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NCI, NCAB TO SEEK $1.036 BILLION IN '79; SENATE COMMITTEE APPROVES $920 MILLION FOR FISCAL '78

The House and Senate last week moved closer to approval of a budget for NCI for the 1978 fiscal year starting next Oct. 1 in actions that were both discouraging (by the House) and encouraging (by the Senate).

Meanwhile, the National Cancer Advisory Board put its stamp on the budget recommendation for the following fiscal year which NCI will submit to the White House late this summer. Unfortunately, the disparity in the perception of National Cancer Program needs as determined by NCI and its advisors and as voted by Congress is growing ever wider.

(Continued to page 2)

In Brief

RESOLUTION WASN'T STRONG ENOUGH, REIZEN THOUGHT; TWO MORE CHEMICALS REPORTED OUT OF BIOASSAY

MAURICE REIZEN, director of the Michigan Dept. of Health and a member of the Cancer Control & Rehabilitation Advisory Committee, explained why he voted against the motion to tighten up guidelines for mammography screening in the Breast Cancer Detection & Demonstration Projects (*The Cancer Letter*, May 13): "I thought the resolution was not strong enough, that it might be misinterpreted as opening the door for routine screening of other high risk groups. Apparently, that was not the case." Reizen said he supported the decision to limit mammography for women under 50 to those with a previous history of breast cancer and those whose mothers or sisters had the disease. . . . **"THE SINGLE** most important reason for disapproval of contract and grant applications (in NCI's Div. of Cancer Control & Rehabilitation) is that there is no adequate provision for evaluation." Donald Buell, DCCR program director for medical oncology, passed on that bit of advice at the ASCO annual meeting. . . . **ROBERT FRELICK**, director of the Delaware Cancer Program, also talking to ASCO members: "The oncologist must use his experience and skills to provide leadership for the cancer program in his community." Reciting the long list of tasks this involves, Frelick acknowledged this was a considerable drain on the physician's time and energy, "but we love it". . . . **ROBERT SCHONFELD**, chief of the Program Liaison Branch in NCI's Office of Cancer Communications, is leaving that job to become deputy executive officer of the National Institute of Mental Health. . . . **TWO MORE** chemicals tested for carcinogenicity in NCI's Bioassay Program have been reported on—nitrilotriacetic acid (NTA), was found to be carcinogenic to the urinary tracts of mice and rats at higher doses, not significantly so in lower doses; phenformin, a drug used to control maturity-onset diabetes, was not found to produce any pathologic or statistical evidence of induction of tumors in rats and mice.

CONGRESSMAN PLANS FLOOR FIGHT TO ADD $40 MILLION TO HOUSE TOTAL FOR FY '78

(Continued from page 1)

The House Appropriations Committee approved the Labor-HEW Appropriations bill with the same figure for NCI recommended by Chairman Daniel Flood's subcommittee—$831.9 million, an increase of only 2% over 1977 funding.

The full committee beat back an attempt by Rep. Silvio Conte (R.-Mass.) to add $40.2 million for NCI. A spokesman for Conte told ***The Cancer Letter*** the congressman was convinced the Cancer Program needed an increase of more than 2% and that the increase should be at least as large as NCI received last year, about 7%. The spokesman said Conte planned to take his fight to the floor of the House when the bill reaches there and submit his amendment for a vote by the entire House.

Rep. David Obey (D.-Wisc.), who now has to be considered the Cancer Program's No. 1 adversary in Congress, led the fight against Conte's amendment. "Normally it's hard to vote against cancer," Obey said, "but NCI has become a grant feeding machine."

It appears that Flood has lost control of his subcommittee to Obey, at least in matters relating to NCI. Obey sold the subcommittee on adding 22 more slots for NCI, earmarked for environmental epidemiology and environmental pathology. This followed Obey's successful effort last year to cram 77 positions in the Carcinogenesis Program down NCI's throat, at least twice as many as NCI executives felt they needed.

Obey also wrote in the report on the bill that $4 million from NCI's appropriations should be made available to the National Institute of Occupational Safety & Health, but did not add that amount to NCI's funds. The money probably will come out of the carcinogenesis budget.

On the positive side, Obey sold the full Appropriations Committee on rejecting an attempt by Rep. Robert Michel (R.-Ill.) to cut back the entire bill to the amount recommended by the President. Despite noises from the White House that President Carter would veto any bill that exceeded his request (seven of the last eight HEW appropriations bills have been vetoed), Obey convinced the committee that Carter would sign it if no more increases above the subcommittee's level were added on.

It was up to Chairman Warren Magnuson's Senate HEW Appropriations Subcommittee to save the Cancer Program from stagnation, and it came through. Birch Bayh (D.-Ind.) and Edward Brooke (R.-Mass.) pushed for an NCI appropriation of up to $1 billion, and wound up getting $920 million.

If in conference with the House the Senate can obtain a 50-50 split of the difference, that would give NCI about $876 million, a figure that would keep most programs intact and permit the funding of around 46% of competing grants.

The final 1978 figure will help determine what NCI will get in 1979, but the '79 budget request must be submitted to the White House by Sept. 1. NCI and the Office of Management & Budget will debate the figures through the end of the year, with the end result to be incorporated into the President's budget recommendations to Congress in January.

NCI staff developed two sets of figures for 1979 for consideration by the NCAB. The more conservative estimate called for a budget of $1.036 billion, the other $1.2 billion. Those figures were drawn up before the House committee action, and the Board and staff agreed it would be futile now to pay much attention to the higher total.

The Board accepted most of NCI's suggestions for distributing funds among programs and mechanisms in both the 1978 and 1979 budgets. The exception for 1978 involved adding $3 million to investigator initiated grants and $1.9 million to program project grants, primarily at the expense of the Centers Program.

At the suggestion of its Subcommittee on Planning & Budget, chaired by Frank Dixon, the Board approved taking $1 million from cancer centers core support, dropping it to $63 million; $1.9 million from centers planning grants, reducing it to $1.8 million; $1 million from research support contracts, dropping it to $97.1 million; and $1 million from Cancer Research Emphasis Grants, leaving it at $8.9 million.

Dixon said the changes were made to reflect the Board's policy of increasing the percentage of NCI's budget for investigator initiated grants by 1.5% a year. "In three more years we'll have the total percentage for investigator-initiated grants up to about 65%," Dixon said.

Dixon said the subcommittee's intention was to make center planning grant funds available only for patient data systems. "There will be virtually none for regular planning grants," he said.

The subcommittee also recommended and the Board accepted similar changes for 1979, taking $1.25 million from centers planning grants and adding it to traditional research grants. In the $1.036 billion budget, this would put traditional grants at $176.6 million and planning grants at $4 million.

The staff recommendations for program distribution of 1978 funds were based on a final appropriation of $905 million. "We guessed that the final figure will be somewhere between the $831.9 million approved by the House committee and $905 million," Dixon said. He recommended that the amount for each program be adjusted on a proportional basis to reflect the final figure.

At the $905 million projection for 1978, NCI expected to fund 264 out of 426 approved competing renewal traditional grants (62% of approved), and 479 out of 1,058 new approved grants (45%). Cost

would be $54.3 million.

For 1979 at the $1.036 billion projection, the figures would be 261 of 390 approved competing renewals (67%), and 555 of 1,086 new approved grants (51%), with a cost of $63 million.

The estimates for program project and core grants for 1978 included funding 73 of 80 approved competing renewals (91%), but only 13 out of 60 approved new grants (22%), at a cost of $69.5 million.

For 1979 at the $1.036 billion level, figures for program projects and core support would be 59 out of 64 approved renewals (92%), and 17 out of 53 approved new grants (32%), at a cost of $62.9 million.

Clearly the emphasis in support for cancer centers and program projects will be to attempt to adequately fund existing centers and programs but cut back drastically on the number of new ones.

NCAB OKAYS GEORGETOWN, YALE NEW CONSTRUCTION; STANFORD TURNED DOWN

The National Cancer Advisory Board last week approved final distribution of the $16 million budgeted for construction with 1977 fiscal year funds, including the $10 million that NCI had attempted to transfer to other programs.

The largest award went to Georgetown Univ., $3.124 million, which will be used in the construction of a new facility for basic sciences and clinical activities in the Vince Lombardi Cancer Center. The center is part of the Georgetown-Howard Univ. Comprehensive Cancer Center. The award fell $1 million short of the amount approved as NCI's contribution to the project, and the university presumably will be first in line for that money from the 1978 budget.

Georgetown still has one more hurdle to clear to get its money. The award will finance new construction, and the restriction on federal funding of new health facility construction left over from the Nixon-Ford years is still in force. It will require special clearance from HEW Secretary Joseph Califano.

Theoretically this could set up an immediate confrontation between Califano and either Acting NCI Director Guy Newell or the new director. The Cancer Act clearly gives the director final authority to make construction awards with concurrence of the Board. The previous administrations ignored that authority and objected in every instance when a new construction award was made, although backing down each time to pressure from Congress and others.

The Board also approved another award for new construction, $1.064 million to Yale Univ. Comprehensive Cancer Center, for expanded radiotherapy facilities. This one also will require Califano's approval.

All other awards approved by the Board last week were for alterations and renovations which should not arouse any opposition at HEW or the White House:

—Cold Spring Harbor, $1.4 million for animal and biohazard facilities.

—Massachusetts Institute of Technology, $1.5 million for animal and biohazard facilities.

—Ohio State Univ. Comprehensive Cancer Center, for facilities to house programs in chemical carcinogenesis, viral oncology and human tumor work.

—Roswell Park Comprehensive Cancer Center, $600,000 for biohazard and environmental carcinogenesis facilities.

—Sidney Farber Comprehensive Cancer Center, $2.86 million for the Jimmy Fund building for biohazard, epidemiology and biometry facilities.

Awards made last year but carried over for funding with 1977 money accounted for the balance of the $16 million. They were Howard Univ., $750,000; Northwestern Univ., $895,000; and the Univ. of Rochester, $2.1 million.

The Board rejected the application from Stanford Univ. for $7.6 million which would house facilities for radiobiology, medical oncology, immunology and virology. The rejection was based entirely on the size of the grant. With the 1978 budget for construction estimated between $9 million in the President's request and $16 million (at the $90.5 million level for the entire NCI), the Board decided the Stanford grant would take up too much of the construction budget, considering the number of pending applications for biohazard and animal facilities.

Stanford has the option of withdrawing the application completely, or resubmitting it at a more modest cost.

The Board concurred in NCI's decision to limit federal participation in future construction to $4 million. Coupled with the newly adopted limit of 50-50 matching funds, the total cost of a new facility with NCI construction support could not exceed $8 million. The new policy will be effective for submissions dated Feb. 1, 1978, with Oct. 1, 1977 the final deadline for receipt of applications.

In effect, the policy is in force now, since NCI is already discouraging applications that would exceed $4 million.

DEVITA FROWNS ON L-PAM FOR STAGE I BREAST CANCER, PREFERS ANTIMETABOLITES

"The problem of second cancers is the kind of problem we need more of," Vincent DeVita said at a press conference in Denver after assuming presidency of the American Society of Clinical Oncology. "I would like to have the problem of second cancers with lung cancer and colon cancer patients. Ten years ago, it wasn't a problem at all because most patients died of the primary cancer."

DeVita said physicians should keep "tight surveillance of their successes because we know it will happen," particularly those treated with alkylating

	1970 ACTUAL		1971 ACTUAL		1972 ACTUAL		1973 ACTUAL	
	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL
Group I — Investigator Initiated								
Regular Research Grants	$ 39,576	29.1	$ 44,133	24.2	$ 59,207	18.9	$ 73,412	21.1
Clinical Cooperative Groups	6,112	4.5	7,013	3.9	10,102	3.2	12,791	3.7
Program Projects	21,021	15.4	30,205	16.6	38,415	12.2	52,008	14.9
Radiation Development Program	—	—	—	—	—	—	—	—
Clinical Education Program	—	—	—	—	—	—	—	—
Research Career Program	1,919	1.4	2,012	1.1	2,026	.7	1,818	.5
Fellowships	1,691	1.2	1,786	1.0	1,921	.6	988	.3
Training Grants	10,774	7.9	10,774	5.9	16,474	5.3	12,900	3.7
Task Forces (Grants)	—	—	—	—	638	.2	3,950	1.1
Cancer Centers — Core Support	4,554	3.4	6,174	3.4	10,090	3.2	13,002	3.7
Subtotal	85,647	62.9	102,097	56.1	138,873	44.3	170,869	49.0
Group II — Co-Initiated								
Cancer Res. Emphasis Grants (CREG)	—	—	—	—	—	—	—	—
Research Contracts	15,740	11.6	27,547	15.1	46,802	14.9	61,187	17.6
Subtotal	15,740	11.6	27,547	15.1	46,802	14.9	61,187	17.6
Group III — NCI/NCP Initiated								
Research Support Contracts	29,237	21.5	44,945	24.7	63,194	20.2	64,838	18.6
Interagency Agreements	4,727	3.4	5,704	3.1	12,053	3.8	10,136	2.9
Subtotal	33,964	24.9	50,649	27.8	75,247	24.0	74,974	21.5
Group IV — Other Resources								
Cancer Centers — Planning Grants	769	.6	1,889	1.0	1,698	.5	2,500	.7
Construction Grants	—	—	—	—	47,004	15.0	34,737	10.0
Construction Contracts	—	—	—	—	3,999	1.3	4,067	1.2
Subtotal	769	.6	1,889	1.0	52,701	16.8	41,304	11.9
Total	136,120	100.0	182,182	100.0	313,623	100.0	348,334	100.0
Percent of Total NCI Budget		77.8		80.3		84.2		81.9
In-House Research	18,625	10.7	20,594	9.1	25,696	6.9	33,032	7.8
Management & Support	20,178	11.5	24,176	10.6	33,246	8.9	39,072	9.2
(NIH Management Fund)	(9,455)	(5.4)	(10,917)	(4.8)	(12,910)	(3.5)	(15,194)	(3.6)
Cancer Control (Grants & Contracts)	—	—	—	—	—	—	4,969	1.1
Subtotal	38,803	22.2	44,770	19.7	59,942	15.8	77,073	18.1
Total NCI	**$174,923**	**100.0**	**$226,952**	**100.0**	**$372,565**	**100.0**	**$425,407**	**100.0**

The budget history by mechanism is shown here as presented to the Board. The figures do not include changes made by the Board in 1978 and the 1979 level A columns. (See accompanying article, pages 1 - 3.)

agents which have proven carcinogenic effects. He emphasized that the risk of second cancers caused by treatment was still very low.

NCI is developing a research program on preventing the carcinogenic effects of treatment. This is in addition to the effort by the Div. of Cancer Cause & Prevention to develop vitamin A analogs, or retinoids, which would be available to high risk groups including cancer patients who have been successfully treated.

Alkylating agents such as cytoxan and L-PAM are the biggest offenders, DeVita said. Studies have shown an increased incidence of acute myelogenous leukemia among patients who were treated with those drugs, usually occurring after five years. He said, "We've made some progress in treating AML but it is still a tough disease to treat. Those occurring as second cancers don't respond as well to treatment as primary AMLs."

DeVita said he was concerned about what he feels is widespread use of L-PAM as adjuvant treatment for women with stage I breast cancer. "It's freely available. . . I don't have any solid information to back this up but I have the feeling that those who are aware of the Fisher studies with L-PAM are demanding it and are getting it, perhaps more so among doctors' wives than any other group."

Stage I breast cancer survival rate is about 80% with surgery alone. Patients who attempt to improve those odds by following surgery with L-PAM increase their chances of getting AML by 1 to 5%.

DeVita suggested that antimetabolites should be the preferred drug for stage I adjuvant therapy. "If I

1974 ACTUAL		1975 ACTUAL		1976 ACTUAL		FY 1977		FY 1978		FY 1979 LEVEL A	
LLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL	DOLLARS	PERCENT OF TOTAL
99,415	21.5	$112,258	20.9	$129,021	22.4	$135,538	22.3	$149,691	22.5	$ 175,328	22.9
16,196	3.5	19,213	3.6	23,263	4.0	26,836	4.4	30,000	4.5	36,000	4.7
71,997	15.6	83,468	15.5	77,805	13.5	80,653	13.2	92,748	13.9	109,550	14.3
—	—	4,005	.7	3,836	.7	4,175	.7	4,500	.7	6,000	.8
—	—	5,033	.9	7,698	1.3	8,996	1.5	10,250	1.5	12,000	1.6
1,673	.4	2,806	.5	3,243	.6	3,081	.5	3,440	.5	3,982	.5
6,004	1.3	13,368	2.5	13,401	2.3	18,236	3.0	19,723	3.0	24,000	3.1
17,558	3.8	9,736	1.8	4,759	.8	1,764	.3	277	.1	0	—
10,007	2.2	11,167	2.1	14,090	2.5	14,700	2.4	16,812	2.5	19,950	2.6
17,575	3.8	30,096	5.6	47,803	8.3	57,000	9.4	64,000	9.6	73,750	9.6
40,425	52.1	291,150	54.1	324,919	56.4	350,979	57.7	391,441	58.8	460,560	60.1
—	—	—	—	2,577	.5	7,824	1.3	9,993	1.5	11,890	1.6
94,964	20.5	105,076	19.5	111,524	19.3	113,112	18.6	119,533	17.9	134,320	17.5
94,964	20.5	105,076	19.5	114,101	19.8	120,936	19.9	129,526	19.4	146,210	19.1
72,365	15.7	82,916	15.4	96,509	16.7	92,373	15.2	98,127	14.7	105,611	13.8
13,031	2.8	11,593	2.1	13,262	2.3	19,842	3.3	21,739	3.2	24,663	3.2
85,396	18.5	94,509	17.6	109,771	19.0	112,215	18.5	119,866	17.9	130,274	17.0
2,880	.6	2,568	.4	2,803	.5	1,727	.3	3,750	.6	5,250	.7
31,692	6.9	30,000	5.6	20,000	3.5	16,000	2.6	16,000	2.4	18,000	2.3
6,398	1.4	14,976	2.8	4,721	.8	6,001	1.0	6,000	.9	6,000	.8
40,970	8.9	47,544	8.8	27,524	4.8	23,728	3.9	25,750	3.9	29,250	3.8
61,755	100.0	538,279	100.0	576,315	100.0	607,858	100.0	666,583	100.0	766,294	100.0
	79.5		77.0		75.7		74.6		73.6		74.0
40,3[illegible]	6.9	50,532	7.2	61,243	8.0	64,538	7.9	73,871	8.2	81,256	7.8
46,169	7.9	61,935	8.9	69,876	9.2	85,766	10.5	101,146	11.2	114,000	11.0
16,754)	(2.9)	(20,248)	(2.9)	(23,037)	(3.0)	(26,940)	(3.3)	(32,000)	(3.5)	(35,000)	(3.4)
32,826	5.7	48,574	6.9	54,016	7.1	56,775	7.0	63,400	7.0	74,450	7.2
19,359	20.5	161,041	23.0	185,135	24.3	207,079	25.4	238,417	26.4	269,706	26.0
31,114	**100.0**	**$699,320**	**100.0**	**$761,450**	**100.0**	**$814,937**	**100.0**	**$905,000**	**100.0**	**$1,036,000**	**100.0**

was treating a stage I patient and felt obliged to give a drug I would give an antimetabolite instead of an alkylating agent," he said.

NCI might consider supporting clinical trials using antimetabolites for breast cancer, designed to demonstrate whether they increase survival of stage I patients above that 80% rate. Using stage I patients in the trials would take too long to find the answers, DeVita said, suggesting that stage II patients would provide a quicker answer. He later said it might be done with poor risk stage I patients.

Other items covered by DeVita at the press conference included:

- Div. of Cancer Treatment clinicians are experimenting with a "space suit" as a means to increase body temperature in heat therapy trials. Hot water is circulated to raise the temperature as high as 106 degrees farenheit while cold water circulates through the headpiece to keep the brain temperature down.
- He disagrees with David Fisher, who urged that ASCO be more aggressive in taking positions on national issues. "The board felt we should not take stands on issues, especially if we have to put it to a vote of the membership." A committee is looking at the problem of reimbursement (raised by Fisher). "I don't think we should be too aggressive on that. It does not come across well for physicians to be too loud about protecting their economic interests."
- Immunotherapy "is in the bow and arrow stage . . . it is effective in some cases, but it can be better. We need to refine the tools."

- "When you are ignorant, randomized trials do not dispel that ignorance. They just make you feel better.
- "I'm optimistic. No cancer patient ever died of optimism, but a hell of a lot of them have died from pessimism."
- The colon cancer adjuvant study by George Higgins of the Veterans Administration using 5-FU

AMOUNT (IN THOUSANDS)			RESEARCH PROGRAMS
1979 LEVEL A	1978 ESTIMATE	1977 LEVEL	
$ 47,694	$ 39,237	$ 32,941	EPIDEMIOLOGY
135,442	116,930	98,997	CARCINOGENESIS (PHYSICAL AND CHEMICAL)
110,011	102,915	99,950	VIRAL ONCOLOGY
11,946	8,975	6,261	NUTRITION
91,138	79,522	70,989	TUMOR BIOLOGY
90,615	79,171	72,511	IMMUNOLOGY
36,076	31,592	28,000	DIAGNOSTIC RESEARCH
127,072	113,429	104,469	PRECLINICAL TREATMENT RESEARCH
155,533	134,966	121,691	CLINICAL TREATMENT RESEARCH
4,199	3,641	3,353	REHABILITATION RESEARCH
$809,726	**$710,378**	**$639,162**	TOTAL RESEARCH

This chart showing distribution of funds by research programs is based on $905 million for 1978, and $1.036 billion for level A for 1979. The 1979 level B estimate was based on an appropriation of $1.2 billion, which the Board concluded was an unrealistic figure at this point.

and methylCCNU "is clearly positive, although Chuck Moertel and I are on opposite sides of the fence on that." Bernard Fisher is considering having his group undertake a similar study. "Surgeons who work in breast cancer usually do a lot of colon cancer surgery. Bernie thinks he can get 800 colon cancer patients a year into a study."

DeVita said he would be willing to discuss clinical tests with laetrile. "My personal feeling is that it is worthless, but it is not an outlandish suggestion to test it. It was a mistake not to have tested it years ago." He acknowledged that the mere fact that NCI would undertake such a test might encourage some patients to use the substance, and that "we won't discourage the laetrile proponents even if the tests proved conclusively that it has no value. But we don't need to convince them (the proponents), we need to convince the people who might use it."

If laetrile is tested, it would be handled like any other investigational new drug, with double blind crossover with placebo involving advanced patients for whom all other treatment had failed, DeVita said.

JUNE MEETING OF PRESIDENT'S CANCER PANEL MEETING CANCELED; NEXT, JULY 12

The meeting of the President's Cancer Panel scheduled for June 7 has been canceled. Panel Chairman Benno Schmidt agreed to call off the meeting when he learned that most senior NCI executives would be attending a meeting of the American Cancer Society in San Diego June 6-9.

The next meeting of the Panel is scheduled for July 12, 9:30 a.m., at NIH in Building 31, conference room 4.

ABSTRACTS OF 'MOST NEWSWORTHY' PAPERS PRESENTED AT AACR MEETING

The various subcommittees of the Program Committee for the 68th annual meeting of the American Assn. for Cancer Research selected 17 papers they considered to be "newsworthy." Papers chosen included reports on research in virology, experimental chemistry, clinical investigation and clinical chemistry, and carcinogenesis. Abstracts of the virology papers and one carcinogenesis abstract appeared last week in *The Cancer Letter.* Others follow:

CARCINOGENESIS

STRUCTURES OF NUCLEIC ACID ADDUCTS FORMED IN HUMAN BRONCHIAL EXPLANTS EXPOSED TO BENZO(a)PYRENE – A.M. Jeffrey, K. Grzeskowiak, K.W. Jennette, I.B. Weinstein, C. Harris and R.G. Harvey, Columbia Univ., NCI and Univ. of Chicago

Evidence exists that benzo(a)pyrene (BP) is metabolically activated through epoxidation at the 9,10-positions of BP-7,8-dihydrodiol. Using reverse phase high pressure liquid chromatography (HPLC) we have been able to show that, following metabolism of BP by human bronchial explants, a single major BO-guanine adduct is present in the DNA. Evidence was obtained that this adduct was derived from 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydro-BP. Derivatives from the enantiomeric dihydrodiol epoxide, or from the sterioisomers (±)-7β,-8α-dihydroxy-9β,10β-epoxy-7,8,9.10-tetrahydro-BP, were not detected. In vitro studies show that differences in reactivities with nucleic acids of the enantiomeric or stereoisomeric dihydrodiol epoxides are insufficient to explain the observed in vivo specificities. Thus, a stereoselective oxidation of BP occurs in vivo. HPLC and circular dichroism studies indicate that the same enantiomer of BP dihydrodiol epoxide is involved in the binding of BP to both DNA and RNA in human and bovine brochial explants. The BP-guanine moiety of the major DNA and RNA adducts fromed in all cases appears to have the same structure as that previously described (A.M. Jeffrey, et al, J. Am. Chem. Soc., 98, 5714, 1976).

MECHANISM OF MICROSOMAL METABOLISM OF BENZO(a)-PYRENE TO 7,8-DIOL-9,10-EPOXIDES: CHARACTERIZATION OF INTERMEDIATES AND PRODUCTS AND INTERACTION WITH DNA – Shen Yang, Harry Gelboin and Tsuyoshi Kakefuda, NCI.

Benzo(a)pyrene is metabolized by the microsomal mixed-function oxidases (MFO) from rat liver to an optically active 7,8-epoxide. The 7,8-epoxide is subsequently hydrated by epoxide hydratase to an optically pure (—)trans-7,8-diol. The (—)trans-7,8-diol is further metabolized by the MFO to mainly r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene (diol-epoxide I) and a small amount of r-7,-t-8-dihydroxy-c-9,10-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene (diol-epoxide II). The metabolically formed diol-epoxides are unstable in aqueous medium and are hydrolyzed to tetrahydroxytetrahydrobenzo-(a)pyrenes (tetrols). Diol-epoxide I is hydrolyzed trans-selectively at C(10) position to form a major (7,10/8,9)-tetrol and a minor (7/8,9,10) -tetrol. Diol-epoxide II is hydrolyzed cis-selectively at c(10) position to form a major (7,9,10/8-tetrol and a minor (7,9/8,10)tetrol. Diol-epoxides I and II are reduced by NADPH or NADH to (7/8,9)-triol and (7,9/8)-triol respectively. The in vitro binding of BP metabolites and formation of locally denatured regions of double-helical structure of Colicin E1 and SV 40 DNA were studied by endonuclease S1 treatment and electron microscopy. Diol-epoxide I and trans-7,8-diol metabolized by microsomal enzymes created the largest number of structural modifications per unit length of DNA molecules. These metabolites were also the most active in skin tumor initiation.

PROMOTING EFFECT OF BILE ACIDS (BA) ON COLON CARCINOGENESIS IN GERMFREE (GF) AND CONVENTIONAL (CONV) RATS – Bandau Reddy, K. Watanabe, J.H. Weisburger, and E.L. Wynder, American Health Foundation

There is a strong association between colon cancer and fecal excretion of BA in man. The promoting effect of cholic acid (CA), chenodeoxylcholic acid (CDA) and lithocholic acid (LA) was studied in GF and Conv female F344 rats. Animals received intrarectal (ir) dose of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) for 2 weeks (total dose, 8mg/rat), then three times weekly ir doses of BA under study for 48 weeks (total dose, 38mg/rat). Control rats received either MNNG for 2 weeks followed by normal saline or BA for 48 weeks. No tumors were found in colon of GF and Conv rats given BA alone. Rats given MNNG had fewer tumors than those on MNNG+BA. GF rats given MNNG+LA developed more colon tumors than did those on MNNG, MNNG+CA or MNNG+CDA. A slight increase in colon tumor incidence was observed in GF rats given MNNG+CA or MNNG+CDA compared to MNNG. Conv rats given MNNG+CA or MNNG+CDA developed more colon tumors than the rats on MNNG alone.

The data indicate that primary BA upon further modification to secondary BA by intestinal bacteria exert a strong promoting effect in colon carcinogenesis.

EXCEPTIONAL MUTAGENICITY OF BAY REGION EPOXIDES OF BENZO(a)ANTHRACENE 3,4-DIHYDRODIOL – A.W. Wood, R.L. Chang, W. Levin, R.E. Lehr, M. Schaefer-Ridder, J.M. Karle, D.M. Jerina and A.H. Conney, Hoffmann-La Roche Inc., and NIAMDD

Since the diastereomeric 7,8-diol-9,10-epoxides of benzo(a)pyrene possess exceptional mutagenic and cytotoxic activity, we have synthesized six diol epoxides, two tetrahydroepoxides and the K-region arene oxide of benzo(a)anthracene (BA) and evaluated their mutagenic activity in bacterial and mammalian cells. The two diasteriomeric 1.2-epoxides of trans-BA 3.4-diol are 16 to 33 times more mutagenic to S. typhimurium strain TA 100 and 65 to 125 times more mutagenic to Chinese hamster V79 cells than are the diasteriomeric BA 8,9-epoxides. 1,2-Epoxyl-1,2,3,4-tetrahydro BA is 5 and 25 times more mutagenic than 3,4-epoxy-1,2,3,4-tetrahydro BA in TA 100 and V79 cells respectively. BA 5,6-oxide has less than 15% of the activity of any of the 1.2-eppxides in either cell system. These data, supported by metabolic activation studies and preliminary tumorigenicity studies with BA and its five possible vicinial trans dihydro-diols, support the hyposthesis that the carcinogenic activity of polycyclic hydrocarbons results from metabolic formation of extremely reactive benzo-ring diol epoxides in which the epoxide moiety forms part of the bay region of the polycyclic hydrocarbon.

Remaining abstracts from AACR papers will appear next week in *The Cancer Letter.*

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 NO1-CP-75919-69

Title: *Dietary patterns, nutritional assessment and cancer incidence of American Vegetarians*

Deadline: *July 18*

The objective of this project is to survey, examine, and evaluate the diet, nutritional status and cancer etiology of American vegetarians in an effort to determine the effect of diet and nutrition on cancer incidence among vegetarians. Dietary patterns among specified vegetarian groups will be recorded and nutrition intake assessed. Data on cancer incidence will be included in the survey and possible correlations will be analyzed. The survey will evaluate nutritional, dietary, metabolic, physiologic and socio-economic parameters. A report on the findings of the project will be produced.

RFP NO1-CP-75918-69

Title: *Evaluation of pharmacologic agents for the treatment of anorexia in the cancer patient*
Deadline: *July 18*

The objective of this project is to review the relevant literature, develop and validate one or more suitable animal models for cancer cachexia that occurs in humans, and test a variety of potential therapeutic substances for positive effects on food intakes. The contractor will be required to follow specific procedures in animal husbandry, diet composition and feeding, laboratory assays, and data recording and processing.

Contract Specialist for above two RFPs: Linda Waring
Carcinogenesis
301-427-7575

RFP NCI-CM-87157

Title: *Operation of an animal disease diagnostic laboratory*
Deadline: *July 15*

The successful offeror shall supply NCI with viruses, bacterial and parasitic profiles of rodents from the animal suppliers serving the Drug Screening Program. The importance of these services cannot be overemphasized since NCI will use these profiles to evaluate the technical ability of individual rodent suppliers.

The successful offeror will supply services, qualified personnel, material, equipment and facilities not otherwise provided by the government under the terms of the contract to perform the following procedures: (1) Gross physical observations including activity, alertness, condition of hair etc.; (2) necropsy with observations for gross lesions (followup histopathological observations when indicated); (3) culture of respiratory tract, (nasal passages through lungs), ear canal and intestinal tract for pathogenic microorganisms; (4) examination for ectoparasites and endoparasites, and (5) virus antibody determination.

It is recognized that offerors with the ability to perform this workscope will have varying areas of expertise. However, the successful proposal should reflect staff capability in overall rodent health diagnosis including viruses, bacteria and parasites. The principal investigator should have achieved professional recognition in one or more of these areas and of equal importance, he should have acquired sufficient practical experience to be able to evaluate the significance of diagnostic findings in concert with the project officer.

The principal investigator should be a veterinary pathologist or PhD in microbiology and devote 15% of his time to the project. It is anticipated that award will be for three years, incrementally funded.

Contracting Officer: D.M. Abbott
Cancer Treatment
301-427-7463

CONTRACT AWARDS

Title: Continuation of cervical cancer screening program
Contractor: Arkansas State Dept. of Health, $244,808.

Title: Technical support services of the Systems Planning Branch, OPPA/OD
Contractor: Mitre Corp., $266,307.

Title: An education program for the Tyler asbestos workers and their families
Contractor: Texas Chest Foundation, $150,000.

Title: Continuation of studies and investigations on endocrine therapy plus chemotherapy in patients with breast cancer
Contractor: Univ. of Minnesota, $90,200.

Title: Continuation of radiation therapy treatment research
Contractor: Mary Hitchcock Memorial Hospital, Hanover, N.H., $424,809.

SOLE SOURCE NEGOTIATIONS

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

Title: Curatorial preservation and development of reference-grade tumor viruses
Contractor: American Type Culture Collection, Rockville, Md.

Title: Breast Cancer Detection Demonstration Project, one year renewal
Contractors: Univ. of Michigan, Univ. of Pittsburg, Good Samaritan Hospital, Iowa Lutheran Hospital, Cancer Research Center, Rhode Island Hospital, Univ. of Southern California, Vanderbilt Univ., Emory Univ., Univ. of Kansas Medical Center, Stella and Charles Guttman Institute, Mountain State Tumor Institute, Univ. of Louisville, and Medical College of Wisconsin.

Title: Hormone markers for the detection and diagnosis of cancer
Contractor: Harbor General Hospital, Torrance, Calif.

Title: Mammography Training Program
Contractor: Univ. of Texas System Cancer Center, and New York Medical College.

The Cancer Letter—*Editor* JERRY D. BOYD

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