THE CANCER LETTER

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ADMINISTRATION'S FY 1981 BUDGET WOULD LEAVE GAPS, CURTAIL MANY PROGRAMS, WITHOUT NEW CUTS

Members of the congressional appropriations subcommittees and the House Health Subcommittee tried without much success to get NCI Acting Director Vincent DeVita to explain how he would spend any

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In Brief

NCI TO MOVE TODARO'S LAB TO FCRC; CINNAMYL ANTHRANILATE WAS CARCINOGENIC IN BIOASSAY

NCI'S LABORATORY of Viral Carcinogenesis, part of the Viral Oncology Program in the Div. of Cancer Cause & Prevention, will be moved to the Frederick Cancer Research Center within a few months. The lab, headed by George Todaro, includes sections for cell biology, immunology, viral leukemia and lymphoma, viral control, ultrastructural studies, tumor virus detection, viral pathology and clinical studies. The Viral Leukemia & Lymphoma section, which Todaro heads himself in addition to his lab chief responsibilities, is presently housed at Meloy Laboratories in suburban Virginia; the contract with Meloy will be phased out and the section moved to FCRC with the rest of the lab. Approximately 75 staff members will be involved. FCRC Director Michael Hanna said the scientific staff there is "very excited" about the prospect of working closely with Todaro and his scientists. . . . **CORRECTION**: Stephen Carter, director of the Northern California Cancer Program, was elected to the Assn. of Community Cancer Center board of directors, in addition to those reported in ***The Cancer Letter*** March 14. . . . **ALSO**: ***The Cancer Letter's*** account of actions by the Clearinghouse Data Evaluation/Risk Assessment Subgroup (March 14) erred in stating that the Carcinogenesis Testing Program report on the cinnamyl anthranilate bioassay said the compound was not carcinogenic. In fact, the report concluded it was carcinogenic, with significant increases in liver cancer in both sexes of mice and kidney and pancreatic cancer in male rats. The subgroup agreed with the program report. The compound is used as a grape and cherry flavoring agent in soft drinks, ice cream, baked goods and other foods. . . . **WHAT MAY BE** the final meeting of NCI's Cancer Control & Rehabilitation Advisory Committee is scheduled for May 5. When the reorganization is approved merging the Div. of Cancer Control & Rehabilitation into the new Div. of Centers, Community Activities & Resources, CCRAC will be replaced by a new Board of Scientific Counselors. . . . **BIRCH BAYH** received the annual award presented by the Assn. of Community Cancer Centers for "outstanding contributions to community cancer care." The award said Bayh was being recognized for "his personal involvement, commitment and national leadership on behalf of this nation's cancer patients". . . . **CARLO CROCE** has been appointed institute professor and associate director of the Wistar Institute.

BYPASS BUDGET: 45% R01 FUNDING, NO 7% SOLUTION FOR CENTER CORE GRANTS, P01s

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extra money Congress might give him above the President's FY 1981 budget request. When that didn't work, they tried also without success to encourage him to discuss the adverse impacts of maintaining the Cancer Program at the 1980 budget level.

DeVita believes in playing the game by the rules, and as the Administration's spokesman for the NCI budget request, he was under order not to permit himself to be led into any "budget busting" effort.

DeVita did play his ace in the hole—NCI's unique "bypass budget" which the National Cancer Act decrees it must submit to the White House without alteration by NIH or HEW. He was able to do that without being a budget buster only because the bypass budget is a public record.

Details of the bypass budget were not discussed at the congressional hearings; instead, DeVita was asked to submit it for the hearing record.

With the apparent determination developing in both the Administration and Congress to balance the 1981 budget, the issue could be what programs will NCI be able to salvage if the funding level is reduced below $1 billion, rather than what would NCI be able to do with $170 million more. The White House is expected to release details of its proposed $15 billion cut by mid-April. Congress is working on its own plan.

Cancer Program advocates may have a real fight on their hands just to save the $1 billion budget. However, they should be aware of just where the sacrifices will be made if that is all NCI ends up getting; severity of the sacrifices would be even more intense, of course, if there are any reductions from $1 billion.

The bypass budget presents most of the information on how NCI would spend its money at four levels: $900 million, $1 billion, $1.092 billion, and $1.17 billion. It does not spell out what the real impact would be if Congress appropriated all the money NCI said it could effectively spend—$1.17 billion, or $170 million more than requested in the President's budget—nor what the adverse impact would be at any level less than that.

Here are some of the implications of the 1981 budget at the $1 billion and $1.17 billion levels:

Traditional Investigator Initiated Research (R01s)

This has been called the highest priority category for NCI and NIH. The Administration and the congressional appropriations committees have agreed. NIH Director Donald Fredrickson has said this is the year when an all out effort will be made to achieve stability in support of individual investigators. All have acknowledged that basic research is the key to continued progress, and most (but not all) R01 grants are for basic research. The R01 grant pool will be the last place where cuts will be made.

It might come as a surprise to some, therefore, to learn that the money requested by the Administration for NCI R01 grants—$229 million—will fund only about 31 percent of approved competing grants, new and renewal. With the bypass budget, $262.8 million had been earmarked for R01s, which would permit funding of 45 percent of approved competing new and renewal grants.

After the National Cancer Act was passed in 1971, the surge of additional money enabled NCI to fund more than 50 percent of approved grants; one year it hit 61 percent. That percentage has steadily eroded, although the total amount of money for R01s has increased. The difference: increasing dollar amounts awarded, and a huge increase in the number of grant applications submitted and assigned to NCI.

Perhaps the single most important result expected from the National Cancer Act was the stimulation of interest in basic biological research which could provide the knowledge base required for further progress. That stimulation has occurred, yet 70 percent of the scientists whose research plans are approved in peer review will not be funded in 1981.

Further, the stability Fredrickson and the White House think they are providing is an illusion. With only 31 percent of approved grants being funded, the many excellent projects under way which fall in the next 20 percent will be cut off at the pockets. They have to be doing excellent work to rate in the top 50 percent, and they will be well into their studies, with people and facilities busily engaged. Without NCI funds, they will have to scramble around for scarce local funds or close down. That is stability?

The fierce competition to get into the top 30 percent will mean that only those new applications the study sections feel offer the best opportunity for success will have a chance of being funded. The risky, offbeat, innovative approaches will be left at the starting gate.

Cancer Centers

The President's budget has $66.4 million for center core grants, the same amount as in the current year; the bypass budget asked for $73 million.

There will be 34 cancer center core grants up for renewal in 1981. Those include 10 comprehensive centers—Alabama, Farber, Hopkins, Howard, M.D. Anderson, Michigan, Northwestern, Roswell Park, UCLA and Yale.

With $66.4 million, NCI will have to leave at least four and as many as six of the 34 renewals unfunded. New center grants competing successfully would cut into the money available, pushing up further the number of existing centers with no NCI support.

That is only part of the story. None of the competing renewals would be funded at levels recommended by peer review. The "seven percent solution" would have to be invoked—each would receive the 1980 amount plus a seven percent cost of living increase.

Pressure on the comprehensive centers is further increased by the requirement approved by the National Cancer Advisory Board last year that if a center loses its core grant, its right to continue with official NCI recognition as comprehensive would be questioned. Loss of core support for more than a year could lead to loss of comprehensive recognition.

Incredible pressures have been building on the core support budget during the last two to three years, as centers have completed their planning and early development stages and moved into full implementation. They have built their administrative staffs, recruited and/or trained new scientific staff, initiated and expanded basic research capabilities, started clinical trials, developed outreach programs. As their early grants have expired, they submit renewal applications based on their new ability to do the job Congress and NCI expects of them—only to learn that they won't get the money to do that job.

NCI Centers Program staff has been drawing up new core grant guidelines to deal with the problem. However they come out, more money will have to be made available to centers one way or another, or the demands made on them will have to be scaled back.

The extra $7 million NCI asked for core grants in the bypass budget would support all 34 centers, probably at full recommended levels, or an equivalent number of new and renewal grants.

Program Projects

The President's budget requested $101.5 million for program project grants (P01s); the bypass budget had $113.6 million. There will be 46 competing renewals in 1981, including five which were up this year but were left unfunded when their priority scores fell below the pay line.

Seven of the 46 are grants supported through the Div. of Cancer Cause & Prevention, with three in carcinogenesis, one each in epidemiology and nutrition, and two in biological carcinogenesis. Twelve are in the Div. of Cancer Biology & Diagnosis, with eight in immunology, three in tumor biology and one in diagnosis. Twenty-seven are in the Div. of Cancer Treatment, with 21 clinical and six preclinical.

Adding to the pressure on the program project budget are the new applications coming in from investigators who have been supported for years by contracts, for the most part in the virology and immunology programs. They have been told that their research henceforth will be supported only by grants, and many have decided to put together program project applications. They are competing very well, NCI staff members say.

The amount allocated to program projects is flexible and will depend to some extent on the final division of funds between R01s and P01s. That makes it difficult to determine how many of the competing grants will be funded. One thing is certain, however—unless a substantial increase is made, the seven percent solution will apply to program projects as well as to centers. At the $113.6 million level, they would be funded at the recommended levels.

Construction

When the budget started getting tighter about five years ago, NCI started reducing construction funds. That trend has continued, as the constfuction budget has been the favorite target of the budget cutters. The President's budget has only $1 million for construction grants, a devastating reduction from the bypass budget figure of $20 million.

The National Cancer Advisory Board last year asked that $25 million a year be budgeted for construction for at least six years, to enable cancer centers and other cancer research institutions to catch up on the horrendous backlog which has built up in recent years. Most of that is required to enable the institutions to upgrade their animal facilities and biohazard containment capabilities as required by federal regulations. Arthur Upton, then NCI director, agreed, and the bypass budget included the $20 million for grants plus another $5 million for contracts (construction of federal facilities and at the Frederick Cancer Research Center are grouped under contracts). But when the President's budget came out, those commitments had been forgotten.

Cooperative Groups

The Groups are getting $35 million in the current fiscal year; the President's budget would slash that to $32.8 million. NCI had requested $38 million in the bypass budget.

The $2.2 million reduction coupled with inflation would mean a severe cutback in clinical trials throughout the U.S. It is possible that at least one group would be phased out, although more likely that some individual members of Groups would lose their funding, with all the Groups surviving.

Several of the larger Groups are up for renewal this year, and that increases the severity fo the cuts since it means they probably would not be funded at recommended levels, further restricting their efforts to expand their multimodal capabilities.

The Cancer Letter has learned that NCI, at least before the situation was clouded by the budget balancing rage, intended to restore the Cooperative Group budget to at least the 1980 level, and probably a little bit more.

Treatment Research

NCI is spending $314.6 million this year on treatment research (this includes the Cooperative Group budget, clinical program projects and preclinical as well as clinical research). The bypass budget includes $364.2 million for treatment.

At the President's budget level of $318.4 million, DCT would be very limited on new initiatives, and would be able to continue most existing projects only at the 1980 level or less. Further development of the Biological Response Modifiers Program would be limited, although Congress could be in a mood to exert pressure for increases there regardless of the

total budget amount.

The budget bypass narrative says that at the President's level, "preclinical drug development will be continued, but the number of compounds entering the drug screen must be reduced by about 10 percent in order to maintain ongoing clinical trials, eventually decreasing the support of antitumor agents available for clinical evaluation."

Additional funds over the President's request would be used, the bypass budget narrative says, to:

–Develop new screens for biological response modifiers involving the development and use of a series of in vitro and in vivo model systems.

–Initiate studies on the prevention of the adverse toxic effects of antitumor agents including not only their acute effects on various organ systems (marrow, GI, liver, kidney, etc.), but also their chronic effects on the ovaries, testes and their mutagenic and carcinogenic potential.

–Expand existing clinical studies on biological response modifiers and initiate new trials, as recommended in the Mihich Committee report.

–Further establish systems for the management and analysis of phase 2 data on investigational new drugs for FDA regulatory requirements as well as proper drug development and resource decisions.

–Provide additional support in the areas of radiotherapy, surgery, pathology and statistics to facilitate the implementation of multimodality Cooperative Groups.

–Institute clinically controlled prospective studies on radiosensitizers and radioprotectors in selected cancers such as the esophagus and brain.

–Implement a coordinated local and systemic approach to the treatment of esophageal cancer involving surgery, radiotherapy, and chemotherapy.

–Further studies on anorexia pathogenesis, prevention and treatment on cachexia metabolism as well as studies on the potential role of specific dietary nutrient manipulation and regulating tumor growth.

Biology and Diagnosis

The President's request for the Div. of Cancer Biology & Diagnosis was $178.9 million; the bypass budget, $197.5 million. This includes the division's program projects, the immunology and virology programs, Breast Cancer Task Force, and the division's large intramural basic research operation.

Here are some of the research projects that would be supported with additional funds for the division, as described in the bypass budget:

–Study mechanisms by which cells of the immune system recognize chemical structures around normal and malignant cell surfaces.

–Expand studies on specific and nonspecific stimulation of the immune system using natural and synthetic materials.

–Emphasize studies of how metastatic cancer cells break down intercellular barriers during invasive migration.

–Develop methods of identifying specific genes which play a role in malignancy.

–Initiate studies to determine the role of hormones in cancer.

–Further explore the role of viruses and the immune system in modifying the carcinogenic process.

–Isolate and identify the human cell genes which are responsible for malignancy using recombinant DNA technology.

–Analyze newly discovered protein in blood which regulates the growth of normal cells, looking for factors capable of controlling the growth of cancer cells.

– Investigate the effects of cell membrane lipids and sugars on the growth and mobility of cancer cells.

–Expand the studies of genetic control of the immune response to tumors in animal models and in humans.

–Develop and produce short lived isotopes to be used in detection and diagnosis of cancer.

–Clinically evaluate devices to aid the passage of fiberoptic colonoscopes through the large bowel to improve its visual examination.

–Develop solid state x-ray image recorders to facilitate digitalization, data transmission, compact storage and rapid retrieval of x-ray records.

–Investigate charge transfer electroradiographic x-ray imaging.

–Standardize multidisciplinary diagnostic protocols according to the most useful and cost effective approaches.

–Develop automated techniques for identifying bladder cancer cells in urine along with preneoplastic mutants.

Cause and Prevention

The President's budget request for the Div. of Cancer Cause & Prevention was $288.2 million; the bypass budget, $317.6 million. This includes the division's program projects, NCI's contribution of $65 million to the National Toxicology Program, the division's carcinogenesis research projects, the Field Studies & Statistics Program, and the division's intramural research.

The bypass budget, which was finalized in late summer of 1979, comments that the National Toxicology Program would get under the President's budget funds only to continue the bioassays on chemicals already under test. An additional 50 would go on test under "enhancement level 1" (in which NCI would receive $90 million above the President's request); and another 50 would be added under the "enhancement level 2" or the final bypass budget request.

As it turned out, the budget approved by the White House and submitted to Congress in January lists the $65 million for NTP which is enough to add 100 compounds to those already on test. Obviously, the decision was made to give NTP the bypass level, the only NCI supported program so favored.

Here are some of the other projects DCCP would support if it had the extra money:

–Expand research in the area of radiation toxicology, including problems related to the late effects of radiation in humans and animals.

–Further the studies to inhibit or reverse tumorigenesis, ultimately preventing or reversing the malignant process.

–Initiate studies focusing on the development of chemopreventive agents more potent and less toxic than those now available.

–Conduct model studies on a variety of systems, employing promoters of many types to understand basic biological responses to promoters and their interaction with cells.

–Define cancer risk in populations subjected to low levels of ionizing radiation.

–Assess the role and mechanism of action of dietary components such as fiber in the carcinogenic process.

–Extend measurement of cancer incidence to populations not now covered in the search for factors associated with occurrence of various cancers.

–Initiate prospective epidemiologic studies of current cigarette smokers to identify characteristics associated with high risk for cancer.

Control and Rehabilitation

The Div. of Cancer Control & Rehabilitation is getting $69.6 million in 1980; the President's budget requested only $64.4 million for 1981, the only NCI division to suffer a major budget cut. The bypass budget had requested $78.9 million.

The termination of three of the Community Based Cancer Control Program contracts and reductions in the other three, if they are carried out, would probably save about $4 million. The rest of the reduction would come from other contracts which are expiring or winding down.

Here are some of the projects DCCR might fund if it could keep the money being saved by the phase outs and also pick up the rest of the money in the bypass budget:

–Develop a program to evaluate the effectiveness of school health education as it relates to cancer.

–Study the specific problems of cancer in the elderly and develop information of value to the physician who must deal with the cumulative effects of aging and its interaction with the cancer process.

–Develop specific programs in school health education as it relates to cancer. The target audience would include students from grade school to graduate school.

–Develop a set of patient management programs for special training of physicians and allied health professionals in cancer patient care.

Manpower Training

The President's budget requested $26.6 million for institutional training grants and individual fellowships, $4.6 million less than the current year total. The bypass budget had requested $34.9 million.

NCI awarded a great number of five year institutional training grants in 1975. They are up for renewal this year, and most if not all will be renewed.

That means there will be a big shift of money from competing to noncompeting next year–$11 million to $19 million, and very little if any available for new awards. Reviewers are cutting back on amounts requested, especially at those institutions which did not fill all trainee slots available in their previous grants. The number of individual training grant applications has been declining, probably due to the low stipends–those were increased this year, but so far it does not appear that will stimulate more applications. The funding level has been high, with the cutoff at 280 score in 1979, and probably will remain the same this year.

Organ Site

The four Organ Site Programs–large bowel, prostate, bladder, and pancreas–are getting $17.2 million this year. The President's budget cut that to $16.5 million, and the bypass budget set the figure at $20.7 million.

The programs involve the support of investigator initiated research through grants, which are administered through the four headquarters, each of which is itself supported with a grant. The reduction in funds would mean a reduction in the number of grants awarded. NCI estimates that with the $16.5 million, 148 grants will be supported, down from 169 awarded this year and 190 in 1979.

Of the 148 total grants to be supported in 1981, 45 will be competing awards, new and renewal, out of 123 applications approved by peer review. One third of approved applications were funded this year.

Grants and funds in the 1980 fiscal year are distributed as follows:

Large bowel, 53 grants, $5.692 million; prostate, 45 grants, $4.73 million; bladder, 44 grants, $5.039 million; pancreas, 27 grants, $1.8 million.

GRIESEMER WILL LEAVE NTP TO RETURN TO OAK RIDGE AS HEAD OF BIOLOGY DIV.

Richard Griesemer, who took over NCI's Carcinogenesis Testing Program in the dark days of the backlog and guided it through its transition into the key element of the National Toxicology Program, will leave this summer to return to Oak Ridge National Laboratory.

Griesemer has been on extended leave from Union Carbide, which contracts with the government for the operation of the Oak Ridge facility, for three years. When he left, he was head of the Cancer & Toxicology Group. He will return with a promotion as director of the Biology Division.

Under Griesemer's direction, the backlog of more than 200 reports on completed bioassays was cleared up and the reports published. In 1978, the program was integrated into the hybrid NTP, which included

elements from FDA, National Institute of Occupational Safety & Health, and National Institute of Environmental Health Sciences. Griesemer was named NTP associate director, under NIEHS Director David Rall.

As NTP evolved, it became apparent that NCI would have to loosen its hold on the carcinogenesis portion of it despite the fact that NCI funds were making up the largest share of NTP's support. The program is getting $45 million this year from NCI and is scheduled to receive $65 million in 1981.

Griesemer's operation was removed from the Div. of Cancer Cause & Prevention last year and placed directly under the NCI director. In effect, this has tightened Rall's grip on the program.

The decision to move most of carcinogenesis testing to the NIEHS campus in Research Triangle Park, N.C. (*The Cancer Letter*, Feb. 22) further removes it from NCI ties.

Griesemer's role had to be a difficult one. Most NIH executives consider themselves fortunate if they get along with one institute director; Griesemer had to contend with two, along with other senior staff of two institutes as well as the developing bureaucracy of NTP itself.

Rumors have been circulating of behind the scenes jurisdictional and, possibly, personality clashes between the NCI and NIEHS contingents. Speculation developed that Griesemer is leaving because of those clashes, and because he had not been given all the authority he felt he needed. ***The Cancer Letter*** was told, however, that Griesemer's relations with Rall and his staff have been good. Griesemer declined comment, except to say he was leaving "because I have a better offer." He will start his new job July 1.

INVESTIGATOR SAYS DHEA MAY PREVENT BREAST CANCER, PROMOTE WEIGHT LOSS

A steroid that not only prevents breast cancer and possibly other tumors but also is an effective weight reducing agent?

That miracle substance might be the adrenal steroid dehydroepiandrosterone (DHEA), according to Arthur Schwartz, associate professor of microbiology at Fels Research Institute, Temple Univ. Schwartz discussed his research with DHEA at the annual American Cancer Society Science Writers Seminar this week:

The sulfated form of dehydroepiandrosterone (DHEA) is a major adrenal secretory product in men and women. Approximately 99 percent of the plasma form of this steroid is sulfated, while the remainder is unconjugated DHEA. The plasma concentration of the sulfated form of DHEA exceeds that of any other steroid hormone, yet its biological role is unknown. After the second decade of life, the blood level of this steroid begins to decline, reaching levels in the very old of about five percent of its maximum value.

Most investigators refer to the conjugated form as DHEA-sulfate. According to the late Dr. Oertel, the sulfated form of the hormone found in human plasma is DHEA-sulfatide—the DHEA ester of sulfatidic acid —which must be isolated under gentle conditions, since it readily decomposes to DHEA-sulfate.

It is well documented that DHEA is a potent noncompetitive inhibitor of mammalian glucose-6-phosphate dehydrogenase. DHEA-sulfate, however, has essentially no inhibitory activity against this enzyme. According to Oertel, the synthetically prepared DHEA-sulfatide is a substantially more potent inhibitor of human glucose-6-phosphate dehydrogenase in vitro than is DHEA. At a concentration of 2×10^{-6}M (the approximate plasma concentration of DHEA-sulfatide in humans) glucose-6-phosphate dehydrogenase is inhibited in vitro by about 60 percent. This has led to the very reasonable hypothesis that human glucose-6-phosphate dehydrogenase may be physiologically regulated by DHEA-sulfatide.

We have prepared DHEA-sulfatide and have confirmed the observation of Oertel that this substance is a more potent inhibitor of human glucose-6-phosphate dehydrogenase than is DHEA. We have also confirmed that DHEA-sulfatide is a labile material which readily decomposes to DHEA-sulfate. Currently we are attempting to corroborate Oertel's observation that DHEA-sulfatide represents the predominant form of DHEA in human plasma. It must be emphasized, however, that until this latter observation is substantiated, we cannot be certain that DHEA-sulfatide is the predominant form of the steroid in plasma.

On the basis of a 10-year prospective study involving over 5,000 apparently healthy women, Bulbrook et al. concluded that women with subnormal excretory rates of androsterone and etiocholanolone experience an increased risk of breast cancer. Urinary androsterone and eiocholanolone are derived primarily from DHEA and DHEA-sulfate (possibly DHEA-sulfatide), and subnormal excretory rates of these two steroids reflect low plasma concentrations of DHEA and its sulfate.

In 1977 Yen et al. reported that long term treatment of mice with DHEA very significantly inhibits weight gain without suppressing appetite. The authors reported reduced lipogenesis rates in the steroid treated animals. They speculated that DHEA might play a physiological role in weight regulation by inhibiting glucose-6-phosphate dehydrogenase, thereby limiting the supply of NADPH available for fatty acid synthesis.

It is well documented in laboratory mice and rats that reducing weight gain by food restriction inhibits cancer formation and delays the rate of aging. This led us to speculate that long term DHEA treatment, which has a marked anti-obesity effect, might also have an anticarcinogenic effect. We found that long term treatment of C3H mice with DHEA, in addition to reducing weight gain without suppressing appetite, markedly inhibits the development of spontaneous

breast cancer and delays the rate of aging.

We now have evidence of a very probable mechanism by which long term DHEA treatment inhibits breast cancer formation. These new data also make it very likely that the prophylactic value of DHEA is not specific to breast cancer and will apply to cancer in other organs.

Carcinogenesis is a two-stage process involving initiation and promotion. Initiation refers to the events immediately following carcinogen application, i.e. carcinogen activation and binding of the activated carcinogen to DNA. If mice are initiated by a single topical application of a carcinogen to the skin and are then treated for prolonged periods with croton oil, (or the active ingredients in croton oil, which have been identified as phorbol esters), there is a marked enhancement in the rate of appearance of tumors. The phorbol esters alone are noncarcinogens and are referred to as tumor promoters.

When phorbol esters are applied to mouse skin, they induce marked epidermal hyperplasia within 48 hours. Apparently this hyperplasia acts on the initiated cells, and by some unknown mechanism, increases their likelihood of developing into tumors. The degree of stimulation of epidermal hyperplasia can be quantitated by injecting the animals with ^{3}H-thymidine and measuring rhe rate of DNA synthesis, a necessary precursor to cell hyperplasia. The application of 10 μg of the phorbol ester, TPA, to mouse skin produces, in approximately 20 hours, a 2 to 3 x stimulation in the rate of DNA synthesis, which can be readily quantitated.

We have found that a single oral or i.p. dose of DHEA (at levels which, on long term treatment, inhibited breast cancer development) immediately before the application of a tumor promoter to mouse skin, prevents the stimulation in the rate of DNA synthesis normally observed. Injected DHEA-sulfatide is also active in antagonizing the action of the tumor promoter, while DHEA-sulfate shows no apparent activity.

Very probably inhibition of glucose-6-phosphate dehydrogenase by DHEA explains its ability to antagonize the action of the tumor promoter. Glucose-6-phosphate dehydrogenase is the rate controlling enzyme for the pentose-phosphate pathway in glucose metabolism, which produces ribose, a necessary precursor for DNA and RNA synthesis.

Since a promotion phase probably exists for carcinogenesis in most, if not all, organs, and since DHEA inhibits glucose-6-phosphate dehydrogenase from many different organs, it is reasonable to assume that long term DHEA treatment may inhibit cancer formation in sites other than breast.

Epstein-Barr virus (EBV), a member of the herpesvirus group, is a human pathogen which has been demonstrated to be the etiological agent for infectious mononucleosis. EBV infection has also been associated, through epidemiological, serological, and molecular means, with several malignant orders, including African Burkitt's lymphoma and nasopharyngeal carcinoma. In collaboration with Dr. Henderson of the microbiology department at Temple, we have found that DHEA prevents EBV induced transformation in human umbilical cord leukocytes.

Although the mechanism by which EBV induces transformation is unknown, there is some evidence that a promotion phase may exist. Whatever the mechanism, DHEA does prevent transformation of human cells by a putative human carcinogen (i.e. EBV).

In conjunction with Daniel Swern and Magid Abou-Gharbia of the chemistry department at Temple we have prepared a derivative of DHEA that is about 50 times as potent as the parent steroid in inhibiting mouse and human red blood cell glucose-6-phosphate dehydrogenase. The DHEA analog is also about 50 times as active in antagonizing the TPA-induced stimulation in the rate of DNA synthesis in mouse skin. A dose of 0.4 mg/kg i.p. of the derivative is about as active as 20 mg/kg of DHEA.

In addition, the DHEA analog is at least 20 times as potent as DHEA in preventing transformation of human cord leukocytes by EBV.

The correlation between the increased activity of the DHEA analog in inhibiting glucose-6-phosphate dehydrogenase and its increased activity in blocking the action of the tumor promotor on mouse skin as well as its enhanced capacity to prevent transformation of human leukocytes by EBV, suggests that inhibition of glucose-6-phosphate dehydrogenase may be critical to the antitumor promoting effect of these steroids. As mentioned previously, glucose-6-phosphate dehydrogenase is the rate controlling enzyme for the pentose-phosphate pathway in glucose metabolism, which produces ribose, a necessary precursor to DNA and RNA synthesis.

The DHEA analog is a potent antitumor promoter that may have value as a drug in the prophylaxis of cancer.

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR APRIL AND MAY

Cause & Prevention Scientific Review Committee—April 3, NIH Bldg 31 Rm 9, open 9–9:30 a.m.
Biometry & Epidemiology Review Committee—April 8, Landow Bldg Rm E, open 8:30–9 a.m.
Diagnosis & Treatment of Neoplastic Disorders: Medical, Surgical & Radiotherapeutic Aspects—April 10-11, Johns Hopkins Univ., registration required—phone 301-955-3636.
Clinical Cytopathology for Pathologists—April 14-25, Johns Hopkins postgraduate course.
Hormone Manipulation in the Therapy of Human Malignant Disease—April 15-16, Chicago Drake Hotel, sponsored by Rush Cancer Center.
National Cancer Advisory Board Working Group on Board Activities & Agenda—April 17, NIH Bldg 31 Rm 9, 1 p.m., open.
Cancer Prevention & Detection—April 17-19, Chicago Palmer House, American Cancer Society.

Clearinghouse Chemical Selection Subgroup–April 23, NIH Bldg 31 Rm 7, 9 a.m., open.
Endocrinology–April 24, Roswell Park continuing education in oncology.
Diagnostic Research Advisory Group–April 24-25, NIH Bldg 31 Rm 10, 9 a.m.–5 p.m. first day; 8:30 a.m.–adjournment second day, all open.
Physiological, Psychological & Sociological Aspects of Cancer–April 25, Roswell Park continuing education in oncology (nursing seminar).
Second International Conference on Immunotherapy of Cancer: Present Status of Trials in Man–April 28-30, NIH Masur Auditorium, open.
Div. of Cancer Cause & Prevention Board of Scientific Counselors–May 1-2, NIH Bldg 31 Rm 9, open May 2, 9 a.m.–5 p.m.
Hospice–May 2, Roswell Park continuing education in oncology.
International Conference on Cancer Among Blacks–May 5-6, Roswell Park Memorial Institute, contact Curtis Mettlin.
Cancer Control & Rehabilitation Advisory Committee–May 5, Blair Bldg Rm 110, 9 a.m., open.
Cancer Research Manpower Review Committee–May 8-10, Landow Bldg Rm A, open May 10, 9–10 a.m.
Recent Advances in the Diagnosis & Management of Breast Cancer–May 8, Roswell Park continuing education in oncology.
Clinical Trials Committee–May 13-14, NIH Bldg 31 Rm 9, open May 13, 9–9:30 a.m.
Multidisciplinary Advances in Adolescent Oncology–May 16, Roswell Park continuing education in oncology.
Div. of Cancer Biology & Diagnosis Board of Scientific Counselors–May 16-17, NIH Bldg 31 Rm 7, open May 16, 9 a.m.–5 p.m.
National Cancer Advisory Board–May 19-21, NIH Bldg 31 Rm 6, open May 19, 8:30 a.m.–3:30 p.m.; open May 20, 9 a.m.–adjournment at Frederick Cancer Research Center; closed May 21.
EORTC Symposium on Progress in Treatment of Gastrointestinal Tumors–May 22-23, Brussels.
Cancer Research Manpower Review Committee–May 25, San Diego Kings Inn, open 9–10 a.m.
American Society of Clinical Oncology–May 26-27, 16th annual meeting, San Diego Town & Country Hotel.
American Assn. for Cancer Research–May 28-31, 71st annual meeting, San Diego Town & Country Hotel.
Oncology Nursing Society–May 28-30, 5th annual meeting, San Diego Sheraton Harbor Island.

NCI CONTRACT AWARDS

Title: Seventeen additional alteration/renovation/-maintenance/upgrading projects necessary to support the research program being conducted at Frederick Cancer Research Center
Contractor: Litton Bionetics, $155,408

Title: Breast Cancer Detection Demonstration Project, six month extension
Contractor: Georgetown Univ., $50,036

Title: Breast Cancer Detection Demonstration Project, long term followup
Contractor: Univ. of Kansas Medical Center, $389,166.

Title: Facility for supplying immune related cell lines
Contractor: Salk Institute, $120,710.

RFPs AVAILABLE

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

RFP N01–CP-05630-70

Title: *In vitro evaluation of chemical candidates for in vivo testing*
Deadline: *May 15*

NCI is a major source of chemical candidates for testing by the National Toxicology Program. In many cases in reviewing certain compounds or classes of compounds, in vitro data could facilitate the process of chemical selection. The contractor will be required to test up to 75 compounds per year in one or both of two assays, the Ames bacterial mutagenicity system and either the mouse lymphoma system or an acceptable mammalian cell system alternative.

Five salmonella strains will be used in all tests. The Ames assay and the mouse lymphoma assay will be run with and without activation–rat and hamster for the Ames and rat only for the lymphoma. All tests will be repeated as a check and each accompanied by positive controls as well as by solvent or negative controls and bacterial checks as required.

The Ames assay will have four dose levels and will be reported on in no more than 20 working days; the lymphoma assay will have five levels and will be reported on in no more than 40 working days. If a mammalian cell replacement is selected for the lymphoma system, suitable requirements will be designed.

Reports on each compound will be of two kinds, a completed computer input (NCI supplies) and an abbreviated narrative of a format authorized by NCI. An incrementally funded three-year contract is anticipated.

Contract Specialist: Lynn Greenfield
Carcinogenesis
427-8764

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