THE CANCER LETTER

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HOW NCI WOULD APPORTION NEW ROUND OF BUDGET CUTS – 1980 $17 MILLION, 1981 $42.7 MILLION

NCI Acting Director Vincent DeVita and the institute's division directors and other senior executives are in the midst of agonizing over

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In Brief

DEADLINE JUNE 1 FOR NEW ACS PREVENTION AWARDS; MONEY AVAILABLE TO FUND FIVE MORE

THIRTEEN APPLICATIONS for the new American Cancer Society institutional grant program in cause and prevention have been submitted; the deadline is June 1. Frank Rauscher, ACS senior vice president for research, said he has raised $3.5 million so far in the special donors program to fund the new awards. That would fund five awards, and Rauscher would like to be able to support five more. At least 80 institutions have indicated they plan to compete. Mount Sinai School of Medicine received the first award, to collect and analyze information and respond to questions from the public and Congress (***The Cancer Letter***, Nov. 16, 1979). . . . **CORRECTION**: First notice from NCI to three Community Based Cancer Control Programs that their contracts would be terminated did not say terminations would be effective March 31, as reported in ***The Cancer Letter*** (March 21). The termination date was originally established as July 31, NCI staff members say. That date remains in effect, although subject to modification by the National Cancer Advisory Board at its May meeting. . . . **HOWARD SKIPPER**, who won the 1980 Bristol-Myers $25,000 award for distinguished achievement in cancer research, "bridged the gap between basic and clinical research with his discovery of the basic principles for prescribing doses and schedules of anticancer drugs that permit the drugs to kill malignant cells faster than they can grow back." Alan Sartorelli, chairman of the Yale department of pharmacology, made that comment at the award ceremony last week. Sartorelli was chairman of the award selection committee. Skipper is president of Southern Research Institute and director of the Kettering-Meyer Laboratory. . . . **WORKSHOP ON CULTURING** human mammary epithelial cells will be conducted by the Experimental Biology Working Group of the Breast Cancer Task Force April 22-23. The meetings will be in the NIH Bldg 31 Room 6, 8:30 a.m.--5 p.m., all open. Contact Chester Piczak, 301-496-6718. . . . **JOINT MEETING** of the Society of Surgical Oncology and the Society of Head and Neck Surgeons will be held in San Francisco May 13-17. Annual James Ewing Memorial Lecture will be presented by Arthur Hollet; the Hayes Martin Lecture by Condit Moore; the Lucy Wortham James Clinical Award will be presented to George Higgins and the Research Award to Elwood Jensen; and the Society of H & N Surgeons talk by Robert Chambers. Contact Robert Schweitzer at the Univ. of California School of Medicine.

NTP CUT OF $20 MILLION PROPOSED FOR 1981; CHOP PROBABLY NOT AFFECTED

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decisions on where the $17 million cuts from the 1980 budget and the $42.7 million in the 1981 fiscal year budget, as ordered by the White House last week.

Final decisions probably will not be made until the fate of the 1980 recision request and the amount for NCI in the 1981 appropriations bill are known. Even then, changes could be made as priorities change and the impact of various cost cutting measures becomes more clear. But here is how DeVita and his staff would apportion the cuts, if they had to do it today:

The $17 million recision

* Research grants—$200,000 from career awards, $300,000 from the organ site programs, $500,000 from clinical education grants.
* Research and development contracts—$8 million cut, including $1 million from the National Toxicology Program.
* Construction grants—$2 million reduction.
* Cancer control—$5 million reduction.
* Intramural research—$500,000 down.
* Direct operations—$500,000 down.

Apportioned by research thrust, the 1980 recision would take $4.5 million from cause and prevention, $600,000 from detection and diagnosis, $3.4 million from treatment, $700,000 from biology, $700,000 from manpower development, and $5.1 million from cancer control (differs from the $5 million shown above because it includes overhead).

Cutting $17 million this late in the fiscal year is especially difficult, since a major portion of NCI's $1 billion appropriation has already been committed. It is even more difficult considering the restriction against making any cuts against traditional (R01) grants, program projects and young investigator awards. There are some programs which simply cannot be cut without risking long term, permanent damage, such as the Cooperative Groups and cancer center core support.

None of the 1980 recision would come from the budgets for the groups or center core grants.

FY 1981 reduction of $42.7 million

* Research grants—$300,000 from career awards, $700,000 from organ site programs, and $2 million from clinical education.
* R & D contracts—$34 million, including $20 million from the National Toxicology Program, the entire additional amount over the 1980 budget NTP was to get from NCI in the original White House request for 1981.
* Cancer control—$3.1 million, for a cut from the original 1980 budget of more than $8 million.
* Intramural research—$1.5 million reduction.
* Direct operations—$1.1 million reduction.

Again, Cooperative Groups and center core grants would not suffer cuts from the original 1981 request.

Construction grants were not cut again because the original request had only $1 million in the first place, practically wiping out that program.

The new 1981 cuts apportioned by research thrust would take $28.2 million from cause and prevention (including the $20 million from NTP), $1.7 million from detection and diagnosis, $5.8 million from treatment, $1.4 million from biology, $2.3 million from manpower development, and $3.3 million from cancer control.

The impact in terms of numbers of awards eliminated:

—Manpower development down five career awards in 1980, nine more in 1981, down five in clinical education in 1980 and 16 in 1981.

—Organ site—down three awards in [illegible], nine more in 1981.

—Construction—down two to three awards in [illegible]

The cuts in intramural research and in clinical operations will be made by "hard tightening" and by not filling many positions as they become vacant. Hard tightening, staff members said, includes cancellations and delays in purchase of some supplies and equipment, reductions, delays or abandoning some research support contracts. DeVita also hopes his plan for moving and consolidating some NCI offices now scattered throughout four rented buildings in Bethesda and Silver Spring will result in some savings.

The long awaited reorganization, still on HEW Secretary Patricia Harris' desk at last word, is also expected to yield some cost reductions.

The impact of the recision and new 1981 cuts on cancer control is being evaluated by William Terry, acting director of the Div. of Cancer Control & Rehabilitation, and his staff. It had seemed bleak enough with the original $5 million reduction in the President's 1981 budget. Moving that cut up a year and taking away another $5 million for 1981 is adding insult to injury.

DCCR's major new initiative in 1980—the Community Hospital Oncology Program—would seem to be a potential victim of the new reductions. However, NCI considers CHOP a high priority program, and it it not likely to be eliminated or even reduced substantially.

CHOP may be delayed, with the first awards not being made until well after the 1981 fiscal year has started. The delay, if it happens, will be due to problems in review of the many proposals rather than to budget considerations. The original review has been completed, but the new program has generated many questions on the part of DCCR staff which had to be submitted to applicants and proposals reviewed again after the responses come in. The lengthy process will require several more months.

Cancer control grants are not among those protected in the Administration's effort to "stabilize" investigator initiated research. Control grants are

R18s, and only R01s, P01s, and R23s are protected from the latest round of cuts.

NCI's R & D contracts will bear the largest burden of the cuts, with $8 million in 1980 and $34 million in 1981. That includes $21 million proposed to be sliced from NTP (see below). The remaining could come from:

* Speed up in the already planned phaseout of virology and immunology contracts.
* Renegotiation of some contracts, reducing some aspects, delaying others.
* Putting off until FY 1982 some new contract supported clinical trials, and other contract research.

Another potentially vulnerable new initiative is the Biological Response Modifier Program. This could be touchy, because some congressmen have already criticized NCI for not spending enough in that area, yet it could be one of the easiest to cut, at least in 1980. Most of the money earmarked for interferon purchase could be withheld in 1980 and the substantial new procurements made with 1981 funds, without causing any significant delays. Other development work in the program also could be stretched out without harm.

This new flurry of frantic budget cutting may well come to nothing. Congress does not seem disposed to make such drastic immediate cuts in health programs as proposed in the 1980 recision. Best guess for now is that there will be no recision for NCI in 1980. On the other side, while it also does not seem likley that Congress will go along with the $42 million reduction proposed for 1981, neither does the prospect seem promising for getting any money above the $1 billion originally requested for 1981.

BUDGET CUTS WOULD HAVE MAJOR IMPACT ON NTP GOALS; REPORT REVIEW PLANNED

The proposed 1980 recision and 1981 reduction in the National Toxicology Program budget would have a major impact on the program's plan to reach a level of 100 new compounds going on test each year.

It is highly unlikely that Congress will go along with the cuts. The House HEW Appropriations Subcommittee, with Congressman David Obey a strong proponent of increased carcinogenesis testing, in all probability will put the $20 million addition to NCI's NTP contribution back into the 1981 budget, either adding that to the total amount or demanding that NCI switch it from other programs.

Nor is Congress going to swallow the Administration's massive recision request from 1981 health appropriations, which includes $1 million sliced from NTP.

That $1 million loss probably would not harm NTP very much, especially since the program still does not have the authority to fill the 28 new positions mandated by Congress. "I'm more concerned about what will happen down the road," NTP Director David Rall told *The Cancer Letter* this week. "It doesn't cost much money to start testing a compound. It starts getting expensive later."

The White House finally has authorized 25 of the new positions, but right now that is academic—the governmentwide freeze on new hiring applies to NTP and every other federal agency. "It will make it tough on us if we don't get at least some of those positions filled," Rall said. He has been given some assurance that an exception will be made for NTP, permitting him to hire a few new people.

Rall said he did not yet know how many new compounds will go on test in the current fiscal year; 75 had been the goal, before the recision request. If the $20 million cut for 1981 stands, that could reduce by half the number of compounds added to the program next year.

The NTP Board of Scientific Counselors met this week, primarily to start developing a mechanism to replace the Clearinghouse function in providing peer review of program reports on compounds which have been tested. The Clearinghouse on Environmental Carcinogens charter expires next month and will not be renewed.

Board Chairman Norton Nelson had previously appointed a subcommittee with himself as chairman to work on the problem of peer review and release of data. James Huff, NTP senior toxicologist, presented the staff's proposal for external peer review of reports to the Board: contract with the appropriate professional societies to review the various aspects of the reports.

Rall suggested that the new system might have "a mixed option—the routine reports would have the professional society review. Any potentially fascinating or controversial aspects would come back to this Board, critical issues that might need further massaging."

Rall acknowledged that establishing contracts with the professional societies would "take months. . . Up to a year and a half."

Meanwhile, Nelson said, "products are continuing to roll off the line. I foresee a situation with the Clearinghouse machinery dismantled and reports coming in before a replacement has been designed. Should we take interim action, establish a standing subcommittee (to do the peer review), which could be terminated when a substitute is available? Or we could continue the subcommittee as well as contract with the professional societies and have the mixed option."

Rall suggested the review could be conducted by mail or phone, instead of a meeting. "If we have meetings, they have to be open."

"I prefer the open meeting," Nelson said. The format developed by the Clearinghouse Data Evaluation/Risk Assessment Subgroup, with a primary and a secondary reviewer for each report, was acceptable, he said. "Each would have a short statement prepared, and it would be discussed around the table at a

meeting of the Board of Scientific Counselors."

Program Associate Director Richard Griesemer said that reports on 10 compounds would be ready for review by the end of June.

The Board authorized Nelson to establish an ad hoc report review panel, to include members of the Board and consultants.

Rall commented that "it might be useful to go through the process once" before a permanent arrangement is established.

"If the process is found unsatisfactory, would the 10 compounds be reviewed again?" asked Board member Curtis Harper.

"The process will not be found unsatisfactory," Rall decreed.

The Clearinghouse included representatives of organized labor, public interest groups and industry, and those groups participated—often vociferously—in the review of reports. The NTP Board is made up entirely of scientists.

Nelson told *The Cancer Letter* after the meeting that "we still have to decide" whether the new peer review will be limited to scientists or will include the other interested groups. He said, "We would expect the action to be the same as that taken by the Clearinghouse—yes or no on agreeing with the conclusions of the reports," as well as whether the compound posed a potential carcinogenic threat to humans.

The Board agreed to meet in Bethesda June 27-28 for the peer review session. A date in July was rejected when both Nelson and Rall insisted that Griesemer be available for the meeting. He starts his new job at Oak Ridge July 1 and had planned to take a vacation prior to leaving NTP.

DCT BOARD OKAYS NEW SURGERY RFA, TO CONSIDER SUPPORT FOR 30 CENTERS

The NCI Div. of Cancer Treatment Board of Scientific Counselors has approved issuing a new request for applications in surgical oncology research similar to the one last year which resulted in funding 11 surgical oncology grants at a cost of about $1 million a year. No dollar amount was suggested by the Board for the new round; issue date of the RFA will depend on availability of funds, which might delay it until the 1982 fiscal year.

The Board approved a motion establishing a formal standing subcommittee, the Surgical Oncology Coordinating Subcommittee, with Board member Walter Lawrence as chairman. Lawrence is director of the Medical College of Virginia/Virginia Commonwealth Univ. Cancer Center and is current president of the Society of Surgical Oncology. Board member E. Carmack Holmes, UCLA professor of surgery, is also a member of the subcommittee.

The Board also approved the concept of providing more funds for supporting advanced training in surgical oncology research, in amounts "commensurate with funds available in the budget." Again, no time schedule was established.

Lawrence presented a preliminary report on the workshop on surgical oncology research planning held last month in Chicago, supported by NCI and the American Cancer Society. Workshop Chairman Donald Morton is preparing a detailed report, but Lawrence discussed the workshop recommendations, which include NCI support for as many as 30 new surgical oncology research programs or centers at a cost of about $100,000 a year each.

The Board decided to delay until its fall meeting any action on that recommendation and on workshop recommendations on associated training programs and establishment of a new peer review group to review the applications.

Lawrence's report:

In October 1978, Dr. Vincent DeVita, director of DCT, requested Dr. Walter Lawrence Jr. to initiate a subcommittee of the Board of Scientific Counselors to study means for enhancing participation of the surgical oncology community in the research thrust of the National Cancer Program. The steps that have been taken since that time to analyze the problem and develop initial recommendations can be summarized as follows:

1. As an initial step in this process, Dr. LaSalle Leffall, then president of the Society of Surgical Oncology, established a Surgical Oncology Manpower and Government Relations Committee at the request of Dr. Lawrence who was then serving as president-elect of the SSO in addition to his role on the Board of Scientific Counselors. This committee established in late 1978 included Dr. Lawrence as well as other appropriate leadership members of this society and Dr. Donald Morton was appointed chairman. The tentative conclusions of the initial meeting of this committee in December 1978 on the basis of data available at that time were:

a. There are too few surgical oncologists overall and too few active investigators in surgical oncology to provide the necessary support to the national effort in cancer research, cancer education, and cancer patient care.

b. It was concluded that this deficiency was probably due to a relative lack of appropriate training and funding opportunities to recruit young surgeons into this discipline in academic centers.

c. Additional evaluation and planning was required to allow recommendations for correcting these perceived deficiencies.

d. A workshop for planning in surgical oncology research should be sponsored by the SSO to evaluate and develop preliminary plans for the surgical oncology thrust within the national cancer effort.

2. To respond to the recommendation that a workshop in surgical oncology research planning should be instituted, Dr. Morton as chairman of the above SSO committee and Drs. Lawrence and Holmes

of the Board prepared an application to NCI and the American Cancer Society for a surgical oncology research planning workshop which was subsequently funded by both of these agencies. Dr. Morton was then the principal investigator of this application with Drs. Lawrence and Holmes of the Board of Scientific Counselors and members of the Manpower and Government Relations Committee of the SSO serving as the planning committee. The stated purposes of this workshop were to evaluate the problem on the basis of data obtained during the planning process, develop an outline of research objectives specifically relevant to surgical participation in the National Cancer Program, and to develop additional recommendations for the long-range process needed for implementation of surgical oncology research.

3. In view of the assumption that the university surgical community is a key to the effective participation of surgical oncology in the overall cancer effort, a survey of cancer research and training efforts in 123 university departments of surgery in the United States was performed between July 1979 and February 1980. The data obtained in this survey and those data from the NCI sponsored Workshop on Graduate Education in Surgical Oncology (September 1978) were utilized as a data base for the Surgical Oncology Research Planning Workshop that was subsequently held in Chicago March 12-15, 1980.

4. The Surgical Oncology Research Planning Workshop included a group of national leaders in general surgical oncology, surgical oncologists from the surgical specialties and nonsurgical oncologists who were leaders in their respective fields. This meeting addressed the problems revealed by the planning process described, defined potential areas for increased and effective activity in surgical oncology research on all fronts, and made recommendations for action by both the surgical oncology community and the NCI that were considered to provide some solutions to the problems described. A detailed formal report of the observations, conclusions, and recommendations of this workshop is in the process of preparation for transmittal to the agencies funding this activity (NCI and ACS) as well as the oncologic community, but a brief summary of the outcome of the workshop is included in this report. There was a sincere hope on the part of all of the participants that some initial actions would be taken at the March 1980 meeting of the Board of Scientific Counselors as a response to the major recommendations made.

5. General Findings and Conclusions of Surgical Oncology Research Workshop (March 1980)

There were a number of positive consensus items developed:

a. A major problem at present is a significant manpower deficit of general and specialty surgical oncologists at the university medical center and cancer center level (approximately 150) as well as at the community level (1,500-2,000).

b. The development of a critical mass of leaders in surgical oncology research needs to be a national priority in order to establish stronger support of the current national cancer research effort as well as providing a cadre for future needs in cancer research in the area of surgical oncology.

c. Training programs in surgical oncology research are extremely limited in number and scope, and a mechanism for expansion of this activity is a basic national need from the standpoint of the entire cancer research program.

d. There are too few surgical oncologists actively involved in the ongoing assessment and planning for future needs in oncology as well as the review of projects for funding by NCI and other agencies due specifically to observation "a". Although partial correction of this deficiency may well be achieved by organizing current surgical oncology manpower and educating them in the details of the review process, the ultimate solution of this problem requires specific attention to items "b" and "c".

e. There are many specific areas of laboratory and clinical investigation in which the involvement of properly prepared surgical oncologists is necessary and others where this involvement is highly desirable if we are to produce the amount and rate of progress needed in the national cancer effort. The workshop addressed cancer research in terms of specific investigative questions that related directly to more effective utilization of the surgical approach to cancer treatment and specific questions that were either of particular interest to surgical oncologists due to their specific cancer treatment role or investigative questions that required their special skills and expertise. By vigorous multidisciplinary participation in this evaluation process, a preliminary "blueprint" of these areas of research emphasis was developed.

The specific details of this planning will appear in the complete report of the workshop now being prepared by its chairman, Dr. Morton. The observations made strongly supported the prior presumption that there is a critical need for expansion of surgical oncology research activity. These observations regarding specific areas of surgical oncology research activity that are both needed and feasible should provide also a guide, stimulus and recommendation to the surgical oncology community regarding the areas of research need at this time. Also, the outline developed should provide an initial guide to the DCT regarding areas of investigation that require immediate stimulation and funding as well as serving as a stimulus to an immediate budgetary allocation of start-up funds designated specifically for investigations initiated by surgical oncologists.

f. A longrange and ongoing planning effort in the area of research in surgical oncology is needed to overcome the deficiencies noted and to capitalize on this preliminary planning effort.

6. Recommendations to the Board of Scientific

Counselors and the Director of DCT

Based on the outcomes on the initial planning efforts described and the uniform support given to the conclusions of the workshop by key members of the nonsurgical oncological disciplines, this subcommittee on surgical oncology makes the following suggestions for Board and subsequent administrative action.

a. Approval of and provision of needed administrative and financial support for the appointment of members to and meetings of an ad hoc committee of the Board for surgical oncology research. This formalized Surgical Oncology Coordinating Subcommittee (SOCS) of the Board will require approximately 15 participants from both the membership of the Board of Scientific Counselors and from the leadership of the oncologic community outside the Board proper. Its charge would be to conduct longrange planning for future development and expansion of surgical oncology research in the broadest sense as well as serving as a communicating interface between the academic surgical oncology community (both general and especially surgery) and the Board of Scientific Counselors of the DCT.

b. It is proposed that the Board advise the director of DCT that specific budgetary allocations be developed for: 1) a project of funding programs or centers for surgical oncology research in universities and cancer centers to act as a base for initiating surgical oncology research training programs in which trainees will be funded through other mechanisms both inside and outside NCI. The eligibility requirements for such surgical oncology research programs or centers would include the existence of a specific surgical oncology clinical division or section within the applicant institution with adequate staff personnel and facilities in both surgical oncology and basic research to conduct oncologic research and provide an environment for high level investigations. Provision of partial core support to surgical oncology and basic science faculty conducting programs of varying magnitude would establish the critically needed base for expanding both surgical oncology research activity and the production of academic surgical oncologists capable of reducing the deficit in needed research contributions from this area.

Being aware of the relatively low number of institutions now capable of establishing these surgical oncology research centers (from the survey described earlier), it is recommended that budgetary allocations for this program be made in a stepwise fashion over the next three years. It is recommended that 10 such centers be established and funded in the initial year and the total number be increased to 20 the following year and 30 in the third year of the program. At an approximate allocation of $100,000 of direct costs per individual program, the total budgetary allocation would be $1 million, $2 million and $3 million for the respective three years of development of the total program.

Stipends for research trainees in this program would be sought from other research training sources in the NCI and American Cancer Society, but it is further recommended that the Board of Scientific Counselors support in principle the development of these complementary programs. Assuming $15,000 per trainee stipend and one trainee at each level of a two year program in each institution, the estimated specific allocation required from these other sources would be $150,000, $450,000 and $750,000 for the three year period.

c. A specific allocation of funds for grant applications initiated by surgical oncologists and the establishment of a specific review group involving both surgical and nonsurgical oncologic investigators. This review group should be both scientifically qualified and properly prepared for the administrative process of review so that the problems associated with the previous project of this type will be avoided. A specific funding allocation of $1-2 million in an RFA for these research projects specifically designated for surgical oncology research would allow the initiation of research efforts considered both urgent and specifically relevant to the field of surgical oncology research.

Conclusion

The current status and the recent planning process for enhancing surgical oncology research has been reviewed. Recommendations for initiation of steps to resolve the urgent immediate needs and the longterm planning efforts required have been made. The needs are critical from the standpoint of the National Cancer Program.

Board members in general went along with the concept of increased support for surgical oncology.

Holmes commented that progress in treating solid tumors depends largely on progress in surgical oncology. Proper staging and control of primary tumors, usually the function of surgeons, is critical, he said.

"It's not too late to teach old dogs new tricks," Board member James Holland commented. "Surgeons are underfunded in the Cooperative Groups. One way to stimulate surgical oncology is to provide more funds for surgeons in the Groups."

"Can't surgeons apply for traditional grants?" Board member Harris Busch asked.

"Pitifully few surgical oncologists are academically trained as researchers," Lawrence answered.

Board member Carlos Perez said he felt it was "important to continue the support for targeted surgical research initiated last year. We must continue trying to bring surgical oncologists into the mainstream."

BRMP TOLD TO REEVALUATE SKIN CANCER PREVENTION STUDY ON ALBINO AFRICANS

One of the clinical studies in the Biological Response Modifiers Program approved last fall by the Div. of Cancer Treatment Board of Scientific Coun-

[redacted] Subcommittee Chairman Enrico Mihich presented this report at the Board's recent meeting:

"Recent evidence derived from studies in hairless albino mice demonstrates that retinoic acid administered topically may enhance the yield of UV induced skin tumors. Furthermore, work in progress in two laboratories suggests that systemically administered retinoic acid or 13-cis retinoic acid does not convey resistance to carcinogenesis induced by repeated topical administration of dimethylbenzanthracene or repeated UV irradiation. Because of these findings, it is recommended that the proposal to study the chemopreventive ability of 13-cis retinoic acid in a population of albino Africans highly susceptible to actinic skin cancer, be reevaluated.

"An early report by Epstein[1] that all trans-retinoic acid (RA) caused enhanced UV skin carcinogenesis in hairless mice, was associated with great interpretational difficulties since a high concentration of topical drug was used (0.3%). This induced major increases in the proliferative activity of the skin and systemic toxicity. It is known that physical and chemical carcinogenesis requires the proliferation of target cells. Thus, the enhancement could be due to cell cycle effects.

"A recent report by Forbes[2] was commissioned by the drug industry to examine the effects of lower concentrations of retinoic acid. Their results with simulated sunlight confirmed previous findings and utilized essentially nontoxic concentrations of RA (0.001, 0.01% topical cream). It is significant that RA produced more tumors than did the treatment with the tumor promoter croton oil.

"It was reported at a recent symposium at Frederick on "Retinoic acid and photocarcinogenesis" that systemic retinoic acid 5 mg/kg had no acute photosensitizing effects but did not affect tumor yields.

"Work in progress at Roswell Park on skin carcinogenesis induced by near UV (320 nM) irradiation in hairless mice has shown that dietary supplementation with 13-cis retinoic acid at nontoxic levels, causes significantly greater UV induced skin lesions than in animals fed a control diet. No tumors have yet developed.

"Because of the concerns raised by the work of Epstein, the FDA issued a warning concerning UV exposure and use of topical retinoic acid[3].

"There seems no doubt that retinoids will inhibit the development of skin tumors induced by a single exposure to carcinogen and subsequent promotion by phorbol ester[4]. Studies have also shown that retinoids will cause regression of papillomas and certain [redacted]

"Moreover, recent studies by Bollag presented at the New York Academy Symposium on Retinoids (March 26-29, 1979) suggests that systemic retinoic acid does not inhibit skin tumorigenesis in mice induced by repeated applications of dimethylbenzanthracene. These experiments are still in progress, but the preliminary results look encouraging[6].

Summary

"Retinoids can inhibit skin carcinogenesis in animals induced by the classical 2-stage system of carcinogenesis, but do not appear to inhibit carcinogenesis when promotion is induced by repeated applications of carcinogen (UV or DMBA). This type of exposure is that experienced by albino Africans.

"Whether the albino mouse model is a valid model for human skin carcinogenesis is not known in this specific instance. It would appear prudent to conduct more experimental animal studies on effects of UV carcinogenesis before moving to man. It should be noted that the BRM subcommittee recommended that that retinoids be further evaluated at the preclinical and clinical phase 1 level before large scale studies on intervention in man were attempted."

1. Epstein, J.H., Australia J. Dermatol 18, 57, 1977.
2. Forbes, Urback, F. and Davies, R.E., Cancer Letters, 7, 85, 1979.
3. Retinoic acid and sun-caused skin cancer, FDA Drug Bull. Aug./Sept. 8, 20, 1978.
4. Weeks, C.E. et al., J. Natl. Cancer Inst. 63, 401, 1979.
5. Mayer, H., Bollag, W. et al, Experientia 34, 1105, 1978.
6. Boutwell, R.K. and Verma A.K., Annals of N.Y. Acad. Sci. Modulation of Cellular Interactions of Vitamin A and Derivatives. In Press.

MIHICH SUBCOMMITTEE LISTS STUDY AREAS FOR BRMP BY PRIORITY RATING

Mihich also presented the Board with a list of proposed study areas for the Biological Response Modifiers Program, with a priority rating by the subcommittee.

"The subject areas listed by title below represent items selected from a large number of topics considered to be of interest; the selected items have been given a further priority rating by the BRMP Subcommittee through mail ballots where 1 was the top rating and 5 the worst one.

"The topics are grouped as follows: I. Those items which have an average priority rating of 2.0 or better; II. those items which have a priority from 2.1 to 2.5 included; III. those items which have a priority of 2.51 or lower. Some of the highest priority items may be construed to be part of formulated RFPs (T.O) or of documents already scheduled to be formulated, but are listed again as evidence of the importance they have in the eyes of the BRMP Subcommittee.

"The items are submitted without any indication of whether they should be handled through the RFP, RFA or PA mechanism; the subcommittee wishes to

emphasize, however, that whatever mechanism will be chosen by DCT, in each case the inputs from the investigator should be actively sought and seriously considered by DCT officers. These inputs are considered to be essential during the difficult developmental work that is expected to be required for an optimal implementation of the BRMP.

"Finally, it is obvious that, depending on the stage of development of the topic listed, fundamental and/or preclinical studies should be done before clinical studies; in each case, whenever appropriate, clinical investigations should be implemented as rapidly as possible."

Group I

In vitro monitoring of correlates of antitumor activity of BRMs in humans.

Correlation of direct measurements of interferon and thymic hormone levels in blood, body fluids and tissues with antitumor and other biological responses modification in humans.

Definition of human cancer antigens: serology and immune reaction (including monoclonal antibodies).

Purification and modification of cancer antigens; preparation of specific cancer vaccines.

Specific immunotherapy with monoclonal Ab and activated cells/specific reactive T cells in continuing culture.

Study of thymic polypeptides and factors for selectivity of action on tumor and on immune balance.

Studies of the mode of action of thymic factors.

Study of the modulation of macrophage function and definition and measurements of these functions.

Effects of retinoids on immune functions; comparisons of natural and synthetic retinoids and interactions with other BRMs.

Studies of the mechanisms of action of retinoids at the cellular and biochemical level.

Study of BRMs in combination with antitumor agents and study of combined modalities.

Mechanisms of escape from tumor immunity.

Immunoregulatory role of prostaglandins and prostaglandin inhibitors.

Studies of the cellular and molecular basis for the antitumor effect of interferons and comparison of antitumor vs. antiviral activity.

Study of the specificity of interferon for selective tissues.

Studies of the immunomodulatory effects of interferons and effects on cell-cell interaction.

Studies of the selective modification of suppressor cell function as immunotherapy.

Studies of the in vitro modification of a tumor response by BRMs. Use of antigens and syngeneic and histocompatible allogeneic cells.

Study of interferon inducers and modification of induction.

Study of antileukemic plasma factors.

Group II

Lymphokines: production, purification and study of in vivo antitumor effects.

Studies of the effects of chemotherapy and radiotherapy on biological response modulation.

Definition of mechanisms of specific and nonspecific immunosuppression in cancer patients and investigations of methods of abrogating immunosuppression.

Pharmacokinetic studies and drug distribution studies with retinoids.

Study of the effect of BRMs on metastatic tumor cells and sequestered cells in animal models.

Identification of effector cells in adoptive immunotherapy.

Development of reference Type II interferon (mouse and human).

Development of hybridomas for monoclonal antibodies against interferons.

Identification, isolation and purification of the active core molecule of interferons and their testing in vivo.

Study of purified microbial adjuvant subcomponents.

Group III

Studies of the effects of nutritional factors on BRM activity.

Study of delivery and targeting systems for BRMs.

Study of the BRM modulation by noncancer agents.

Studies of the modulation of nonimmune mediators and regulators of immune response and of host-tumor interactions.

Purification and development of radioimmunoassay for promising thymic factors which have not yet been characterized.

RFP CANCELLATION

Due to the overall lack of interest shown by the scientific community, RFP NCI-CP-FS-01015-75, "Support services for studies of immunological and immunogenetic determinants of high risk cancer families," the government has decided to cancel the procurement in its entirety.

NCI CONTRACT AWARDS

Title: Breast Cancer Detection Demonstration Project, indirect cost adjustment

Contractor: College of Medicine & Dentistry, $91,080.

The Cancer Letter _Editor Jerry D. Boyd

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