THE CANCER RESEARCH EDUCATION CONTROL LETTER

P.O. BOX 2370 RESTON, VIRGINIA TELEPHONE 703-620-4646

Vol. 4 No. 9

March 3, 1978

Subscription $100 per year

CCIRC STARTS PREPARING FOR CLINICAL RESEARCH REVIEW; TO INCLUDE GROUP ACHIEVEMENTS, PROBLEMS

The full scale review of cancer clinical research which NCI is planning to do in a two-three day meeting in 1979 will include all clinical research programs supported by the institute. The largest and most extensive of those efforts is the Cooperative Group Program; those involved in the program, some of whom are feeling more than a little

(Continued to page 2)

In Brief

NCI AUTHORIZATION SHOULD BE $1.3 BILLION, HUMPHREY TELLS KENNEDY; GOG GETS NEW LIFE

MURIEL HUMPHREY, commenting that "we cannot mark time for a year," has asked Sen. Edward Kennedy for an authorization level of $1.3 billion for FY 1979 in his bill extending the National Cancer Act. Kennedy has asked for $1.01 billion. "The level of appropriation that we are likely to achieve, under a lesser authorization level, will not even compensate the rate of inflation," Humphrey wrote in a letter to Kennedy. "It will mean a stalemate in critical NCI programs. I believe we must move forward resolutely in this war on cancer." Humphrey, who was appointed to succeed her late husband as senator from Minnesota, noted that chemotherapy extends the lives of many patients "who can lead relatively normal and rewarding lives and spend more precious time with their loved ones. In Hubert's case, those extra years helped make his life fulfilling and permitted him to extend his public service." She called for expanded drug research to develop less toxic compounds which she said would cost at least an additional $10-15 million, "which is just not possible within a $1.01 billion authorization". . . . **GYNECOLOGIC ONCOLOGY** Group, whose renewal grant was disapproved by the Cancer Clinical Investigation Review Committee in a split vote, was given at least a temporary lease on life by the National Cancer Advisory Board. The Board accepted the CCIRC minority report and approved a two year extension for GOG with the provision that NCI staff may determine that the second year will be the final one if the group does not shape up. The CCIRC majority felt GOG should be phased out because of poor patient accrual (500 compared with 4,000 for ECOG, 5,000 for SWOG), poor study design and few publications. The Board decided to give the group another chance because it is the only cooperative group doing gynecological work and because results of its reorganization, with George Lewis of Jefferson Medical College as chairman, have not yet taken full effect. . . . **CCIRC MEMBER** Louise Chevalier, Montreal Children's Hospital, is recovering from severe injuries she received in an auto-pedestrian accident. . . . **HOLLIS BIVENS**, Baylor College of Medicine, has been appointed head of the anesthesiology department at M.D. Anderson. He succeeds William Derrick, who retired from the position he has held since 1954.

CCIRC MEMBERS LIST 10 MOST IMPORTANT FACTORS IN ASSESSING GROUPS' SCIENCE

(Continued from page 1)

defensive about the review, are gearing up for the most extensive and penetrating look at the Groups' accomplishments and problems in their history.

The Div. of Cancer Treatment Board of Scientific Counselors will be the reviewing body. The Cooperative Groups' case will be presented by their chairmen and by the Cancer Clinical Investigation Review Committee, the NCI "study section" which reviews the groups' grant applications.

DCT Director Vincent DeVita told the CCIRC this week that the review essentially will be in four parts. With a nod toward Stephen Carter, CCIRC member and his former deputy who is an opera buff, DeVita said, "The overture will be the structure of clinical research. Scene 1 will be its accomplishments, scene 2 how clinical research is reviewed, and the finale will address the questions, Should anything be changed and if so, how?"

CCIRC and the Groups should come to the review prepared to make proposals to either continue what they are doing or to suggest changes, DeVita said.

CCIRC Chairman Jerome DeCosse said there are two charges from the Board of Scientific Counselors to the committee and Group chairmen—assess the CCIRC standards for review, and to review the science in the Groups' research.

DeCosse said he was concerned that the reorganization of NCI, in which the CCIRC will be moved to the Div. of Cancer Research Resources & Centers while the Cooperative Groups remain within DCT, could result in changing the scope of the review or abandoning it. "Perhaps some of my apprehensions are unwarranted," DeCosse said. "I support this activity (preparing for the review), but the last thing we want is busy work without a useful end. I would like reassurance of committment for the review, with our removal to DCRRC."

DeVita said the reorganization might delay the review for one Board meeting, from spring to fall, but that it would not have any other effect on it.

"The key issue is how clinical research should be reviewed," DeVita said. "How do we keep science from being overwhelmed by logistics? Maybe we shouldn't have a CCIRC."

DeVita discussed the need for a therapeutic research study section in NIH to review clinical research grant applications (other than the Cooperative Groups). "If you fight a war, you get advice from generals. A group reviewing clinical research should be staffed with people who have done clinical research."

Considering the difficulty in getting HEW approval for a new study section, DeVita said an alternative would be to have all cancer clinical grants reviewed within NCI. A beefed up CCIRC, possibly with twice the number of members it now has, has been suggested as one possibility. The combined DCT contract technical review committees was another.

Prior to the meeting, DeCosse had developed a list of 36 factors to be considered in assessing the scientific potential of a Cooperative Group study. He submitted the list to CCIRC members, asking them to evaluate the relative importance of each. He sent their responses for analysis to CCIRC member Carol Newton, a professor at the UCLA Health Sciences Computing Facility.

DeCosse said he hoped answers from the members would help the committee "see more clearly" what had to be considered in the review of science. But some members felt that rephrasing some of the factors, or questions, could have changed their evaluations. They asked that not too much weight be given to their responses.

Even so, the 10 most important factors as determined by the CCIRC membership should provide Cooperative Group investigators with some clues on what the committee looks for in reviewing their grants:

1. The study design is good (realistic); the question(s) being asked will be answered.
2. The protocol is important (if only we had this information. . .).
3. Investigators participate in Group committees or Group administration, or both.
4. Investigators participate in study design.
5. Institution has a high proportion of evaluable patients (i.e. quality data).
6. The study design accounts for important prognostic variables.
7. The study is unique (original).
8. Case evaluability is high.
9. Data is returned promptly.
10. Results are being analyzed to learn everything possible (ancillary information).

DeCosse said that "an easy way" to approach the review would be to select eight or 10 areas of achievement by the Groups and write them up into objective, concise presentations to the Board of Scientific Counselors.

"More at issue is the larger problem," DeCosse said. "There is a view that the Cooperative Groups have enjoyed more than their share of the largess. We've been challenged by competing units, and by Congress. A formal statement from NCI, justifying clinical trials, is being asked."

DeCosse said he assumed the presentation will be disease related, in essentially comparable formats; Cooperative Group trials will be compared with those conducted by NCI contractors; "and I assume we'll (CCIRC) arrive at tentative judgments and discuss tactics at our June meeting, and complete it by late fall."

Carter suggested that the committee include, in a written document, "four critical aspects: One, pick

a period, say the last 10 to 15 years, and note the significant achievements in treating particular diseases. Two, tell the role of Cooperative Groups in those achievements. Three, where appropriate include the role of contract programs in those achievements. Four, list the critical questions that need to be answered and the potential for each Cooperative Group to contribute to finding those answers."

Committee members agreed that the presentations would be objective and would "show the warts" as well as the achievements. Committee member Arvin Glicksman asked, "Are we going to show the warts on the Groups while all the others are still Prince Charming?"

Stephen Jones, a new committee member from the Univ. of Arizona, said, "I would like to know what's going on. Is there going to be a major shift in funding, or major changes in the Cooperative Group Program? Why is this suddenly coming up now?"

"There is no great surprise in having this review," DeCosse responded. "Every three years or so this committee is asked to report to the Board of Scientific Counselors. Where we've been, what we've accomplished, where we're going. Nothing more than that. There is no hidden agenda."

DeCosse said the review should focus "really, on projections for the future. What's been done is factual; what will be fun is the discussion of what is needed."

GROWTH, IMPACT OF GROUPS OVER LAST FIVE YEARS SHOWN BY HOOGSTRATEN DATA

Barth Hoogstraten, who heads the Cooperative Group Chairmen's Committee, has worked up some figures in preparation for the review of Group accomplishments which show in part the extent of the program and its growth since 1973.

The figures "do not show the improvement in patient care, nor the educational value of the program," said Hoogstraten, who is chairman of the Southwest Oncology Group. "The Cooperative Group Program has been more responsible for the training of cancer specialists than any other program in the U.S."

The figures do not include data from the Gynecologic Oncology Group, "whose chairman declined to provide them," Hoogstraten said. Also excluded are data from the Groups no longer operating.

From 1973 through 1977, the number of publications produced by the Groups increased from 57 in 1973 to more than 100 in 1977. Total manuscripts submitted, accepted and published was successively 59, 78, 92, 151 and 207. "These are manuscripts only of the protocol studies undertaken by these Groups," Hoogstraten said. "Not included are the numerous other reports related to these studies, such as biostatistical data, and evaluation of prognostic factors. Also not included are the many publications of inhouse studies." The number of publications has gone up sharply in the last two years.

Hoogstraten's group, SWOG, leads with a total of 84 during the five years (excluding any published in December 1977, when Hoogstraten presented his analysis). The Brain Tumor Study Group followed with 42, Polycythemia Vera Study Group and Eastern Cooperative Oncology Group with 38 each, Cancer & Leukemia Group B with 33, Children's Cancer Study Group with 32, VA Surgical Adjuvant Group with 30, Southeastern Cancer Study Group with 23, Primary Breast Cancer Therapy Group and Wilm's Tumor Study Group with 19 each, VA Lung Cancer Study Group with 15, Radiation Therapy Oncology Group with 14, and the Radiotherapy Hodgkin's Disease Group with 3. The Northern California Oncology Group was formed too recently to have published yet.

Strength of the Groups is demonstrated by the number of institutions that are members or affiliated, Hoogstraten pointed out. "Allowing for some overlap, it can be safely stated that less than a handful of medical schools are not participating in the program. All but two comprehensive cancer centers are members of at least one Cooperative Group and practically all other cancer centers are actively involved in the Groups. Most VA hospitals are included and 41 foreign institutions participate. The impact of the Cancer Control Program is clearly seen in the number of affiliated hospitals which reached 493 in 1977.

"Most impressive are the number of physicians actively involved. While there is a steady increase in medical oncologists and pediatric oncologists over the years, the surge in numbers of pathologists, radiotherapists, surgeons and other physicians in 1976 and 1977 is enormous and is a direct reflection of the move towards multidisciplinary clinical research of cancer. More than 4,000 investigators were involved in 1977."

THREE YEARS LATER, CCIRC DECIDES THAT NEW HOME ISN'T SO BAD AFTER ALL

Those who were following the Cancer Program in 1975 will recall the fight put up by the Cancer Clinical Investigation Review Committee and members of the Cooperative Groups against the proposal to move their program from the Div. of Cancer Research Resources & Centers to the Div. of Cancer Treatment.

NCI Director Frank Rauscher went ahead and moved them anyway. Now, less than three years later, new NCI Director Arthur Upton is planning to move the CCIRC back to DCRRC, in line with his reorganization plan in which all review and evaluation activities will be conducted out of that division (the Cooperative Group Program itself will remain in DCT).

You guessed it—CCIRC members want to stay in DCT.

"I've been concerned that the return to DCRRC will separate us from DCT staff," CCIRC Chairman

Jerome DeCosse said. "Our own activities are probably different from most or all other study sections. It is difficult or impossible to look at an individual grant from an institution out of context of that Cooperative Group and what other Cooperative Groups are doing. The reason for the move is to protect us from staff influence. Staff does not influence us now, but we are heavily dependent on DCT staff for information."

DeCosse said he has written to Upton asking that the committee be left in DCT. "Since the move to DCT, reviews are better. I've been impressed with the open process, and I'm reluctant to see success altered by a change in structure."

Other committee members agreed with DeCosse. However, DCT Director Vincent DeVita said the shift should not affect the liaison with DCT staff. "The only difference is that the chairman will have to deal with two division directors instead of one, which should add to his gray hair. . . . I'm reluctant to ask that all other review groups should move except for those in DCT. I don't think that I've tried to influence you. Well, yes, I have a couple of times, and got my brains beaten out."

HOW LASKER AND ALLIES PLAYED POLITICS, LAUNCHED NATIONAL CANCER PROGRAM

Cancer Crusade: The Story of the National Cancer Act of 1971. By Richard Rettig. Princeton Univ. Press, $15.

When Frank Rauscher left his job as director of NCI to become a senior vice president of the American Cancer Society in 1976, he received a letter from Richard Nixon wishing him well. The former President added that he considered the initiation of the National Cancer Program the single most important accomplishment of his Administration.

He may be right. There is little question that in the pre-Watergate days of 1971, Nixon's support was essential in getting the National Cancer Act through Congress. Richard Rettig has written an absorbing chronicle of the process in which Mary Lasker and her allies generated public pressure, and skillfully applied that pressure to Congress to gain massive increases in federal support for cancer research and control.

Nixon, as Rettig points out, was at first cool toward any major new cancer initiative. Then Ted Kennedy became chairman of the Senate Health Subcommittee and quickly adopted the recommendations of the Panel of Consultants on the Conquest of Cancer calling for expansion of federal support for cancer research and for establishing a "National Cancer Authority," independent of NIH, to take over NCI's functions. Nixon, fearing that Kennedy might be his 1972 opponent, decided not to let him reap all the benefit from what was certain to become a very popular issue, and threw his full support behind the Panel's recommendations.

From that moment on, there was never any real doubt that new cancer legislation with big new spending authority would be enacted into law. The remaining issues, however—involving how this new program would be administered—were thrashed over throughout 1971. Kennedy, the Panel, the American Cancer Society and eventually the Senate were arrayed against Paul Rogers (Kennedy's House counterpart), scientific professional organizations, NIH and eventually the House of Representatives. In a fascinating development, Nixon wound up in Kennedy's camp; both were defeated by Rogers who succeeded in keeping NCI within NIH although giving in on NCI's separate budgeting authority and establishing the President's Cancer Panel.

Rettig's account of these events reads almost like a suspense novel (some of those he writes about may be inclined to comment that indeed it is a work of fiction). He quotes extensively from available records —transcripts of Senate and House hearings, recommendations of the Panel of Consultants, public speeches. Where Rettig gets on shaky ground is in attributing motives and actions to various individuals without supporting documentation: "By mid-September (Benno) Schmidt had made up his own mind (on an independent agency). . . . Lee Clark and Solomon Garb concluded that the primary mechanism for implementing new work in an expanded cancer program should be the contract. . . . Schmidt had remained aloof from the planning and management recommendation until the separate agency question was resolved. In fact, the staff had been frustrated for many months at their (sic) inability to get him to focus on the issue."

Perhaps the most serious criticism of the book, at least from the view of those who supported greater independence for NCI, is Rettig's total brushoff of their arguments and his total acceptance of the position that God, mother, country, apple pie and the territorial integrity of NIH should be defended to the last breath. Since Rettig limited his chronicle to events leading up through enactment of the legislation, he may be forgiven for not acknowledging that subsequent events have demonstrated fears of the independence advocates were well founded:

- Every NIH director and every HEW asst. secretary for health since 1972 has looked greedily upon cancer funds. They have argued that "there are a limited number of health dollars," and "we've got to keep a proper balance" between cancer and other health programs.

The legislative history of the Act makes it clear that increased funds for NCI were not to be at the expense of other health programs. The new money was to come out of a committment by the American people to spend whatever it takes to defeat cancer. But when that increased money started coming in, the Charley Edwardses and the Don Fredricksons

added them to the total HEW and NIH pie and tried to parcel them out to everyone else.

• HEW went along meekly with White House efforts to ignore the Cancer Act and deny construction appropriations approved by the National Cancer Advisory Board and the NCI director. When Caspar Weinberger was secretary, HEW took the lead in killing research training grants, a blow from which the Cancer Program and all other biomedical research have not yet recovered.

• HEW has shown absolutely no consideration for increasing demands on NCI staff when apportioning positions available under the ceilings imposed by the White House. When cuts were ordered, HEW insisted that NCI suffer its full share of reductions despite managing a program that had grown by 400% over five years.

• The failure of HEW to act after nearly three years on NCI's request for a new study section to review grant applications in environmental carcinogenesis is exactly the sort of thing the Panel of Consultants had in mind in talking about the "layers of bureaucracy" which inhibit cancer research. This failure has been probably the most important single deterrent to the advancement of carcinogenesis research.

Now that it appears a new study section finally will be approved, how long will it take to get another one for clinical research? NCI Director Arthur Upton is determined that grants will replace most of NCI's contract research, including clinical studies. Unless a new study section is formed (or unless clinical grant applications are sent to an NCI committee for review), existing NIH study sections will continue to reject or assign low priorities to clinical research which they simply do not understand.

Rettig accurately describes a compromise offered by Kennedy which would have left NCI within NIH "for rations and quarters" but reporting directly to the President. NCI would have remained on the NIH campus, paying NIH for space and facilities it uses (which it does anyway), and permitting the continued close association among NCI and NIH scientists which the critics of independence felt was so important. But the author presented a one sided view of that compromise, overtly siding with the critics.

Deficiencies aside, this is an important book which records in considerable detail the magnificent efforts of those who helped bring about the National Cancer Program. Many are still familiar names in the Program—Lasker, Clark, Schmidt, Rhoads, Garb, Murphy, Amos, Baltimore, Brennan, Burchenall, Frei, Holland Hutchinson, Kaplan, Krim, Letton, Luria, Pollard, Rusch, Skipper, Temin, and many others. Still others are no longer around—dead, like Luke Quinn and Sidney Farber, or otherwise out of the picture, like Carl Baker, Elmer Bobst, Ancher Nelsen, Ken Endicott, Emmerson Foote. Most of the key congressmen and senators are still around and will have everything to say about renewal of the Act—Kennedy, Rogers, Tim Lee Carter, Alan Cranston, Charles Mathias.

Rettig, a senior social scientist with the Rand Corp. in Washington, has performed a valuable service in recording for future historians the people and events that launched the National Cancer Program.

GAO EPPLEY REPORT OFFERS LESSONS FOR ALL; SHUBIK LISTS ACHIEVEMENTS

There are a few lessons for NCI contractors and grantees (and others doing research for NIH) out of the GAO investigation and report on the Eppley Institute contract (***The Cancer Letter***, Feb. 14):

1. Get it in writing. Don't do anything that is not spelled out in the contract without written permission from NCI. Grantees have considerably more flexibility, which is one of the major advantages of grants over contracts.

2. Keep accurate records of personnel time, and use of government supplied equipment and facilities. This does apply to grantees—many have been much worse offenders in this respect than Eppley. From now on, anytime a congressman wants some headlines or an investigative office of the government decides it needs to justify its existence, NIH grantees as well as contractors will be fair game.

3. Don't give excess test animals to industry. If you can't give them to other government supported investigators or sell them to industry, give them to zoos or feed them to the buzzards before giving them to industry.

4. Do a much better job of periodically summing up the progress and accomplishments of the project—what it has meant to the Cancer Program, to science, to the betterment of mankind, whatever. Don't just list publications—obviously, this doesn't mean much to GAO.

It was alleged offenses committed along the lines suggested by Nos. 1, 2 and 3 that got Eppley in hot water. And it was the failure of anyone at NCI (so GAO said) to be able to cite any substantial benefit from all the money spent at Eppley that permitted Eppley to charge that there must not have been any benefit.

Copies of the report—HRD-78-44, titled "Need to Improve Administration of a Carcinogen Testing and Carcinogenesis Research Contract"—may be obtained from U.S. General Accounting Office, Distribution Section Rm. 4522, 441 G St. NW, Washington D.C. They cost $1 per copy, but federal, state and local government officials may receive up to 10 copies free. Members of the press, college libraries, faculty members, students, and non-profit organizations may receive up to two copies free.

Eppley director Philippe Shubik did prepare a seven-page summary of accomplishments under the

contract, after he had seen the GAO report. The accomplishments are impressive; considered objectively, it makes GAO's complaints seem rather nitpicking (edited to conserve space):

Since 1968, Eppley Institute has conducted studies in several areas of chemical carcinogenesis with emphasis on topics which have the greatest impact on the human cancer burden. These researches have led to more than 400 publications in peer-reviewed scientific journals of international reputation. Individual highlights are listed by program area:

1. Drugs

Metronidazole, widely used to treat trichomas vaginalis, was in 1973 shown to induce lung tumors and lymphomas in mice. Recent studies suggest this drug may be a mammary tumorigen in rats.

Antischistosomal agents: Large scale studies on hycanthone have shown that this has no effect in hamsters and in mice gives rise to a marginal increase in hepatomas. The alternate drug, niridazole, is potently carcinogenic in mice, hamsters and rats.

Griseofulvin, widely used in the treatment of fungal infections, induces hepatomas in mice and has been shown to be a thyroid carcinogen in rats.

Diethylstilbesterol: Transplacental administration to hamsters produces very similar changes to those seen in humans, with the exception of vaginal adenocarcinoma. This model is being used to assess the effect of other carcinogens on hamsters transplacentally exposed to diethylstilbesterol. Imcomplete results indicate the transplacentally-exposed population of hamsters may be more sensitive than those not receiving transplacental treatment. This suggests the possibility that the human population exposed in utero may also be at a greater risk.

Phenylethylhydrazine, used clinically as an antidepressant, led to the induction of tumors of the blood vessels and lungs in mice.

A considerable number of other important clinically used drugs has been assayed with negative results, i.e., no indication of carcinogenid activity.

2. Food Additives and Contaminants

Chlorinated pesticides: DDT induces hepatomas in mice, but is not tumorigenic in rats or hamsters. Metabolism studies have shown that these species metabolize DDT very differently and thus explain the different results of carcinogenicity tests.

The edible false morel, gyromitra esculenta, (a mushroom) contains appreciable quantities of N-methyl-N-formulhydrazine. This hydrazine derivative is extremely hepatotoxic in mice, but when fed at doses compatible with survival, leads to malignant liver tumors in the unusually short period of 30 weeks.

The commonly eaten, cultivated mushroom agaricus bisporus, contains 4-hydroxymethylphenylhydrazine. Feeding the acetyl derivative of this relatively unstable substance led to tumors in mice.

Succinic acid-2,2-dimethylhydrazide, a widely used herbicide, has been shown to be carcinogenic to tumors in mice.

3. Skin studies

Epply has tested numerous agents for skin carcinogenesis, including solvents, insect repellents, fixatives, sun-protecting agents, dispersing agents, as well as chemicals used in photography and dye manufacture. No evidence of carcinogenicity was found in these studies.

The use of alternate species for skin carcinogenesis studies was investigated. The miniature pig, whose skin in structurally similar to that of man, and the octagon degus were treated with DMBA and it was shown that these species were disadvantageous compared to mice because only a few tumors of long latency were obtained. A comparison of the tumorigenic effects of ultraviolet radiation to the skin of mice, rats, guinea pigs, and hamsters showed that mouse skin was the only one to produce tumors as a result of treatment.

4. Respiratory tract studies

The system developed by Eppley for the induction of respiratory tumors by the intratracheal administration of carcinogens has been used to study various polycyclic hydrocarbon constituents of cigarette smoke. Some carcinogens such as 7[H]-dibenzo(c,g)carbazole, are effective tumorgens in the absence of a carrier dust, while others such as benzo-(a)pyrene, required it. Biochemical investigations are in progress to determine the factors underlying this difference. The specificity of the carrier dust has also been examined.

Various nitrosamines present in cigarette smoke also induce respiratory tract cancer in hamsters. The chemical structures underlying the induction of these tumors and the morphology of the lesions have been investigated in depth.

5. Model systems

The demonstration that the hamster, after treatment with one of a limited number of nitrosamines, rapidly develops cancer of the pancreas morphologically similar to the tumor in man, provides a new and useful model system for the study of this type of cancer.

Peripheral nervous system tumors have been induced by transplacental administration of the carcinogen, ENU, to pregnant hamsters. Castration experiments on offspring show development of this tumor is inhibited by androgen. The model appears to be advantageous for the study of hormonal effects on the development of these tumors.

Colorectal cancer: Administration of a specific nitrosamine to rats leads to tumors of the colon and rectum whose distribution and histological type resembles that in man. This model requires further development and should then be useful for the identification of dietary and other factors which influence carcinogenesis in this system.

There is considerable evidence that esophageal

cancer in man is environmentally related, but the precipitating factors have not been identified. Demonstration that in rats, a single dose of esophageal nitrosamine carcinogens inhibits [^{3}H]-thymidine incorporation into esophageal epithelial DNA, whereas carcinogens not affecting the esophagus do not produce this effect, offers a rapid method for the identification of esophageal carcinogens. Since these carcinogens produce similar effects in isolated rat esophagus, and also in the separated esophageal epithelium in vitro, it is apparent that this tissue is able to activate these carcinogens locally. This is some of the first evidence for the tissue specific activation of nitrosamine carcinogens.

6. Classes of chemicals

N-nitrosocompounds have been extensively studied at Eppley. They are often very potent carcinogens and this leads to concern about their presence, even in trace amounts, in the human environment. Eppley regards the following as highlights:

N-nitroso compounds are formed from nitrite and amides or secondary amines in the acidic conditions of the stomach. This means that man may be exposed to a much greater extent than might be expected from their environmental occurrence.

It was shown that ascorbic acid and certain naturally occurring phenols inhibit the nitrosation reaction by competing with the amine or amide for the nitrite. The inhibition of N-nitroso compound formation has been studied by determinig the yield of lung adenomas and other tumors in animals given nitrite and an appropriate amine or amide. These observations offer a practical way in which exposure to carcinogenic N-nitroso compounds may be reduced.

Techniques for the analysis of volatile N-nitroso compounds in food and air samples have been developed and strictly calibrated. These techniques are sensitive at fractions of 1 ppb. Low levels are now attainable with greater ease using the Thermal Energy Analyzer, loaded to Eppley by NCI. These techniques have been used to monitor laboratory air samples to ensure lack of hazard to Eppley staff and to the general population, nitrosamines in cigarette-smoke-filled rooms and nitrosamines in food and tissue samples.

Nitrosamides, such as N-nitrosoethylurea, are far more potently carcinogenic given transplacentally than when given to the adult animal. This has led to the view that the fetus is generally more sensitive to carcinogens than the adult. A careful series of observations on transplacentally administered N-nitrosamines has clearly demonstrated that is not generally true for all carcinogens. The treated pregnant mothers developed more, the same number, or less tumors than their offspring, depending on the compound administered.

The presence of a hydrazine group in a molecule appears in most cases to confer carcinogenic properties in that molecule. Twenty new hydrazine carcinogens have been identified by Eppley.

Three hydrazine carcinogens have been found to induce intestinal cancer. 1,1-dimethylhydrazine is a tobacco constituent, while methylhydrazine derives readily from another hydrazine present in the edible wild mushroom, gyromitra esculenta. Both these hydrazines are present in rocket fuel. Presently, the third chemical, trimethylhydrazine, is not known to be present in the environment.

Pyridoxine hydrochloride (vitamin B_6) has been shown in this institute to inhibit the toxicity of four substituted hydrazines (methyl-, ethyl- and butylhydrazine and ß-N[*a*-L(+)-glutamyl]-4-hydroxymethylhydrazine). Studies are currently under way to determine whether pyridoxine also inhibits the carcinogenicity of these carcinogens.

Polycyclic aromatic hydrocarbons occur environmentally as complex mixtures. Current analytic techniques fractionate these mixtures incompletely, methyl derivatives which differ widely in carcinogenic potency from each other and the parent compound being inadequately separated. A method has been developed for the easier synthesis of alkylated polycyclic hydrocarbons which depends on photocyclization of styrene derivatives, and proposals made for the quantitation of these substances.

The mechanism by which polycyclic aromatic hydrocarbons induce cancer is not fully known. Much current research is directed towards the importance of a diol-epoxide intermediate. Eppley is investigating a different possibility, that the production of radicle cations by one electron oxidation is the fundamental reaction. This occurs readily at the 6-position in benzo(a)pyrene.

7. Anticarcinogenesis (in addition to above described studies of ascorbic acid to inhibit formation of nitrosamines)

Isopropylvaleramide and allylisopropylacetamide partially inhibit the depression of DNA synthesis induced by 7,12-dimethylbenz(a)anthracene in rat intestinal epithelium, adrenal gland, and testes. These drugs substantially increase the acute toxicity of aflotoxin B_1, but do not affect that of dimethylnitrosamine. Both amides suppress the adrenocorticolytic effect of 7,12-dimethylbenz(a)anthracene. Both amides partially, but significantly, inhibited 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene induced transformation of C3H1OT½ cells in culture.

The powerful steroid enzyme-inducing agents, pregnanolone-16*a*-carbonitrile and its analogs, protect the rat mammary gland against cancer induction by 7,12-dimethylbenz(a)anthracene.

These steroidal agents induce P-450 and all the steroids examined except ethylestenol, also induce NADPH-cytochrome reductase. They induced these enzymes in all strains of mice examined, which indicates they may have a wide spectrum of action.

However, they were not effective in cultured cells.

8. In vitro carcinogenesis

Malignant transformation in cell culture promises well as a screening test for chemical carcinogens, but is disadvantageous because with many available systems, tests take an appreciable time to complete. The use of scanning electron microscopy demonstrates morphological differences between normal and transformed cells and such morphological differences may be exploitable in the search for a more rapid cell transformation system.

The mechanism by which DDT induces tumors in mice is not known. DDT and certain of its metabolites caused morphological transformation in C3H1OT½ cells. This suggests that this cell transformation system may be of value in elucidating the mode of metabolic action of these carcinogens.

Prescreening tests for carcinogens: Quicker and more economic alternatives to animal tests generallly consist of adding a carcinogen activating system to bacteria or mammalian cells which are capable of specific mutations. Activating systems are generally crude minces of rodent liver and suffer from the possibility that the enzymes concerned may act differently when they are present in intact cells. A system for liver carcinogen detection has been devised by Eppley in which the mutatable cells are grown in the presence of intact liver cells to activate the carcinogen.

9. Epidemiology

There have been several recent reports of a possible association of oral contraceptive use and the development of benign and sometimes malignant liver tumors. In Nebraska, more than 20 such cases have been identified. With one exception (a 15-year-old girl), all these women had used oral contraceptives.

10. Eye tumors in cows

Cattle living in areas of high sunlight intensity develop malignancies in the region of the eye. This leads to economic losses to the stock raiser. Eppley has confirmed an Australian observation that these tumors regress when the cows are injected with a preparation of their own tumor. Further work is in progress to discover the therapeutic agent and its mechanism of action.

RFP NO1-CO-75360, Subcontract 3

Title: *Qualitative research regarding public knowledge, attitudes and practice related to breast cancer*

Deadline: *March 31*

Porter Novelli & Associates Inc., under contract with NCI has a requirement to develop a survey instrument for a full scale survey regarding public knowledge, attitudes and practices related to breast cancer. Development of the survey instrument is the first phase of a three-phase project. Interested parties for phase I should contact Terry Baugh, 202-333-4659. The purpose of this announcement is to reopen competition for phase I due to increased public interest.

Interested parties for phases II and III should contact Kris Boyer or Patricia Eigler at NCI, 301-427-7984, and request RFP NO1-CO-85407-04.

Contact: Terry Baugh
Porter Novelli & Associates Inc.
3240 Prospect St. N.W.
Washington, D.C. 20007

CONTRACT AWARDS

Title: Study of role of circulating tumor antigens in immunotherapy, continuation
Contractor: Scripps Clinic & Research Foundation, $124,707.

Title: Breast Cancer Detection Demonstration Project, renewal
Contractor: Georgetown Univ., $265,293.

Title: Isolation and characterization of mammary epithelial cell membranes, continuation
Contractor: Worcester Foundation, $59,700.

Title: Studies on the significance of experimental carcinogenesis data to man, continuation
Contractor: International Agency for Research on Cancer, Lyon, France, $207,614.

Title: Establishment of a rodent production colony, continuation
Contractor: Harlan Industries Inc., Indianapolis, $228,160.

Title: Mammalian cell transport system, supplemental
Contractor: Univ. of Rochester, $67,500.

SOLE SOURCE NEGOTIATIONS

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

Title: Clinical oncology program
Contractor: Valley View Hospital, Ada, Okla.

Title: Demonstration of cancer rehabilitation facilities and/or departments, renewal
Contractor: Institute for Cancer Research, Fox Chase, Pa.

Title: Biological characterization studies of animal mammary tumors, continuation
Contractor: Mason Research Institute.

The Cancer Letter –*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090.