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Studies Are Demonstrating Effectiveness of Drug Combinations As Adjuvant Therapy; NCI Will Support New Clinical Trials

The time may have arrived for massive, new efforts using drug combinations as adjuvant therapy for "the big killers in cancer such as lung, breast, colon, pancreas and prostate."

That was the most obvious message to come out of the annual meeting of the American Assn. for Cancer Research in Houston last week. NCI was listening, and some of its executives agreed that a substantial increase in testing adjuvant therapy against many of the adult cancers is now warranted.

Gordon Zubrod, director of NCI's Division of Cancer Treatment, agreed that findings reported at the AACR meeting and elsewhere support the conclusion that extensive new clinical investigations should be undertaken. "Our apparatus has been poised to do this," Zubrod said. "It may be the time to proceed in a logical but fairly rapid way."

The studies have shown that, while the drug combinations have not been effective against the primary tumor itself, they have prevented or delayed metastases when administered immediately after surgery and maintained for at least a year.

"We're not in a position yet to recommend these combinations be incorporated into treatment," Zubrod said. "We need more, careful studies before we do that." NCI is currently supporting about 30 different studies involving adjuvant therapy on 15 tumor types.

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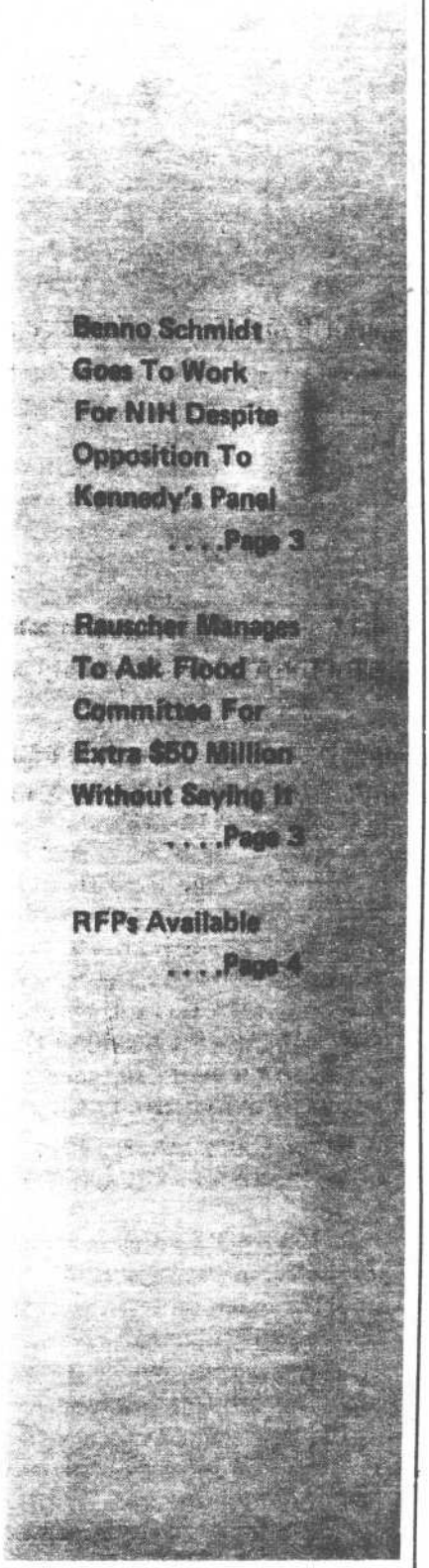
IN BRIEF

Congress Asked To Investigate Dieldrin Danger; Harvard's Rosenberg To Be NCI Surgery Chief

DIELDRIN, the insecticide known to be carcinogenic in animals and which has forced Mississippi poultrymen to kill millions of chickens when it accidentally got into feed, may be even more of a threat, according to Samuel Epstein. Chairman of the panel on environmental determinants of human cancer at the AACR meeting, Epstein called for a congressional investigation into the use of Dieldrin, which he said could be going into poultry feed throughout the U.S., affecting turkeys as well as chickens. . . .**RALPH NADER'S** Health Research Group has petitioned FDA to ban the use of metronidazole, marketed by Searle under the name Flagyl as therapy for trichomonas vaginitis. HRG says that findings by Rustia and Shubik that the drug causes lung cancer and lymphomas in mice are sufficient to warrant the ban. . . .**STEVE ROSENBERG**, Harvard, has agreed to take over one of the two NCI jobs that will be open when Alfred Ketcham leaves Sept. 1. Rosenberg will be chief of surgery under Nathaniel Berlin in the Division of Cancer Biology & Diagnosis; NCI is still looking for someone to handle Ketcham's other position as clinical director. Ketcham will go to the University of Miami as professor of surgery and chief of the division of oncology.



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AACR Papers Suggest Stepping Up Research On Adjuvant Chemotherapy Against Adult Tumors

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J.H. Burchenall, Sloan-Kettering, said in delivering the annual David A. Karnofsky Memorial Lecture that successes in treating some leukemias, Hodgkin's, childhood solid tumors such as Wilms', Ewing's tumor and osteogenic sarcoma with drug combinations have reached the point where they should be followed up with similar efforts on solid adult tumors.

Data from children's tumors "suggest that aggressive chemotherapy which, with a large tumor mass is only temporarily palliative may be curative when there is minimal residual timor," Burchenall said. "Thus, these tumors, which we have been previously stalking, have now become in turn stalking horses for adult solid tumors. Here, then, in carcinomas of the breast, lung and colon is the ideal set-up for multidisciplinary therapy."

Burchenall pointed out a major problem to be considered in subjecting patients who have had primary treatment through surgery and/or radiation to aggressive chemotherapy.

"If combination adjuvant therapy is to be given to an apparently healthy patient, with the intensity which is probably necessary to achieve a cure in these diseases which are relatively refractory to chemotherapy, there is much more risk than in a patient with stage III or stage IV metastatic disease.

"There is a world of difference between giving a toxic regimen to an apparently healthy patient who is capable of carrying on with his usual daily routine and who may even have already been cured by his or her surgery or radiotherapy alone, and giving the same regimen to a sick patient with disseminated disease.

"I submit that to avoid as much risk as possible such adjuvant therapy must be given by a specialist with great expertise in the areas of combination chemotherapy. . . Surgery must be done by a skilled surgeon, radiotherapy by a skilled radiotherapist and chemotherapy by a skilled medical oncologist with access to the best drugs and combination and all the necessary supportive facilities."

Burchenall suggested four criteria to be met in order to use multidisciplinary therapy most effectively:

1. Evidence that the patient to be treated by adjuvant chemotherapy is in a high risk category.

2. Evidence of activity of the compounds or combinations in metastatic disease of the same type.

3. Realization by the patient that the stakes are high—disease free survival or probable recurrence and death—and willingness to accept the temporary discomfort and potential risk of some forms of intensive chemotherapy.

4. Realization that the best chance for chemotherapeutic or immunotherapeutic cures is immediately after surgery when there is minimal residual tumor and that to delay until the appearance of metastatic disease may well mean missing the only chance for cure.

"I submit that we already have the stalking horses," Burchenall concluded. "Let us now get on with the hunt."

Other papers presented at the meeting backed up Burchenall's appeal:

—Edward Henderson and Oliver Glidewell, Roswell Park, reported complete remission in 34 of 50 adults with lymphocytic leukemia using a combination of vincristine, prednisone and L-asparaginase. This was followed with a maintenance regimen of 6-mercaptopurine and methotrexate reinforced with vincristine and prednisone with CNS prophylaxis. There was a median duration of remission of 18 or more months, with only six failures in 26 patients at risk.

—Samuel Taylor, Rush-Presbyterian, NCI's George Canellos and their colleagues reported studies by NCI and the Eastern Cooperative Oncology Group in which drug combinations were used to treat women with recurrent and widespread stages of breast cancer. In the Eastern Group study, 181 women at 20 hospitals were assigned at random to be treated with either phenylalanine mustard (PAM) or a three-drug combination of 5-fluorouracil, methotrexate and cyclophosphamide. Among 90 patients given the three-drug treatment, 48 achieved at least partial response, including 12 patients with a complete disappearance of cancer. Treatment with PAM produced a partial response in 22 of 91 patients, including a complete response in three.

—J.A. Gottlieb and his colleagues at M.D. Anderson, found that adriamycin used in a four-drug treatment produced a response in 55% of patients tested with cancer of the bone that had metastasized. Of 136 patients, there were 19 complete responses and 56 partial responses.

—NCI's Timothy O'Connor and Pauline Schiop-Stansley teamed with Litton-Bionetics' V. Sagar Sethi and his colleagues to study effects of rifamycin antibiotics. They found that four rifamycin varieties (B,O,S and SV) blocked cancerous transformation of human embryonic spleen cells by the Snyder-Theilin strain of feline (cat) sarcoma virus. They also blocked similar transformation of mouse 3T3 cells by the Moloney mouse sarcoma virus. O'Connor said that while rifamycin drugs have comparable effects on actively growing normal cells and thus do not appear to be useful specifically as anti-cancer agents, they might be useful in controlling the spread of cancer if RNA viruses are found to contribute to the metastaticeprocess. He suggested that tests of other antibiotics might yield additional compounds with antiviral activity.

Schmidt Already Working For NIH Despite His Opposition To Kennedy's New Research Panel

Benno Schmidt has told anyone who would listen that he is adamantly opposed to Sen. Edward Kennedy's plan to establish a biomedical research panel to perform for NIH what Schmidt's Cancer Panel does for NCI. The Kennedy plan, included in the bill extending the National Cancer Act for three more years passed 89-0 by the Senate last week, would make the chairman of the Cancer Panel (Schmidt) a member of the new body.

Schmidt's opposition to the new panel does not mean he is opposed to its goal—to help guard NIH programs and appropriations against incursions by OMB, HEW's top brass, or anyone else capable of wielding a budget ax, including Congress and the President. In fact, Schmidt and fellow panel members Lee Clark and Ray Owen met with President Nixon Wednesday, determined to argue the case for increased appropriations for NIH across the board.

In effect, the Cancer Panel is already serving as an ex-officio biomedical research panel on behalf of NIH.

Schmidt said at the Cancer Panel meeting Tuesday that he intended to press the President for substantial increases for all NIH institutes and to try once again to win restoration of the old research training grant program. In previous discussions with OMB, Schmidt managed to win 100 new job positions for NCI, and NIH got another 200. But so far he has had little luck with getting increases for the other NIH budgets or restoring training grants, both of which the Cancer Panel, NCI's outside advisors and nearly everyone else involved with the cancer program feel are vital to cancer research progress.

Schmidt indicated that while he had the President's ear, he also might put in a plug for some way to get the ceiling lifted from federal career salaries. He noted that there are 58 NCI staff members who draw the top salary of $36,000, plus another 15 who are PHS commissioned officers who receive more than their boss. None has had a raise in over five years.

Nixon tried to raise career salaries with the measure that would have increased congressional, cabinet and judicial pay, but it was defeated by the Senate.

Schmidt said he had talked with Kennedy and urged him to drop the biomedical panel when the cancer bill goes to conference with the House. "I told him that I was not available for a full time job (which Schmidt says the dual role of Cancer Panel chairman and member of the new panel would be). That seemed to shake his conviction and I hope dampen his enthusiasm for it."

The bill has been reported out by the House Commerce Committee, without the biomedical research panel and also without the clause forbidding OMB impoundment of NCI funds which is in the Senate measure. It probably will reach the House floor next week.

Rauscher Tells Flood Subcommittee How He Would Spend An Extra $50 Million—On Centers, Grants

NCI Director Rauscher performed his annual tightrope act when he attempted to defend the Administration's budget request of $600 million for cancer in his appearance before Chairman Dan Flood's House HEW Appropriations Subcommittee last week. Rauscher tried not to knock the budget despite the fact that the cancer program will be in serious trouble if NCI doesn't get at least another $50 million. As usual, Flood and other committee members played the game and got Rauscher to admit he needed more money.

"Put a dollar figure on it (amount needed over the budget)," said Rep. David Obey (D.-Wisc.). "Others say you can't effectively use what you have now." Rauscher tried to sidestep by talking about the National Cancer Plan, but Obey pinned him down. "With another $50 million, what could you do?" he asked.

"We could use $10 million for 10 new comphrehensive centers," Rauscher replied. "With the other $40 million, 65-70% would go to research grants and investigator-initiated research."

Flood asked Rauscher when he would like to have the complete lineup of 30-32 comprehensive centers. "In two to three years," Rauscher replied.

"When will you actually get them?"

"Eight to 10 years," an optimistic prediction in view of the Administration's opposition to development of more than the 18 now permitted by the cancer act. The new act will lift that limit.

Flood's subcommittee probably will add $50 million to the budget, although the members seem more concerned about increasing amounts budgeted for the rest of NIH than about cancer funds. If the House does vote $650 million for NCI, the Senate probably will vote $700 million, and they will compromise at $675 million.

CONTRACT AWARDS

Title: Can-Dial cancer public information system

Contractor: Health Research Inc., NY State Dept. of Health, $239,397

Title: Study of the operation of cancer chemistry laboratory facilities, drug distribution service, and genetic center for rodents

Contractor: Microbiological Associates, Bethesda, Md., $99,950

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. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg, HIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

SOURCES SOUGHT

RFP NCI-CN-45090-04

Title: *Motivation of health professionals*
Deadline: *May 6, 1974*

Among the specific obligations of the Cancer Control Program are those of assisting with the education of health professionals in the diagnosis and management of cancer patients, and with the maintenance of their knowledge, skills, and competence to deal with cancer throughout their active careers. Both medical and dental schools supply students with current information on the diagnosis and treatment of cancer, and graduate training programs provide additional knowledge, skills and experience.

Wide variations occur, however, in the breadth, depth and quality of educational activities relative to cancer which are presented at both undergraduate and graduate training levels, as well as in the degree of interest and concern with cancer on the part of individual health professionals. Attitudes toward diseases and health problems are undoubtedly influenced by undergraduate and graduate training programs, and particularly by subsequent clinical experiences.

There is a need to promote the development of programs in continuing education relative to cancer, which will be readily acceptable to physicians and dentists, and which can be shown to be more effective not only in increasing knowledge but in improving the performance of these health professionals relative to cancer than those presently undertaken.

State medical and dental societies are in the best position to reach their members and promote continuing education activities which can be examined as to their effectiveness. The needs for these activities vary from state to state, as do the means whereby they may best be accomplished.

This procurement is directed toward the societies of medicine and dentistry in each state and territory that are official components of the American Medical Assn. or the American Dental Assn. It also is directed toward component medical societies of major cities and counties, specifically those with populations in excess of one million persons.

Specific tasks to be performed are as follows:

Documentation of Current Activities in Continuing Cancer Education—The medical/dental society shall determine the number and types of continuing education activities relative to cancer that were available in its area (state, county, city) during the preceding calendar year. It shall determine which of these were available to all physicians and dentists and which were limited to certain individuals or groups (specialty members, hospital staffs). These activities should be classified as to the type, the site(s) of cancer concerned, the cancer problems dealt with (prevention, detection, diagnosis, treatement, rehabilitation), sponsponsorship, cost number of physicians/dentists participating in the activity.

Evaluation of Current Activities—The society shall conduct an evaluation of the continuing education activities relative to cancer which have been documented to determine their effectiveness as measured in terms of increased knowledge, alterations in attitude, skills and/or performance of specific tasks (i.e., mammography course resulting in an increase in number and/or quality of mammograms).

Development of Improved Programs—Based on the information thus obtained, the society shall plan and demonstrate programs in continuing cancer education that may be expected to result in measurable improvements in physician/dentist performance relative to any aspect of cancer (prevention, detection, etc.). The program content need not be directed exclusively to one health profession (i.e., head and neck cancer program for physicians and dentists). Where feasible, the new programs should be coordinated with other ongoing activities supported by the Cancer Control Programs in the area represented by the society.

Evaluation of Demonstration Programs—The society shall conduct an evaluation of the new programs that have been designed and demonstrated and shall analyze the results in terms of their effectiveness in achieving the desired educational objectives.

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