THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 3 No. 32
Aug. 12, 1977

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Subscription $100 per year

CLEARINGHOUSE DELVES INTO CARCINOGENESIS ISSUES —TEST VALIDITY, INTERPRETATION, IN VITRO METHODS

The Clearinghouse on Environmental Carcinogens, in addition to advising NCI on which chemicals should be tested (*The Cancer Letter*, Aug. 5), has become deeply involved in the far-reaching issues which make the problems of identifying carcinogenic substances and removing them from human exposure so difficult, expensive and controversial.

Those issues include the validity of certain tests, interpretation of test results, the real meaning of certain effects of some tests, development of short term and in vitro tests and how they should be used, and the question of carcinogen promoters. That is by no means a list of all the issues.

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In Brief

HOUSE, SENATE DIFFER ON NCI POSITIONS; UPTON SAYS VIRAL ONCOLOGY RESEARCH WILL BE CONTINUED

NCI POSITION ceiling is in a muddle, thanks to White House and congressional differences on what it should be. The HEW appropriations legislation has a ceiling of 2,042, but the Office of Management & Budget has decreed a limit of 1,955. NCI presently has 1,992 on the books. The congressional total includes either 22 new positions earmarked for environmental epidemiology as demanded by Rep. David Obey in the House measure, or 20 new positions approved by the Senate and not earmarked. The position references are in the reports of the bills and did not have to be reconciled in conference, leaving NCI uncertain as to which directive it will follow. . . . **SENATE, HOUSE** have agreed on all dollar figures in the HEW money bill, with NCI at $867 million. They haven't resolved their differences on federal funding of abortions for low income women, which prevented final passage before the congressional recess. The bill probably will be cleared well ahead of the end of the fiscal year, Sept. 30, and no presidential veto is expected. . . . **40TH ANNIVERSARY** of NCI occasioned a special issue of the *Journal of the National Cancer Institute* which includes a fascinating history of NCI programs, people and policies. A somewhat irreverant account of the first 20 years by Michael Shimkin is one of the highlights. Copies are available from the Office of Cancer Communications, NCI, Bethesda, Md. 20014. . . . **MAMMOGRAPHY CONSENSUS** meeting Sept. 14-16 will be held at NIH, Bldg 1, Wilson Hall. . . . **THOMAS SYMINGTON**, director of the Institute of Cancer Research in London, will deliver the 5th annual Clowes Lecture Sept. 6 at Roswell Park. His topic: "Role of the Scientist and Clinician in the Challenge of Cancer Care" . . . . **"IT IS THROUGH** virology that we are getting close to molecular control of cancer. Our program in viral oncology is very productive and very exciting, and it will be continued"—NCI Director Arthur Upton, at his first press conference.

TENSION BETWEEN CLEARINGHOUSE, NCI STAFF DEVELOPS OVER VARIOUS ISSUES

(Continued from page 1)

The Clearinghouse subgroups may be the hardest working of all NCI advisory bodies, meeting every other month in day-long sessions. It has not been all sweetness and light—there are conflicting views among subgroup members and there has been some tension between the Clearinghouse and NCI staff members in the Carcinogenesis Program.

"The Clearinghouse people wanted to have a greater impact on the program than some staff members felt was desirable," admitted Clearinghouse Chairman Arnold Brown. "We have tried to mesh our interests with theirs. We can bring a slightly different point of view to the discussions, and can offer helpful advice. I think we have developed mutual respect for each other. . . . On balance, I think we're doing the job asked of us."

One of the most important issues is the development of in vitro tests. With animal tests costing up to $250,000 each and requiring three years to complete, the quicker and cheaper tests have obvious attractions. Virginia Dunkel, coordinator for the NCI In Vitro Program, discussed it with the Experimental Design Subgroup of the Clearinghouse.

Dunkel said the goals of the program are (1) to establish a matrix of tests which can be used as an effective prescreen for establishing priorities for in vivo carcinogenicity testing; (2) to define the possible utility of in vitro procedures for assisting in evaluation of marginal carcinogenicity data from animal bioassay; and (3) to provide research tools for investigation of the mechanisms of action of chemical carcinogens.

Specific project areas are directed to validation and utilization of microbial assays; development and validation of mammalian cell mutagenesis assays; and development and validation of mammalian cell transformation systems.

Studies are under way to assess both microbial mutagenesis and repair systems. Four different laboratories are now testing selected chemical compounds in blind studies with eight strains of microorganisms with and without metabolic activation.

About 90 chemicals are being used in the program, half of which are known carcinogens and non-carcinogenic analogues including polycyclic hydrocarbons, alkylating agents, nitrosamines, aminoazo dyes, and metals. The remaining chemicals are those which have been or are being tested in the bioassay program.

The Experimental Design Subgroup recommended that parallel assays be conducted on compounds in the bioassay program and suggested that the Ames test be used on those for which reports have been published and those on which reports are in preparation. The subgroup also suggested that other tests such as pulmonary adenoma, skin painting and a test to monitor other markers be made in parallel with bioassays.

The Experimental Design Subgroup offered some suggestions to both the Chemical Selection Subgroup and the Chemical Selection Working Group (the former a Clearinghouse committee and the latter a committee made up of NCI staff and staff from other government agencies) for refinements in a document, "Data Elements for Use in Selecting Chemicals for Bioassay." The suggestions were:

- The rationale for why a chemical is selected should be spelled out; this would help in the design of the test.
- Science should consider the problem of animal drinking water—what does it contain? It has been said that as many as 400 compounds have been found in municipal drinking water.
- Will pure compounds, mixtures or both be recommended for tests? How will this affect costs and experimental design?
- Are some compounds or mixtures more properly within the interest or authority of other federal agencies?
- Other agencies recommending compounds for testing should provide a rationale for each.
- Will NCI staff ask for design advice before testing begins? (Obviously, one of the sore points contributing to the tension to which Brown referred).

NCI published about two years ago a document, "Guidelines for Carcinogen Bioassay in Small Rodents." The Experimental Design Subgroup suggested refinements for a revision of that document:

—Is consideration given to metabolic pathways?

—In choosing a species, consider the background tumor incidence for that group. Should a given compound be tested in a bioassay system in which background tumor incidence is low or high?

—Animal lifespan should be considered.

—Diet sterilization should be watched for possible introduction of contamination. Semisynthetic diets should be considered.

—Should consideration be given to keeping the survivors from the LD_{50} test alive for two years in order to see if the compound is a one shot carcinogen?

—Staff should consider studying metabolism, pharmacokinetics and metabolic endpoints in the prechronic study.

—The subgroup was sharply divided on the question of the utility of the sub-maximum tolerated dose and agreed to consider it more thoroughly at another meeting.

—Acute weight depression might invalidate a test.

—Consideration should be given to terminating a test when 10% of the animals are dead.

—Histopathology should be performed only on abnormal organs and lesions.

—The major organs should be sliced rather than processed on the block.

—A 5% spot check of pathology should be performed for quality control.

The Chemical Selection Subgroup delved into the question of tumor promoters. Subgroup Chairman David Clayson said he had two concerns regarding promoters—some may be true carcinogens; and if tests prove some compounds to be promoters, of what use is this information to regulatory agencies?

Subgroup member William Lijinsky observed that, while there is good argument that a threshold cannot be established for a carcinogen, one can be established for a tumor promoter. He also noted that because of testing difficulties, promotion is not now an appropriate activity for NCI.

The subgroup agreed that NCI should consider testing promoters in the short-term tests but that the primary effort should remain with carcinogens.

The Data Evaluation/Risk Assessment Subgroup got into the controversy over the biological nature and significance of mouse liver tumors. Robert Squire, former director of the Bioassay Program and now with Johns Hopkins, told the subgroup that in the absence of invasion and/or metastasis, the same lesion could be classified anywhere from a regenerative nodule to a carcinoma, depending upon the view of the diagnostic pathologist. He said that the evidence for regarding lesions as neoplastic include the lack of hepatic degeneration and necrosis, relatively autonomous progressive growth, transpantability, and metastasis.

Squire pointed out the unknown role of nonspecific factors in the etiology of mouse liver lesions, including hepatotoxicity, genetic predeterminants, diet, environment, sex, and/or viral involvement. He said that it is not possible to state that mouse liver tumors are irrelevant in terms of humans without knowledge of the role of nonspecific factors and the mechanism involved. Therefore, he concluded, the induction of mouse liver tumors must be considered as a relevant endpoint in the absence of contrary evidence.

Squire said that in his view, there was no difference between a liver adenoma and a hepatocellular carcinoma in terms of their relevance to malignancy, since the latter neoplasm is merely a more advanced stage of the former. Subgroup member Henry Pitot agreed, and added that benign appearing liver adenomas frequently may be malignant.

Clearinghouse member Verne Ray (not a member of the subgroup), said that the induction of mouse liver tumors may be a consequence of hepatotoxicity caused by the high dose levels tested. He suggested that certain clinical chemistry parameters be considered in establishing dose levels. Richard Griesemer, director of the Bioassay Program, agreed that the establishment of dose levels deserves special consideration.

NCI staff member Gary Flamm noted that the same question of human relevancy must be asked whenever a response is induced at any single organ site and in only one species. The question is even more difficult when the mechanism of action is unknown, Flamm said. In such instances, relevancy falls upon the weight and extent of the best evidence, including the electrophilicity and mutagenicity of the chemical. Flamm cautioned against prematurely dismissing the one hit model of carcinogenesis, as well as the predictive value of mouse liver tumors. He also warned against relying too heavily on the availability of epidemiologic data to correlate with the animal results.

Subgroup member Sidney Wolfe argued that in vitro assays are not sufficiently perfected to negate a carcinogenic response, even if it were in a single organ and species. He added that the absence of epidemiologic data also cannot be used to invalidate a finding of carcinogenicity, because of the inherent limitations of epidemiology. He concluded that continued reliance must be placed in animal studies and that when a chemical is found to be a carcinogen, it must be assumed to pose a human risk.

Griesemer described the three NCI-sponsored research efforts to define the biological nature of mouse liver tumors. These have been under way for about eight months. Their first objective is to evaluate the biological characteristics of spontaneous and experimentally induced liver tumors using a variety of endpoints, including biochemical, immunological, morphological, and transplantation. The second objective is to determine the reversibility of the early lesions and to study their preneoplastic or neoplastic nature. These studies include a comparison of mouse strains with both low and high spontaneous liver tumor incidences. Also, at least two chemicals, one of which has been shown only to induce mouse liver tumors, are being tested in each study.

Although multiple dose levels are being tested, Squire noted that the studies were not designed to investigate bioassay methodology. He said that the metabolism of the test chemicals are not being investigated, since the goal of the efforts is to characterize the mouse liver tumor.

George Cosmides, of the National Library of Medicine, described the Laboratory Animal Data Bank being developed by Battelle-Columbus under contract with NLM. The data bank allows interested users to access an on line computer system to obtain data on lab control animals. It is currently operational and available to subscribers.

Richard Simon of Battelle-Columbus said that LADB collects data on negative, vehicle and sham control animals. Rats and mice have been of primary interest so far, although data also are collected on dogs, monkeys, rabbits, hamsters and guinea pigs. Information in the data base includes clinical and pathology data as well as a wide range of data on environmental and husbandry conditions. Data sources include commercial and university research

labs, animal breeders, industrial organizations and government agencies.

LADB allows investigators to compare the effects of environmental and husbandry conditions on a large number of clinical and pathology endpoints in a variety of animal strains and colonies.

The Chemical Selection Subgroup recommendations for chemical to go on test were reported last week in ***The Cancer Letter.*** The subgroup also considered whether to recommend tests for nicotine and witchhazel but decided against it. Members agreed that the only human exposure to nicotine was in tobacco products and that the carcinogenicity of other substances also in those products was already sufficiently established.

The limited funds for testing should be reserved for suspect compounds in products not so well identified as posing risks to humans, the subgroup determined.

The recommendation against testing witchhazel was made on the basis that it contained too many various elements which would cloud test results. However, the Chemical Approval Group (NCI staff) overruled the subgroup and added witchhazel to the test list, while agreeing that nicotine should not be tested.

BIOASSAY REPORT CLEARS EDTA; NO TUMORS RELATED TO TREATMENT

Ethylenediaminetetraacetic acid (EDTA), used as a food additive and in some medicines, was not found to be carcinogenic in NCI's Bioassay Program, a report published in the Aug. 9 issue of the *Federal Register* said.

EDTA was fed to rats and mice for nearly two years. The summary of the report said, "Although a variety of tumors occurred among test and control animals of both species, no tumors were related to treatment."

The trisodium salt acts as a sequestering agent and is used in some wines and other products that contain possible metal contanimants.

UPTON, PANEL LEAN TO ANECDOTAL LAETRILE STUDY, NOT CLINICAL TRIAL

NCI Director Arthur Upton, backed by the President's Cancer Panel, is leaning toward supporting a retrospective or anecdotal study of cancer patients who have taken laetrile rather than a clinical trial with all the ethical issues that involves.

"I have not arrived at a decision yea or nay," Upton told the Panel at its meeting last week. "One issue is that a clinical trial should not be done merely to prove something ineffective." There is no question that laetrile has been proven not to be effective in animal tests. Upton suggested that anecdotal reports, if they could be validated, possibly could provide enough evidence to justify clinical trials despite the negative animal tests.

Upton said NCI staff members "have deeply divided views that revolve around ethical matters" on the proposed clinical tests. "If the test is inconclusive, it would play into the hands of the laetrile proponents and prolong the controversy. A decision to do a trial would appear to legitimatize laetrile. But you could argue that the movement is gaining anyway."

"I guarantee that the pro-laetrile people will make the most effective use of any trial," Panel Chairman Benno Schmidt said. He agreed that the ethical issues involved in a clinical trial were difficult—whether to administer laetrile to a group instead of proven drugs, or to give it in addition to the most effective known protocol. "That (the latter option) gets away from the ethical issue but accentuates the inconclusivity," Schmidt said. "Whatever is done, it should be done with the cooperation and concurrence of FDA."

Schmidt said he would "consider it far better to evaluate the results of those using laetrile in their own way, for whatever reason, and used in the way advocated by the proponents, rather than have a clinical trial."

Panel member Paul Marks said, "It is important to make clear that the scientific community is not waffling on this issue. There is substantial reason, based on the best scientific data (for doubting laetrile's efficacy)."

"The animal data is not soft," Schmidt said. "It is overwhelming and conclusive. But nothing will stop people from saying 'just because it doesn't work on animals doesn't mean it won't work on humans.' If you depart from that (the normal procedure to go ahead with clinical trials with a drug based on positive tests in animals), then it ought to be based on something affirmative from previous use."

Other items discussed by the Panel:

- Committee reductions "are a vexing matter, at cross purposes with the quality and depth of peer review," Upton said. But he will attempt to go along with it "and do our best."
- Upton said he is in the process of "coming to grips" with the problems Schmidt had suggested as needing his attention and hopes to have a report on his progress at the meeting of the National Cancer Advisory Board in September.
- Schmidt expressed his "profound, personal appreciation to Guy Newell, and that of the staff, the Panel, and members of Congress I have talked with for the way he discharged the difficult duties of acting director for 10 months. It's not so difficult to be acting director for two weeks. You can let the difficult problems stack up in the corner. But you can't when it goes on and on. It's not easy to cut people and programs, to say no. Guy has served with great sympathy for differing viewpoints, and with great resiliency and good humor. I'm sure there were plenty of times when he said to himself, what the

hell am I doing here. His great commitment to the program, to us and to himself enabled him to do the best job he knew how. I personally feel he did an outstanding job."

• Former Panel member R. Lee Clark warned that "We'll have a hard time living with" some of the proposals included in legislation revising FDA's authority now being considered by Sen. Edward Kennedy's Health Subcommittee, particularly that involving phase IV drugs.

Clark, who underwent arterial bypass surgery last April, said, "I'm here to tell you bypass is an effective procedure" (some critics recently have argued that it is not). Clark is now back to work full time as president of the Univ. of Texas System Cancer Center and looks as fit as ever.

HAWAII GETS CBCCP IMPLEMENTATION CONTRACT; L.A. AWARD $7.4 MILLION

Hawaii has officially become the sixth "community" to be awarded an implementation contract in the Community Based Cancer Control Program supported by NCI's Div. of Cancer Control & Rehabilitation.

The Univ. of Hawaii is the lead agency for the program which will encompass the entire state. NCI awarded the university a $129,500, 90-day letter contract to keep the program going while the formal five-year contract is being negotiated. Implementation contracts are worth about $1 million a year in NCI money, which must be matched by the local agencies.

Six communities have now been awarded implementation contracts—New Mexico, Detroit, Long Island, Los Angeles, Rhode Island and Hawaii. One more, Connecticut, is still in the planning phase. Connecticut recently was awarded a nine-12 month extension of its planning contract, but no one at NCI will predict whether or not that one will make it into implementation.

Negotiations have been completed with Community Cancer Control of Los Angeles, the lead agency for the L.A. program. The contract calls for NCI funds of $1.3 million the first year, increasing to $1.7 million the fourth year and dropping to $1.4 million the fifth year, for a total of $7.4 million.

Those are maximum figures. Each contract in the program must justify the annual awards. If the justification falls under them or if the matching funds don't come up to them, the awards could be less. All have more matching funds than they need for the first year.

The Los Angeles program has four co-principal investigators—Ruth Pick, Martin Luther King Hospital; Lester Breslow, UCLA; Robert McKenna, Univ. of Southern California; and Ralph Sachs, retired Los Angeles public health officer. Helene Browne is the project director.

MAGGIE'S BILL PAID OFF – PERSONALLY AND FOR THE COUNTRY, 40 YEARS LATER

NCI observed its 40th anniversary last week in ceremonies attended by most staff members, four former directors and the wife of the legislator whose bill authorized establishment of the National Cancer Institute in 1937.

Mrs. Warren Magnuson delivered the speech the senator had intended to give. It was the last day before the congressional recess, and Magnuson had to stay on the job.

It was the bill introduced by Magnuson, then a young congressman from Washington, and signed into law by Franklin D. Roosevelt, which created NCI. Thirty-three years later, Mrs. Magnuson underwent treatment for cancer, and the fact that she is alive and well today could be due at least in part to her husband's foresight.

Magnuson continues to be NCI's most effective champion in Congress, as chairman of the appropriations subcommittee which writes the bills that fund federal cancer research.

In the remarks read by his wife, Magnuson said, "Today, more than a million and half Americans are alive and cured of cancer . . . at least five years after initial diagnosis and treatment. Today, one out of three cancer victims is being saved. And if presently known techniques and new treatment methods were used to their fullest, that figure could be revised downward to one out of two.

"So we have come a long way in finding those effective methods of diagnosis and treatment. I am not convinced that we are doing enough—on any front—especially in prevention. But this is not a day for admonishing anyone. This is a day for celebration . . . It is obvious to me that the billions of taxpayer dollars which we have appropriated over the years have paid off. Those 1½ million Americans who are alive today, cured of any cancer, are ample justification for me for all that we've appropriated over the past 40 years."

Panel Chairman Benno Schmidt mentioned "our most difficult fundamental problem. In spite of the large increases in the budget of NCI since 1970, we have been dealing for the past two years with a budget that is declining in constant dollars. Thus, at a time when both fundamental research and research in prevention, diagnosis and treatment cry out for greater support and greater emphasis we find ourselves without sufficient funds to do the research that must be done. A society that is spending $140 billion per year on medical care, a figure that is increasing at an alarming rate, cannot afford not to do the biomedical research which offers not only the only hope of reducing those expenditures, but also the only hope of relieving our people of the enormous burdens which today's major diseases inflict."

NCI Director Arthur Upton offered more figures

along the same line. "Although there is little prospect that our objectives will be fully attained within the next decade, enormous advances can surely be expected, based on the gains that have occurred since 1937," Upton said. "That the gains will not be inordinately expensive also seems likely, despite the unprecedentedly large magnitude of our existing budget. For example, it would appear that roughly 100,000 more of the victims who develop cancer this year will survive than would have survived if the advances in diagnosis and treatment that have occurred since 1937 had not become available. Pro-rated over our annual budget of some $800 million, the research cost per life saved amounts to less than $10,000—a bargain by any form of reckoning."

The four former NCI directors present were Roscoe Spencer, who served from 1943-1947; Leonard Scheele, 1947-48; Kenneth Endicott, 1960-1969; and Frank Rauscher, 1972-76.

Schmidt expressed "the gratitude and affection of all of use to Dr. Rauscher. He led the Cancer Institute through the five years of its greatest growth and greatest accomplishments. No one could have served with greater dedication, with greater loyalty to the public trust he held, or with greater integrity in supporting what he believed was right."

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. Their addresses, all followed by NIH, Bethesda, Md. 20014, are:
Biology & Diagnosis Section — Landow Building
Viral Oncology & Field Studies Section — Landow Building
Control & Rehabilitation Section — Blair Building
Carcinogenesis Section — Blair Building
Treatment Section — Blair Building
Office of the Director Section — Blair Building
Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP 223-77-6013

Title: *Self-assessment and competency assurance education in diagnostic radiologic technology*
Deadline: *Approximately mid-September*

The Food & Drug Administration has a need to develop a self-assessment program for radiological technicians, credentialed and noncredentialed.

Compare a previous administered test, develop a revised self-assessment test and administer test to approximately 2,000 practitioners. Develop and distribute national, regional and individual scope profiles. Provide institutions and associations nationwide with a practitioner profile for their respective region. Develop a maximum of 25 practitioner educational packages (PEP) to address the needs identified in the national practitioner profile. Develop a program to distribute the PEPs on a continuing basis. The contractor will be required to publicize nationwide to assure maximum coverage.

Contracting Officer: T. Caviness
FDA-HFA-514
5600 Fishers Lane
Rockville, Md. 20857

CONTRACT AWARDS

Title: Radiological Physics Centers, renewal
Contractor: Univ. of Colorado, $337,691.

Title: Coordinating committee for the Radiologic Physics Centers, renewal
Contractor: American Assn. of Physicists in Medicine, $316,947.

Title: Support services for molecular studies of cancer, with emphasis on mammary carcinoma, continuation
Contractor: Meloy Laboratories, $177,613.

Title: Production and maintenance of selected reagent grade SPF animals, continuation
Contractor: Life Sciences Inc., $403,763.

Title: Screening, abstracting, and indexing of cancer-related literature for input to the ICRDB program data base
Contractor: The Franklin Institute, $1,544,528.

Title: Breast Cancer Detection Demonstration Project, renewals
Contractors: Univ. of Southern California, $396,590; Mountain States Tumor Institute, $261,639; and Univ. of Arizona, $330,627.

Title: Clinical evaluation of the use of computerized transaxial tomography in the diagnosis of brain tumors, continuation
Contractor: Cornell Univ., $54,440.

Title: Clinical investigation of the use of computerized transaxial tomography in the diagnosis of brain tumors, continuation
Contractor: Massachusetts General Hospital, $77,327.

The Cancer Letter—*Editor* JERRY D. BOYD
Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090.