methods or means of study; experiments should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease" and "The experiments should be so conducted as to avoid all unnecessary physical and mental suffering and injury." Investigators have a duty to their experimental patient-subjects to obtain by studies in lower animals information that will enable them to take measures to avoid physical harm to human subjects. By legally requiring such information, society has decided that the expenses involved in terms of time and money are justified because human beings (American citizens) are worth it.

Drugs used in the treatment of cancer are among the most toxic drugs in the medical armamentarium. Their adverse effects are often severe and crippling, and sometimes life threatening. They have the lowest safety margin of almost any group of drugs in that the dose that is required to produce a beneficial effect in only a proportion of patients is about the same dose that produces a host of toxic effects. These drugs seldom cure cancer, which means that they must be administered for the remaining life span of the patient, which hopefully may be more than several months. In summary this class of drugs which must be given repeatedly, over months, to patients, if they are to have any beneficial effect at all, has the most severe toxic effects, has the lowest safety margin, and is administered to patients already physically compromised by their disease. One would think that these drugs are candidates for relatively extensive preclinical tests to define precisely the doses that cause toxic effects, what the toxic effects are, which laboratory tests warn of impending overt toxicity, and what measures can be taken to avoid or mitigate their toxicity.

Contrary to expectations, the National Cancer Institute has proposed, the Oncology Advisory Committee has recommended, and the director of the Bureau of Drugs, J. Richard Crout, M.D. has decided that the preclinical toxicology testing of anticancer drugs can be materially shortened. As approved by Dr. Crout, the only required preclinical toxicology tests will be essentially as follows:

1. In mice, a lethal dose-response curve of single doses of the drug and doses administered over five consecutive days. The animals will be observed for 28 days. No laboratory estimates of organ function are required. The microscopic examination of the organs of some of the animals will be required, but need not be examined immediately or probably within months after the start of the human trials.

2. In dogs, the administration of the dose which causes death in 10 percent of the mice and 1/10 of that dose ($^1/_{10}$ LD_{10}) when given as a single dose and as a dose divided over five consecutive days. Laboratory estimates of organ function will be made and the animals observed for 60 days. Tissues would be saved for microscopic examination, but would not be examined immediately or probably within months after the start of the human trials.

In the context of the drugs which are being studied, the NCI proposal can be characterized as "too little, too late." It is too little, because the doses to be studied are too few in number and are to be administered too few times to adequately characterize biologically the adverse cumulative effects of a drug, and the time period of observation is too limited to allow certain delayed toxicities to occur. There will be no dose-adverse response curve, except for death in mice—pretty gross. The maximum potential time over which these drugs are to be repeatedly administered in humans is six months or more. The animals will be dosed with the drug for a maximum of five days. Quite a disproportion between the hoped for time of administration to humans and what is to be studied in animals. There is an additional problem in that the toxicities brought out by the administration of lesser doses over a longer period of time (chronic toxicities) are not always the same as or an extension of those resulting from the administration of high doses for a short period of time (acute toxicities). Although the acute toxicities of a drug are important to define, it is just as important to define a drug's chronic toxicities, which often limit its repeated administration and usefulness.

The proposed program is too late, because microscopic examination of the tissues to determine how they have been damaged by the agent is to be done well after human beings have been exposed to these drugs. Until tissues are examined, no one will actually know what kind of tissue destruction a particular drug causes. This type of information should be in the hands of investigators before they administer drugs to humans, not long after they have done it. Humans should not be used as guinea pigs in experimental sense of the word.

There is an additional problem with the proposed program. It hinges on the use of mice, solely, to define toxic doses of the drug. Toxic doses defined in mice are not readily reproducible. There is a fair amount of variation in results even in the same laboratory with the same strain of mice. Furthermore, there is an inadequate data base regarding the ability of mice to predict for human toxicities. This is simply because this class of agents has not been carefully tested in murine species.

The proposed token toxicology program has been discussed by the Oncologic Drugs Advisory Committee and they have recommended that it be accepted. They appear to believe that the program will be used only to predict the starting dose in man and for that purpose it is a reasonable system. They do not understand that this is all that is required and that there will be no definitive information on the adverse effects of these drugs such as the effect of multiple doses given over periods of time, the reversibility of effects caused by multiple doses of the drug, and the effect of the microscopic and clinical drug on the various organs and tissues. It has been asserted that the information now being provided by a more complete toxicology program is not useful. The burden of production [sic] is on those who claim the data is of no use to show that it is of no use. There has been no data provided that support the allegation that the preclinical toxicologic information is of no use in preventing unnecessary harm to human subjects. The application of findings in animals to humans has been found over years in a wide variety of circumstances to have validity and be useful. The trend has been to study adverse effects of chemicals in animals so that man can be spared. It has been implied that cancer researchers are so smart or careful or both that they can administer drugs to humans without the benefit of preclinical findings. The reaction of the American public, in the form of the laetrile movement, is evidence that a sizable group of citizens is not convinced that these drugs can be administered safely and without toxic effects, even when their adverse effects are already known and well described.

NCI's proposed program is analogous to a jet plane manufacturer arguing that it is safe to test the altitude capabilities of a plane with passengers abord by raising the cruising altitude 1000 feet a day, because the plane has already been tested and found to fly safely at 10 feet above ground. After all, having built and tested many planes, their test engineers will "know" when the plane reaches its design limits of about 35,000 feet. Not examining tissues microscopically for damage is analogous to picking up the pieces of a plane after it has crashed and merely storing them in a warehouse unexamined. After all, the manufacturer has seen all the pieces before and everyone knows some piece must have failed. Why waste time and money trying to determine what went wrong? Besides if the pieces are saved, there will be lots of time to examine them after the next crash.

One of the reasons NCI proposed this token program is that it will save them time and money. I do not disagree that this may be true, but the pertinent question is at what price? Having only very sketchy information on the biological toxic effects of drugs as derived from animal experiments means that toxicity information will almost exclusively be obtained from human subjects made sick by the drugs. Besides the human toll (unnecessary suffering) it costs a lot more monetarily to care for a patient made sick by a drug than it does an animal. NCI has failed to meet its burden of production [sic] to support its allegation that toxicity testing of drugs for the protection of human subjects is what is holding up the development of anticancer drugs that can effectively cure or control cancer.

Short cuts in preclinical anticancer drug testing cannot be justified on the basis that only cancer patients serve as subjects in the clinical trials. The Supreme Court's recent holding in *United States v. Rutherford,* 99 S.Ct. 2470 (1979), though it was directed to the safety and effectiveness of marketed drugs, can be applied to drugs for investigational use. The Court held: "Nothing in the history of the 1938 Food, Drug, and Cosmetic Act, which first established procedures for review of drug safety, or of the 1962 Amendments, which added the current safety and effectiveness standards in section 201 (p)(1), suggests that Congress intended protection only for persons suffering from curable diseases." The court also found: "In implementing the statutory scheme, the FDA has never made exception for drugs used by the terminally ill." Two recent FDA Commissioners (Drs. Schmidt and Kennedy) have explicitly stated that there is no exemption from legal requirements for anticancer drugs being developed by NCI. For legal and humane reasons anticancer drugs should undergo the same preclinical testing as any other drug in order that the necessary information for guidance of the investigator and

protection of the human subject can be gained.

Cancer researchers have lobbied long to exempt themselves from preclinical animal testing requirements. In May, 1972, the Secretary, HEW, Mr. Richardson, wrote Mr. Harley O. Staggers, chairman of the House Committee on Interstate and Foreign Commerce, in opposition to H.R. 12092, a bill which would allow the favorable judgement of three or more U.S. or foreign medical researchers concerning the anticancer utility of a substance to constitute adequate justification for its clinical testing by the NCI. In his 1977 Wall Street Journal article, "Laetrile's Message to the FDA," Mr. Spivak points out that medical researchers have lobbied vigorously to weaken the FDA's animal testing rules for the anticancer drugs they are interested in. They have succeeded in overturning the rule that there must be an objective medical-scientific rationale before drugs are tested in human beings. They have now overturned the requirement that the adverse biological effects of new drugs be adequately characterized before they are given to humans. (It should be noted that NCI's program of choice is less than a week's testing in mice only, with no laboratory or microscopic studies!) Mr. Spivak observed:

"These (cancer researchers) want to be free to test highly potent anticancer drugs in humans without much concern for the results of experiments on animals. The medical men argue they should be given more latitude to ignore possible side effects, because the patients they are treating are terminally ill and have no alternative to these powerful compounds. Curiously enough, this is the very argument that is made on behalf of laetrile: Lack of evidence of effectiveness should not stand in the way of its use, because patients facing death lack any other choice."

In closing it is reemphasized that cancer patients are human beings and should be treated as human beings with a full array of rights. Because the rights of these human subjects are respected, definition of the toxic effects of drug in animals before they are given to humans is required, so that human subjects can be spared unnecessary harm. Justice is respectful of their rights. In his 1978 address to the graduating class of Mt. Sinai Medical School (NYC), Rev. Timothy Healy, President of Georgetown Univ., pointed out that the "test of God's justice, that is whether or not society is ruled and filled by justice, lies in the treatment of its marginal people, the widow, the orphan, the poor, the sick. . . The fate of those at the margins of society is the scale on which we weight and measure the justice of that society." Can the FDA, as the oldest health consumer protection agency of a government dedicated to protecting the rights of all its citizens, pass this test?

Young's statement of his philosophy in the petition clearly points out the major difference which he has had with NCI and clinical investigators around the country who have had to deal with him: His contention that regulations should not take into account differences between drugs being developed for desperately ill cancer patients and any other class of drugs.

Young's petition is still pending. The commissioner will consider comments from the Bureau of Drugs and from any other source before taking action action. FDA could solicit comments from elsewhere by publishing an announcement in the Federal Register but has not yet done so. Comments may be sent to Hearing Clerk, FDA, Room 4-65, 5600 Fishers Ln., Rockville, Md. 20857. Reference Citizens Petition Docket No. 80P-0115.

Young has filed other petitions objecting to FDA's approval of NCI's plan for clinical tests of laetrile, the Group C drug distribution system, and marketing of cis-platinum for certain indications.

The committee considered whether the new toxicology guidelines would make additional safety monitoring requirements necessary in the new clinical guidelines. Chairman Philip Schein said he felt adequate safety was built into the program. Committee member Charles Haskell agreed and said the guidelines should be allowed to stand "unless it could be shown that one patient at least would benefit." The previous requirements were "an unnecessary threat to the animal kingdom," Haskell said. "All the additional animal tests did not add anything."

The committee then gave final approval to the new guidelines for clinical testing of anticancer drugs. This concluded several years of wrangling between FDA staff, the committee, NCI and clinical investigators who objected to earlier guidelines drafted by FDA. The accepted guidelines were written by the committee with NCI staff assistance (***The Cancer Letter***, Oct. 19, 1979). The final version included some changes from the draft published by ***The Clinical Cancer Letter*** in October 1979 and will appear in full in the July 1980 issue.

NEW DIAGNOSTIC RESEARCH SUGGESTIONS CONSIDERED BY DCBD ADVISORY GROUP

The Diagnostic Research Advisory Group, established to render advice on the extramural diagnostic programs of NCI's Div. of Cancer Biology & Diagnosis, offered some suggestions for new research areas at its recent meeting. They included:

—Development of animal studies to investigate early physical parameters that contribute to threshold detectability of tumors.

—Development of NMR imaging techniques.

—Improved detection of tumor antigens and finding new ones.

—Use of monoclonal antibodies for looking at hemopoietic cells and in diagnosis of leukemia. Methods for use of reagents need to be standardized. Specificity of reagents must be confirmed. Determination of their diagnostic and prognostic utility as markers of tumor burden. Determination of reaction with normal cells. Establish an ongoing source of supply with reagents.

—Development of multiple biomarkers. The rationale for clinical studies includes problems associated with single biomarkers, variations in degree of multiple biochemical characteristics of tumors, greater coverage, increased sensitivity to defining early stage of disease, improved degree of significance, distribution of patterns for staging and prognosis, and multiple metastatic sites. Quantitative approaches include the development of multiparamic results to define extent of disease and response categories, and development of models for prospective

Title: Production and maintenance of selected reagent grade SPF animals, continuation
Contractor: Life Sciences Inc., $422,032.

Title: Provision of tissues and cells, and conduct routine tests in support of tumor cell biology studies
Contractor: Litton Bionetics, $1,633,611.

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-CP-VO-01039-78

Title: Holding facility for small laboratory animals
Deadline: Aug. 14

NCI is seeking a holding facility for small laboratory animals. The contractor's facilities must be located within 35 miles of the NIH Campus in Bethesda, Md. Animal holding will involve large numbers of rats (up to 2,000) and fewer numbers of mice (approximately 500).

Space must be provided for 1,000 rats at any one time for administration of carcinogen containing diets and 1,000 rats for injection and skin painting with chemical carcinogens. It is estimated that 160 mice will be required for diet administration and 300 mice will be required for skin painting and injection.

Contracting Officer: Elizabeth Osinski
Biological Carcinogenesis & Field Studies
301-496-1781

RFP NCI-CP-FS-01033-65

Title: A study of environmental factors in the origin of leukemia and non-Hodgkin's lymphoma among adult white males from rural areas in the central U.S.
Deadline: Aug. 7

The Div. of Cancer Cause & Prevention of NCI, Environmental Epidemiology Branch is seeking an organization highly experienced in conducting case-control interview studies to collaborate in a research and support study of the origin of leukemia and non-Hodgkin's lymphoma among white males from rural areas in the central United States. The study seeks to identify environmental agents and other factors associated with the high mortality rates for these tumors seen in this region of the U.S. Particular attention will be paid to farm related exposures. The duration of this contract is expected to be three years and to begin during September 1980.

The contractor will be responsible for selection of cases and controls, preparation of the detailed protocol, data collection via personal interviews and abstracts of hospital records, data processing, and monitoring and quality control. EEB will assume responsibility for analysis and interpretation of test results. The contractor's professional personnel will assist in this phase, and secondary authorship of the resulting publications will reflect this collaboration. The contractor, however, may also undertake secondary analysis of these data, thus ensuring first authorship for any subsequent publications.

Personnel required include: (1) project director (20-40 percent time), experienced (three years) in the field of cancer epidemiology with an MD or doctoral degree in public health or statistics, to supervise all aspects of the study; (2) a field management specialist (full time), experienced (two years) in organizing and managing field interviewing operations, in training face-to-face interviewers, and in evaluating the conduct and quality of interviews and abstracting procedures; and (3) a computer programmer/analyst (full or part-time as required) experienced (three years) in writing, debugging, and documenting computer programs and in creating and manipulating large data files.

Other personnel to be hired as necessary, include abstractors, coders, field interviewers, and keyers. In order to achieve study objectives, 600 cases of leukemia and 600 cases of non-Hodgkin's lymphoma and one or two controls per case will be required, preferably from one or more contiguous states. It may be necessary to select two contractors to achieve the desired study size, in this event each contractor must provide 300 leukemia and 300 NHL cases and appropriate controls.

Contracting Officer: Sydney Jones
Biological Carcinogenesis & Field Studies
301-496-1781

The Cancer Letter _Editor Jerry D. Boyd
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