THE CANCER LETTER
RESEARCH
EDUCATION
CONTROL

1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

Jan. 23, 1976

Vol. 2 No. 4

Subscription $100 per year

"SLOPPY" SEARLE STUDIES DESCRIBED BY FDA AT KENNEDY HEARING; RAUSCHER "OUTRAGED"

NCI and certain clinical cancer investigators have had their problems with the Food & Drug Administration lately, but executives of G.D. Searle Co. would be happy to trade bundles of troubles with them.

It was Searle's problems with FDA, specifically the quality of data supplied by the firm as proof of the safety and efficacy of some of its products, which led to FDA's unreasonable crackdown on NCI's investigational new drug applications and resulted in holding up vital clinical research. "We can't treat NCI any differently than we do the drug companies," one FDA official said.

Searle's problems first came to light last July when FDA witnesses told Sen. Edward Kennedy's Health Subcommittee that they questioned the integrity of the scientific data submitted by Searle to the agency.

FDA launched an investigation, and Tuesday Commissioner Alex-

(Continued to page 2)

In Brief

OVERRIDE FAILURE WOULD LEAVE CANCER PROGRAM WITH NO MONEY FOR NEW PROJECTS OF ANY KIND

IF CONGRESS fails to override the President's veto of the 1976 fiscal year HEW appropriations bill, HEW—and NCI—probably will have to go through the rest of the year funded by a continuing resolution, Congress' term for interim financing. That would leave NCI with essentially the same money it had in fiscal 1975—$691 million. The limited amount of money available for new programs has long since been obligated by NCI, which means there won't be any more new programs funded until fiscal 1977 money is available, next Oct. 1 at the very earliest. None of the long list of high quality regular research grant applications approved and waiting for money would get off the ground this year; no more construction money will be available; the promising new Diet, Nutrition & Cancer Program (see story inside) would be held up for a year; the effort to move the Clinical Cooperative Groups into multidisciplinary research involving more patients with early disease will be hampered or delayed by the lack of money. . . . **CHANCE OF** overriding the veto still seems to be about 50-50 in the House, better than that in the Senate. The House will act first, probably next week. . . . **WILLIAM RAY BRYAN**, who retired from NCI as director of virus oncology, died of emphysema at his home in Gaithersburg, Md. He was 70. . . . **GUIDELINES, REQUIREMENTS** proposed for recombinant DNA molecule research will be considered at a two-day meeting of the NIH Director's Advisory Committee Feb. 9-10. The meeting will be in NIH Bldg 31 Room 6, starting at 9 a.m. both days. Time is reserved from 4-5:30 p.m. Feb. 9 for public statements, limited to 10 minutes each. Contact Charles McCarthy, executive secretary, 301-496-1480, to reserve time.

FDA PLANS NEW PROBES OF INDUSTRY TO DETERMINE EXTENT OF "SLOPPINESS"

(Continued from page 1)

ander Schmidt told the subcommittee his investigators found that:

• A pathology report on the drug Aldactone by the firm Microscopy for Biological Research for Searle in 1973 had clearly shown a dose-related increase in the frequency of liver and testicular tumors but had not been forwarded to FDA.

• Evidence that the drug caused malignant mammary tumors was omitted from data given to FDA.

• Tissue masses were excised from three live animals during a study and the animals were allowed to continue in the study. Two of those tumors were malignant and although they were provided to MBR, they were not reported to FDA.

• After the FDA investigation began, Searle presented "corrected and expanded reports" prepared by a group of Searle scientists to identify differences between initial reports submitted to FDA and the actual raw data. The review found such problems as transcriptional, clerical and typing errors; differences resulting from the use of different statistical methods; computer errors and omissions; inclusion of additional data from reserve animals which had not been included as part of the original submission to the new drug application. And the report Searle prepared which was intended to verify the results expressed in the original report and to correct the errors was itself full of errors.

"It is disconcerting that even today, after three separate reviews by Searle personnel of the same data from the rat study, we are continuing to discover errors that complicate review of this study," Schmidt said.

• Another rat study on Aldactone conducted by Hazleton Laboratories for Searle revealed that only 70% of the tissues scheduled for histopathological examination in the protocol actually were examined. Some animals with gross lesions which required histopathological examination were not so examined.

NCI and FDA appear to be moving toward a resolution of their differences over the monitoring of drugs distributed by NCI to investigators and private physicians. The two are still at odds over the question of FDA's demands regarding NCI's INDs. Details of the proposed agreement and of the continuing fight over INDs will appear next week in *The Cancer Letter*.

• Review of the individual pathology reports on a study Searle did to support its NDA for the drug Flagyl revealed that they did not always contain the same information as the original autopsy records from which they were derived. Moreover, original reports of microscopic examinations were missing for some of the animals.

• Examination of tissue slides from autopsied rats had been conducted by two different pathologists at Searle who reported different findings. Rather than submitting both reports or having a third pathologist review the slides, Searle submitted only the second report which was substantially more favorable to the drug.

• A typed chart summarizing the histopathological findings prepared by the pathologist who examined the tissue slides was changed to reflect different diagnoses for some tumors after the pathologist left the employ of the company. Neither the original nor the revised chart included all the tumors found in the rats, but the revised chart was submitted to FDA as part of a preliminary report on tumors found.

And so it went, Schmidt describing many more examples of errors, distortions, and sloppy work turned up in the investigation which is still going on.

"Our concern does not depend on discovering that results of studies are deliberately distorted, although that would be shocking, or even on discovering that the conclusions of studies are actually altered by the errors that have been revealed," Schmidt said. "It is sufficient grounds for concern that the laboratory practices at a major drug firm can at best be characterized as sloppy. Even if it proves true that the bulk of the errors found were inadvertent, sloppiness is serious in and of itself because it is the enemy of discovery. . .

"Are the problems found at Searle unique or industry-wide? Do these findings cast doubt on the safety of our foods and drugs?" Schmidt asked. "Prudence dictates that we assume the presence of an industry-wide problem until proven otherwise."

Kennedy said that the issues raised by this case "are at the very heart of the regulatory process. Al though judgments in that process may reasonably differ, all judgments are made from the same foundation–scientific data. If the integrity of that data is questioned then the whole regulatory process is questioned.

"Whether the problems at Searle are shared by other pharmaceutical companies is not clear. But I do not believe we can take that chance. This subcommittee will insist that FDA immediately institute a program to review the work of the other drug manufacturers."

Schmidt said FDA planned to undertake a "sampling" of the industry and was in the process of designing a system to do that. A decision on what firms to investigate awaits completion of the Searle investigation.

NCI Director Frank Rauscher was asked to testify on the institute's programs in which animals are used to test drugs for toxicity and therapeutic effective-

ness, and to screen chemicals for carcinogenic potential. Rauscher submitted a statement describing the programs and safeguards which concluded, "I believe that the incentive and actuality for fraud in NCI testing programs is virtually nonexistent. I believe further that because we work directly with the contractor and his raw data, together with NCI systems of checks and cross checks, the opportunity for and the impact of sloppy experimentation is greatly reduced."

Kennedy asked Rauscher for his reaction "to this hearing in terms of misleading scientific information."

"As a scientist, I'm outraged," Rauscher said. "As a citizen and a parent, I'm further outraged."

Daniel Searle, chief executive officer of the firm, categorized the problems as "essentially systems problems. The situations identified could have been minimized, if not prevented, by programs which provided broader systems-based controls. . . an overall systems approach to data definition, collection, verification, storage and retention."

Kennedy challenged that conclusion. "You're saying that these are systems problems, not scientific problems. The FDA commissioner has said they are scientific problems of the most serious nature."

Searle replied that "scientists must work in an overall system to collect, store and retrieve data."

Kennedy pressed Searle for his opinion on whether or not the deficiencies in his operation are industry-wide. "They may very well be, but I can't testify to that, since I haven't gone into anyone else's labs," Searle replied.

Kennedy criticized Searle's statement for a "lack of sense of urgency. . . There's a basic and fundamental issue, involving the health of millions of Americans," Kennedy said. "It calls for a response other than, well, we'll shake up management a little."

"These findings are of such great concern to us that we've assigned a task force to design a system so these errors couldn't be repeated," Searle said.

Sen. Gaylord Nelson (D.-Wisc.) used the occasion to do some lobbying for one of his favorate and perennial bills, to establish a federal independent drug testing agency.

"This case is a compelling indictment of a system inherently defective," Nelson said. "It's defective even when everyone does his conscientious best because of a built in bias. Unfortunately, not everyone does his conscientious best. . . There's no way we can continue a system in which the manufacturer does his own testing. Maybe my bill, setting up third party testing, is not the best way. I recognize difficulties involved. Perhaps there might be a mix of third party testing, use of research labs with no profit motive."

Nelson cited instances of previous FDA commissioners, from 10 years ago, reporting on the conscious withholding of animal data and other problems in quality of science. "I would hate like hell to sit here six years from now and listen to the next commissioner with another case like this."

Schmidt responded, "I don't intend to be in the middle of a list of commissioners who pointed out problems that weren't resolved."

Nelson suggested that FDA should consider monitoring production and testing of all of a firm's products when it is found guilty of intentionally failing to disclose information, or when its scientific work is shoddy.

John Quarles, deputy administrator of the Environmental Protection Agency, made a pitch for the Toxic Substances Act now pending in Congress. Quarles said that a majority of all potentially dangerous materials do not fall under any present regulatory system, yet they expose most Americans at one time or another. The bill would bring most of those under the authority of EPA or other regulatory bodies.

PRESIDENT'S BUDGET WOULD STOP NEW CANCER RESEARCH, HOLD AT 1975 LEVEL

The Cancer Program momentum would grind to a halt with practically no new research and a severe limit on any new projects under the 1977 fiscal year budget request submitted to Congress by the Ford Administration.

Ignoring pleas from the National Cancer Advisory Board, the President's Cancer Panel and NCI executives, the Administration requested only $695 million for 1977, an increase of $4 million over the 1975 fiscal year level. Actually, the figure shown in the budget for NCI is $587 million, with $8 million deducted as NCI's contribution to the $22 million addition being built for the NIH clinical center.

That $8 million came out of NCI's budget of $19 million for construction, with the balance all that would be available for extramural construction, leaving a long list of approved but unfunded projects.

Hardest hit would be NCI's regular research program—investigator-initiated grants. At the $587 level, NCI could fund only 4.5% of approved new grants and 24% of competing renewals. NCI has been funding well over 50% in both categories.

The Diet, Nutrition & Cancer Program is an example of a promising new area that would be able to make little more than a token effort under the proposed budget. The program, mandated by Congress, had been promised $6 million in fiscal 1976 money, but unless the President's veto of the 1976 appropriation bill is overridden by Congress, NCI probably would be held to spending the same amount in FY 1976 as it did the previous year, $691 million (see story elsewhere in this issue). That would mean nutrition would get only $1 million in 1976, probably no more than $2 million in 1977.

NCI's various contract programs would have to take some cuts. With a standstill budget, inflation and built in cost increases would make it necessary to trim at least 10% from contract research.

There would be no additional money for centers,

which probably means that no new comprehensive centers will be identified nor new center grants funded during the year.

No additional money is budgeted for the organ site task forces or for cancer control.

The budget picture for the Cancer Program thus is almost the same as it was this time last year, with the President asking less for next year than Congress has already voted for this year ($765 million in the vetoed bill). Congress probably again will vote additional money for NCI above the budget request. Meantime, however, NCI is more concerned about fiscal 1976 funds.

If the override vote, scheduled for next week in the House, fails, the Administration will attempt to hold all HEW agencies to the 1975 levels. However, an effort will be made in Congress to push through a 1976 supplemental appropriation for health programs and would give some relief to NCI. While the Administration wouldn't take the initiative for a supplemental bill, the President might not veto it if it were limited to health—his main argument with the vetoed bill was in the welfare area.

Most other institutes at NIH fared somewhat better than NCI, although not by much, in the budget request. Amounts shown for 1975 are the actual funds received, 1976 amounts estimated if the veto is upheld, and 1977 the budget request. All 1977 figures are after deduction of each institute's obligation for clinical center construction (dollars in millions):

Institute	1975	1976	1977
Heart	324.6	304.7	342.9
Dental	50	48.6	43.2
Arthritis	173.5	161.8	180.8
Neurology	142.5	135.1	146.5
Allergy	119.5	119.1	135.6
General Med	187.4	167.5	193.4
Child Health	142.4	122.2	129.9
Aging	---	16.1	26.2
Eye	44.1	44.4	47
Environ.	35.2	34	46.1
R. Resources	127.2	83.4	92.3
Fogarty	5.6	5.4	7.5
Library	28.9	29.3	35.2

CONGRESSMAN OBEY ATTACKS CANCER PROGRAM AT HURTING BASIC RESEARCH

The National Cancer Program may have lost another important friend in Congress. David Obey, Wisconsin Democrat and a member of the all-important House HEW Appropriations Subcommittee, has joined the misguided (or merely misinformed) ranks of those attacking the program and NCI because "growth in NCI's budget has been financed at the expense of other research programs at NIH, especially basic research."

Obey's attack follows the attempt by Sen. Alan Cranston (D.-Calif.) to strip $100 million from NCI appropriations which Cranston tried to justify with virtually the same logic. Senators of both parties pointed out the fallacies in Cranston's argument, but Obey either didn't read them or believe them, and apparently did not believe the record of his own committee hearings. NCI support of basic research has been thoroughly documented in every budget hearing since the Cancer Program was adopted.

Obey launched his attack in a newsletter to his constituents. He said the Cancer Program suffers from a misallocation of research funds, a lack of emphasis on prevention and a misdirected enforcement effort.

"One of the major problems with our attack on cancer is that it is being handled largely as a political issue rather than a medical or scientific problem," Obey said. "Because Congress and the Administration have been engaging in a misguided political race to show who cares most about cancer, the budget for NCI has more than tripled in the last five years," he said.

Obey said that many medical experts consider basic medical research one of the most potentially fruitful areas for progress in the fight against cancer, and noted that the budget of the National Institute for General Medical Sciences has not received sufficient funds in the past five years to keep up with inflation.

Obey listed several other federal agencies which have contributions to make in the fight against cancer, and said that "they have been all but forgotten in the rush to pour additional money into NCI simply because it is label 'Cancer Institute'."

A second problem with the federal cancer program, according to Obey "is that the emphasis at NCI has been on finding cures rather than finding ways of preventing human exposure to chemical and environmental agents that cause cancer." He said that few if any cancer researchers expect to find a miracle cure for the disease, and claimed that the "small progress" made in treating some forms of cancer have been overshadowed by the increasing rate at which the disease is striking Americans. He cited a study estimating that the number of U.S. cancer deaths will rise from 365,000 in 1975 to 510,000 in the year 2,000.

Obey said scientists believe that between 80 and 90% of all cancer is the result of human exposure to chemical and environmental agents. In light of this, he said, "it is clear that the emphasis in any effective attack on the disease should be on determining which specific agents cause cancer and how people can be

protected from them." However, he noted that the development of a new testing method (mutagenesis in vitro) pioneered by the National Institute for Environmental Health Sciences which can determine with 85% accuracy whether a chemical causes cancer has been hampered by a lack of funds.

A third flaw in the federal cancer program, Obey said, is a misdirected health and safety inspection program. He singled out the Occupational Safety & Health Administration as an agency which has failed to address major worker health problems, including worker exposure to cancer-causing agents, and in too many cases has gotten bogged down enforcing minor "nuisance" regulations.

Obey cited a number of recent congressional initiatives aimed at improving the federal cancer program—including an amendment he authored designed to redirect OSHA inspection efforts toward serious worker health hazards—but concluded that much remains to be done.

"We need to dramatically redirect our tax dollars into the most medically promising research areas; we need to place a much greater emphasis on preventing human exposure to cancer causing agents; we need to reduce the bureaucratic snarls that are hampering our cancer control enforcement efforts," he said.

NUTRITION RFPs TO BE SO FLEXIBLE THEY'LL REALLY BE GRANTS, GORI SAYS

Members of the Diet, Nutrition & Cancer Advisory Committee made an effort to rate 48 project proposals developed in six workshops, but they spent most of last week's two-day meeting discussing issues and wound up taking the project ideas home for further consideration.

Gio Gori, director of the Diet, Nutrition & Cancer Program, expects committee members to complete their priority ranking before the end of January. He still hopes that RFPs from the top rated projects can be issued by April 30.

The committee did complete the task of apportioning whatever funds the program gets from the fiscal 1976 appropriation. Gori has been promised $6 million, but that won't be definite until Congress either overrides the President's veto of the HEW appropriations bill or passes a new one.

The committee determined that 56% of the funds should go to projects related to therapy, 34% to etiology and 10% to program management and support. Members agreed that those percentages were for use as guidelines only. They may change as the program evolves.

Here's how the percentages were broken down within the two categories:

Therapy—Host-tumor competition and food intake determinants, 19%; anorexia, behavioral and food modification intervention, 15%; artificial alimentation, 22%.

Etiology—Evolution, dietary adaptation and animal models, 7%; dietary excesses and deficiencies, 13%; epidemiologic and dietary surveys, 14%.

The workshop participants had estimated that 17 projects suggested for therapy would cost $5.8 million and 27 projects in etiology would cost nearly $4 million. Program management, to include additional workshops, consultants and information acquisition and dissemination, would add another $500,000.

The workshops had assigned an estimated cost to each of the project proposals, but the committee decided those figures were too indefinite and should not be considered in priority ratings.

Proposals were grouped into six topical areas:

- Anthropology and comparative zoology to define evolutionary determinants of dietary adaptation and natural diet patterns in man. Selection of animal models for laboratory studies relevant to man.
- Acute and chronic studies of dietary alternations in man and animals to identify determinants of dietary carcinogenesis.
- Dietary surveys in relation to cancer incidence in man.
- Priorities in the study of host-tumor competition for nutrients as related to therapy goals.
- Alteration of taste and smell perception and of food characteristics to restore appetite. Definition of basic studies and of clinical trials.
- Artificial alimentation, nutrient media, methods and hardware. Definition of basic studies and clinical trials in chemotherapy, surgery and radiotherapy.

Gori told the committee he expects most of the RFPs to be so broadly written and to permit such flexible investigator initiative that they in effect will be grants, or at least follow in spirit if not form the philosophy of the Cancer Research Emphasis Grant mechanism. With $6 million to obligate before Sept. 30, the end of the 1976 fiscal year, there is not enough time to use CREG, which could not be implemented in less than 14 months.

A number of projects will be opened to CREG for fiscal 1977, Gori and the committee agreed. Committee member William Thurman, Univ. of Oklahoma, said that "some of these projects will fall neatly into CREG." He suggested that the comparative lack of interest in the scientific community in cancer-related nutrition projects would end once the proposed RFPs become available.

Committee members William Darby, Nutrition Foundation, and Harold Sandstead, U.S. Dept. of Agriculture Human Nitrition Laboratory, expressed the feeling that once the money becomes available, interest among scientists will be stimulated. Stanley Dudrick, Univ. of Texas, said, "We'll be overwhelmed with ideas once the program is funded and projects come into being."

"That's the Willie Sutton law of research," com-

mented Ernst Wynder, American Health Foundation. Sutton was the notorious bank robber who, when asked why he robbed banks, replied, "Because that's where the money is."

Another source of funds, in addition to whatever is allocated directly to DNCP, could be through the regular research grants in NCI's Div. of Research Resources & Centers. Gori pointed out that the NIH Div. of Research Grants, which reviews regular research grant applications, has a nutrition study section. "The problem up to now is that we haven't had enough applications," Gori said. Wynder asked if DRRC Director Thomas King could be asked to set aside funds for nutrition research, but Gori said that should be a task for the National Cancer Advisory Board. He asked NCAB member Harold Amos, who is the Board's liaison with the DNCP committee, to consider attempting to extract a pledge from the Board of a certain amount of money for regular nutrition grants.

The committee insisted that members be given the opportunity to review the final RFPs, as developed by NCI staff, before they are issued. Gori agreed, and also went along with permitting the committee to review summary sheets of RFP proposals after they have been rated by ad hoc peer review groups.

The proposed projects were given a tentative rating by chairmen of the workshops. Committee members indicated they disagreed with some, if not most, of those ratings, and Gori agreed to go along with their revisions.

The top projects as rated by the workshop chairmen include the following:

– Optimal nutritional support as an adjunct to cancer therapy in the adult. The objective would be to determine whether optimal nutritional support accelerates or otherwise affects tumor growth, improves tolerance and effectiveness of therapy, and to determine safety and effectiveness differences in gastrointestinal and intravenous forms of nutritional support. The approach would require adult cancer patients in three nutritional classifications–severely malnourished, moderately malnourished, well nourished–and undergoing one of three treatment modes –surgery, chemotherapy, radiotherapy. The contract, for 18 months plus two-year followup of patients, would cost an estimated $1.5 million for the first year.

– The same project as above, for pediatric patients. Estimated cost, $500,000 for the first year.

– Handbook for studies relating diet to the descriptive epidemiology of cancer. The objective would be to provide guidelines for investigators in the methodology of descriptive epidemiology and in the determination of dietary and nutritional data. It would provide instruction for the practical design of epidemiological studies involving the interrelationship of diet, nutrition and cancer. The one year contract would cost an estimated $50,000.

–System for identification of past, ongoing and future cross-sectional dietary and nutrtional surveys and cancer cohort studies. It would include a compilation of past and present surveys, methodoloties, sample sizes, and population descriptions. One year, estimated $50,000.

–Role of dietary fiber on cancer development. The objective would be to evaluate various sources of dietary fiber on intestinal function and fecal composition. Sources of dietary fiber would be analyzed by various methods and subsequently fed to human subjects receiving a known dietary regimen. Physiological and biochemical measurements would be made on the participants and excreta samples during the course of the experiment. One year, $100,000.

–Effect of fat type and level of spontaneous and chemically induced cancers, using lab animals. Two types of fat would be saturated to an iodination value of 50 and then added to a standardized diet at multiple levels. Protein levels would be constant, and fat would be added at the expense of the carbohydrate source dextrose. Several tumor types, spontaneous or chemically induced, would be evaluated in mice of both sexes. Two years, $300,000 first year.

–Relationship between anorexia and weight loss in patients with primary cancer. Objective would include determination of whether weight loss is caused by decreased food intake, altered metabolism or a combination of both. A common protocol would be developed by cooperative institutions. Cancer patients would be compared to normal individuals. Patients in whom a complete remission has been induced would be followed serially to relapse, along with suitable controls. Fifteen months, plus two-year followup. Cost, $500,000 for first year.

–Studies of differential nutritional requirements by host and tumor as the basis for the dietary treatment of cancer. The objective would be to determine whether known differences in host-tumor nutritional requirements can be exploited therapeutically and to develop and evaluate nutritional differences through in vivo and in vitro techniques, preparatory to human studies. The two-year, multi-institutional contract would cost $500,000 for the first year.

CYCLAMATE COMMITTEE FINDS NO PROOF OF CARCINOGENICITY, BUT HAS DOUBTS

NCI's role in the determination of whether or not cyclamate is a carcinogen has ended, for the moment anyway, with the finding by the Temporary Committee for the Review of Data on Carcinogenicity of Cyclamate that "the present evidence does not establish the carcinogenicity of cyclamate or its principal metabolite, cyclohexylamine, in experimental animals."

The ball is back in FDA Commissioner Alexander Schmidt's court now. He had asked NCI to determine

the validity of tests which raised the suspicions about cyclamate. According to a quote attributed to him, he wasn't happy with the committee's statement and demanded "a clean bill of health, not a wishy-washy iffy answer on cyclamates."

Schmidt isn't likely to get a clear-cut statement that would make it easy for him to make a regulatory decision unless he is willing to spend $5-$10 million for a two-year study using 52,000 lab animals which committee members agreed would be required to provide a definite answer.

The problem, as Committee Chairman Arnold Brown said, is that present bioassay techniques are not sensitive enough to prove the case against a very weak carcinogen. If cyclamate is a carcinogen, it is a very weak one, Brown said.

The review of cyclamate tests cost NCI about $20,000, not counting staff time. The money came out of NCI's budget. If FDA decides that the definitive test is needed, the money will have to come from somewhere else—an earmarked appropriation from Congress or from industry. Abbott Laboratories, the principal manufacturer of cyclamate, has not offered to finance any additional testing.

In analyzing the studies conducted at various institutions around the world, committee members and their consultants generally agreed that differences in tumor incidence between test animals and controls were not statistically significant. Because the statistical differences were so small, present bioassay techniques would require using 52,000 animals. "Cyclamate has stretched to the breaking point the capability of the bioassay system," Brown said.

Abbott Vice President Richard Kasperson commented after the meeting that "we see no valid scientific reason for FDA to delay further. This should lead to the early availability of cyclamate to the U.S. consumer."

The committee's conclusions, except for the first one in which it was stated that present evidence does not establish the carcinogenicity of cyclamate, do not tend to support Kasperson's position:

"—No conclusions can be made regarding the question of cyclamate's potential carcinogenicity in humans due to the short post-exposure observation time, the insensitivity of epidemiologic studies to detect relatively small changes in cancer incidence, and other factors.

"—The committee is concerned over the implications of the increased incidence of tumors in the urinary tract of cyclamate-fed animals from several studies, even though those increases were not statistically significant. It is not clear whether this represents a weak carcinogenic response or random variation.

"—An additional concern is the carcinogenic responses obtained in cyclamate-treated animals from studies employing unconventional procedures or observing a response of a questionable nature. The bladder implantation study done by Bryan, et al. was considered to be inappropriate for assessing the carcinogenicity of a dietary constituent. Of particular concern are the results obtained at the Food and Drug Research Laboratories (Oser, et al.) in which cyclamate and saccharin were tested together, as well as with cyclohexylamine in some of the animals. The cocarcinogenicity system used by Hicks, et al. has yet to be validated as a bioassay for carcinogenicity. Although the dose-dependent increase in lymphosarcomas in cyclamate-treated mice (Brantom, et al.) requires close evaluation, the nonspecific nature of this response in mice makes its significance questionable with respect to establishing carcinogenicity.

"—Short-term or in vitro test systems cannot now be used to establish carcinogenicity. However, the results from such systems are useful for determining the need for appropriate carcinogen bioassay studies, as well as for enlarging the mutagenicity-carcinogenicity correlative data base. In this regard, the committee notes that in several studies cyclamate or cyclohexylamine has been found to produce chromosome damage in human and rodent cells.

Brown refused to discuss whether or not he personally felt his committee had given FDA enough reason to lift the ban against cyclamate. "Our report goes to Dr. Rauscher. It's up to him to decide what to do with it. If he sends it on to Commissioner Schmidt, then it is the commissioner's decision to make."

Brown suggested that FDA may have reasons other than cyclamate's possible carcinogenicity for keeping it off the market but would not say what they might be.

Umberto Saffiotti, who heads NCI's Carcinogenesis Program, disagreed with the conclusion that a massive test would be needed to provide more definite answers. "We have a variety of alternatives to a single large study," he said.

"Could you come up with a protocol that would help the committee?" Brown asked.

"I could suggest a number of protocols. I think we could say that further studies are needed."

"But that's so often a cop out," Brown said. "Do you believe the carcinogenicity of cyclamate can be determined with standard bioassay techniques?"

"In combination with metabolic studies," Saffiotti said. "Possibly with in vitro tests in future."

"I mean today," Brown said. "So far as I know, the only data we have is from bioassays."

Serving on the committee with Brown, who is with the Mayo Clinic, were Roswell Boutwell, Univ. of Wisconsin; Paul Newberne, MIT; Bernard Weinstein, Columbia Univ.; Gerald Wogan, MIT; and Maureen Henderson, Univ. of Washington.

The committee used 11 consultants to assist with the study:

Experimental Design & Toxicology Working Group —Morris Cranmer, National Center for Toxicological

Research, and Cipriano Cueto, Norbert Page, and Elizabeth Weisburger, NCI.

Pathology Working Group–Charlie Barron, Tracor Jitco, and Morton Levitt, Robert Squire, and Mearl Stanton, NCI.

Statistics Working Group–Charles Brown and Charles Land, NCI.

Epidemiology–John Bailar, NCI.

James Sontag of NCI was executive secretary.

Individual reports of the working groups, details of the site visits to review the various studies, and the committee's use of a draft document for establishing the carcinogenicity of chemicals will be included in the final report.

The draft document was developed by the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis. Brown, Weinstein and Wogan all serve on that subcommittee, which will meet next month to adopt the final version of the document.

CONTRACT AWARDS

Title: Preparation of oral dosage forms of investigational drugs
Contractor: Philips Roxane Laboratories, $40,000.

Title: In vitro cell culture screening of new materials for cytotoxicity
Contractors: Arthur D. Little Inc.,$649,915; Univ. of Miami, $413,732; Southwest Foundation, $320,180; and Univ. of Wisconsin, $179,297.

Title: Breast cancer detection demonstration project
Contractor: St. Joseph Hospital, Houston, $273,800.

Title: Study of carcinogenesis by radiation plus estrogen
Contractor: Alton Ochsner Medical Foundation, New Orleans, $167,000,

Title: Inelastic laser light scattering studies on nucleic acids, nucleoproteins, and viruses
Contractor: Michigan Cancer Foundation, $74,930.

Title: Research on oncogenic and potentially oncogenic viruses, virus production and vaccine development
Contractor: Merck, $73,490.

Title: Detroit SSMA population-based cancer registry
Contractor: Michigan Cancer Foundation, $60,363.

Title: Comparative leukemia and sarcoma viral studies
Contractor: Univ. of California (Davis), $75,500.

Title: Fibrocystic disease of the female breast and its relationship to mammary carcinoma
Contractor: Vanderbilt Univ., $54,100.

Title: Study and production of avian leukosis and viruses
Contractor: Life Sciences Inc., $43,300.

Title: Support services for immunological and biochemical studies of mammalian viral oncology
Contractor: Meloy Laboratories, $867,732.

Title: Large scale tissue culture virus production for cancer research
Contractor: Pfizer, $1,570,000.

Title: Data processing services for the SEER and Third National Cancer Surveys
Contractor: Geomet Inc., $98,269.

Title: Demographic cancer research program in Hawaii
Contractor: Univ. of Hawaii, $465,550.

SOLE SOURCE NEGOTIATIONS

Proposals are listed here for informational purposes only. RFPs are not available.

Title: Applications of advanced optical and electrical technology to problems in oncology
Contractor: General Electric Co.

Title: Induction of malignant melanoma in the guinea pig
Contractor: Temple Univ.

Title: Standardization of hydrocarbon hydroxylase assay as a screening method to determine smoking hazards in man
Contractor: Microbiological Associates.

Title: Metabolic studies on tobacco smoke constituents
Contractor: Univ. of Maryland (Baltimore).

Title: Studies on carcinogenesis principles of processed tobacco smoke
Contractor: New York Univ.

Title: Chemotherapy studies of central nervous system solid tumors
Contractor: Arthur D. Little Inc.

Title: Planning for special oncologic diagnostic radiology conferences
Contractor: American College of Radiology.

Title: Murine mammary tumor virus production facility
Contractor: Meloy Laboratories.

Title: Development of new data management system for the Connecticut tumor registry
Contractor: Connecticut Dept. of Public Health.

Title: Mortality experience of children inadvertently inoculated with SV40 very early in life
Contractor: Case Western Reserve Univ.

The Cancer Letter—*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., 1411 Aldenham Ln., Reston, Va. 22090.