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CARCINOGENESIS TESTING TO STAY IN NCI, BUT CONTROL WILL GO TO NEW GROUP HEADED BY RALL

HEW Secretary Joseph Califano has made his decision on how the government will administer its toxicity testing programs—including NCI's carcinogenesis testing, *The Cancer Letter* has learned. The de-

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In Brief

MONEY BILL DELAY SEEN UNTIL AFTER ELECTION; ACCC MEETING PLANNED ON COMMUNITY PROGRAMS

IT'S NEARLY CERTAIN that Congress will not pass the HEW appropriations bill before the new fiscal year starts Oct. 1. That means an interim financing measure, a "continuing resolution," will be required to keep HEW activities, including NCI, going after that date. Continuing resolutions limit spending to agreed upon levels for a certain number of days—30, 60, 90—and generally hold them to the previous year's level, to the President's budget recommendation, or to the figures established in the House or Senate bills. If the Senate acts on its bill before a continuing resolution is passed, the figure to be used probably would be the lower of the two, in the Senate and House bills. That would permit NCI to spend at a $888 level (plus about $20 million for training), a level that would allow for inflation and some growth. If the continuing resolution pegs spending at the President's level, or the previous year ($878 and $872 million, respectively), few if any new initiatives could be funded until the regular bill is passed. There is speculation that Congress will stall until after the election, letting members up for reelection off the hook on the abortion funding controversy. . . . **VINCENT DEVITA**, director of NCI's Div. of Cancer Treatment, is back on the job after a summer sabbatical to catch up on his writing. He did an update on the MOPP treatment for Hodgkin's disease, reviewing 198 records of patients entered in the study 12 years ago, will submit it to a professional journal. . . . **ASSN. OF COMMUNITY** Cancer Centers meeting in Denver Oct. 20-21 has the theme "Community Cancer Programs—Reality, Not Rhetoric." Panel discussions, workshops, an address by Colorado Sen. Gary Hart, and a keynote address by Orville Kelly, founder of "Make Today Count," are scheduled. Contact ACCC, Executive Director, 4733 Bethesda Ave., Bethesda, Md. 20014. . . . **WILLIAM POMERANCE**, chief of the diagnostic Branch of NCI's Div. of Cancer Biology & Diagnosis, died of pancreatic cancer Aug. 25. After a distinguished career in obstetrics and gynecology, Pomerance retired as professor at State Univ. of New York (Downstate) in 1973 to head NCI's expanded efforts in diagnosis research. Under his guidance, NCI initiated programs to improve early diagnosis of breast, lung, colon and pancreas cancer. . . . **CANADIAN ASSN.** of Radiologists meeting June 24-28 in Vancouver will include a symposium on charged particle radiotherapy.

GRIESEMER WILL REPORT TO RALL; FATE OF CLEARINGHOUSE NOW IN SOME DOUBT

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cision is a compromise that will place control of all testing efforts in a new organization but will leave the existing programs physically and administratively within their respective agencies.

Details of the new setup are still being worked out and may not be known until Califano formally announces his plans, probably within the month. At a meeting last week, representatives of the participating agencies and Califano agreed that:

- A new organization will be created to operate out of Asst. Secretary for Health Julius Richmond's office. The organization will have a governing board consisting of the heads of the participating agencies—NCI, Food & Drug Administration, Environmental Protection Agency, National Institute of Environmental Health Sciences, National Institute of Occupational Safety & Health, Occupational Safety & Health Administration, Consumer Product Safety Commission, and possibly others.
- The organization will have a program director who will be David Rall, director of NIEHS. Rall will remain as NIEHS chief and in that capacity will continue to report to NIH Director Donald Fredrickson. However, as head of the new organization, he will be responsible only to Richmond, and, of course the governing board.
- The existing testing programs will remain where they are. The program directors, however, will report to Rall and not to the heads of their respective agencies. Thus Richard Griesemer, director of NCI's Carcinogenesis Testing Program, will have a new boss, Rall, and will not be accountable to either NCI Director Arthur Upton or Div. of Cancer Cause & Prevention Director Gregory O'Conor.

Califano's decision to reorganize the government's toxicity testing programs was the result of pressures which have been building up since Congress passed the Toxic Substances Control Act (TOSCA). Regulatory agencies have been pressed by Congress and public interest groups for faster and more effective action in removing dangerous chemicals from the environment. The regulatory agencies in turn have been demanding more and better information from those agencies responsible for conducting the tests, in order to present stronger cases when they have to go into court to defend their actions.

Rall has been conducting a behind the scenes lobbying effort with key members of Congress and with Califano to locate responsibility for all, or at least HEW's, toxicity testing programs within NIEHS. The other agencies have resisted giving up any part of their domain, although most agreed that increased coordination was desirable.

Although Rall did not get all he was asking for, he has emerged as the government's No. 1 man in toxicity testing. He will have the final decision on what chemicals are tested, although the governing board will exert considerable influence, with authority to review his plans, to monitor his program and to offer suggestions.

Califano, of course, can speak only for HEW; EPA and CPSC are independent agencies, and OSHA is part of the Dept. of Labor. But those agencies are expected to go along with the plan, and if they don't, Califano has enough clout with President Carter to bring them into line.

EPA has primary responsibility for enforcing TOSCA, with its requirements for premarket testing of nearly all new chemicals and its more limited authorization for requiring tests of compounds already in use.

NCI has been performing almost all of the government's testing of chemicals for carcinogenicity. Information coming out of the Carcinogenesis Testing Program have formed the basis for most of the regulatory actions against carcinogens by EPA, CPSC and OSHA, and a substantial part of those by FDA.

The compromise decided upon by Califano essentially is "Option 3A" in the series of proposals submitted to him by Upton. The NCI director felt strongly that it would be disruptive and counterproductive to remove carcinogenesis testing responsibility from NCI.

Under the compromise, the testing agencies will commit "certain identified resources" to Rall, and they will be under his direct management. Those resources will include Griesemer and his staff; NCI's contracts with organizations performing the tests, including the prime contract with Tracor-Jitco; and probably that portion of NCI's budget allocated to the testing program.

Whether or not future budgets will include separate categories for Rall's program, or will continue to be handed down through the agencies, is one of the details that will have to be worked out.

Leaving the Carcinogenesis Testing Program physically and administratively within NCI will be a plus for the carcinogenesis research effort being conducted by DCCP. NCI executives have argued that the research and testing belong together, and that research would be seriously hampered if the testing program were to be moved elsewhere.

Actually, there is very little real research that is directly related to the testing. To get and keep good scientists in the testing effort, however, it was felt that they had to be offered some association with research. Few scientists are excited about conducting routine tests. "The program will still be located in a research environment," one NCI executive said.

Upton, O'Conor and other NCI executives have argued that NCI's primary responsibility in environmental carcinogenesis is carcinogenesis research and methodology concerned with evaluation of the risk of human exposure.

O'Conor, in fact, has been planning to establish a new unit within DCCP for risk assessment. He said in a letter to the Clearinghouse on Environmental Carcinogens Executive Subgroup that a go ahead on setting up that unit was awaiting only Califano's decision on the Carcinogenesis Testing Program.

The fate of the Clearinghouse is now unclear. Its main role has been that of reviewing reports on results of the Carcinogenesis Testing Program, attempting to determine if the tests indicate a risk to humans, and advising on test design and selection of chemicals to go on test.

Most of that advice now would have to be directed to Rall, and he also will have to consider toxicities other than carcinogenicity.

O'Conor's preference is known to be to maintain the Clearinghouse, with redefined functions that would emphasize advising him on carcinogenesis research and the risk assessment effort.

The risk assessment unit O'Conor is planning would fill the gap encountered immediately by the Clearinghouse when it undertook the task of determining if compounds found to be carcinogenic in animals did pose carcinogenic threats to humans.

Clearinghouse members quickly, although most reluctantly, agreed that they would have to limit their consideration to the specific NCI tests being reported upon. They admitted that a determination of human risk should include all other data that might be available on the compounds, including other tests and research conducted elsewhere.

Clearinghouse Chairman Arnold Brown had headed a group which spent nearly a year, a substantial amount of each group member's time including travel overseas, and considerable NCI staff time in assessing the carcinogenic risk of cyclamates. Although Brown said to attempt to limit risk assessment to a single test "is not intellectually satisfying," he did not want to go through the same type of task with the compounds coming out of the testing program.

O'Conor has not fully developed his plans for the new risk assessment unit, but its job probably would include collecting and analyzing literature on compounds determined in the NCI tests to be animal carcinogens. The unit also will be involved in research into methodology and risk assessment techniques.

O'Conor plans to ask Brown to establish a planning group within the Clearinghouse to help him formulate risk assessment concepts and objectives.

O'Conor's statement (by letter) to the Clearinghouse Executive Subgroup that a decision on the new risk assessment unit would have to wait until Califano made his decision drew a sharp response from Subgroup member Michael Shimkin.

"I don't see why we have to wait until the tablet comes down from the mountain," Shimkin said. "Where I come from, carcinogenesis testing is a laughingstock."

Brown interrupted. "I think it should be noted for the record that Dr. Shimkin comes from southern California." Shimkin, a former NCI executive, is professor of community medicine at the Univ. of California in San Diego.

"We should not waste a moment to consider criteria for establishing a compound as a carcinogen, even to mice," Shimkin continued. "Dose relationship, route of exposure and other factors are far too loose to be applied to man. I've urged for quite a while that disclosure of a few more lumps in mice who are geriatric at the end of the test, hardly is enough to determine if it causes cancer in man. I urge that we appoint a committee right now, whether the testing program goes to Arkansas, the Triangle, or wherever. Perhaps our great intellectual input could carry over to the new organization."

RESEARCH BEING APPLIED IN COMMUNITY, D'ANGIO SAYS; MORE ETIOLOGISTS NEEDED

The fruits of cancer research are being applied by community oncologists, at least in the treatment of Wilms' tumor and childhood leukemia, Giulio D'Angio, Children's Hospital of Philadelphia, said in his presentation on "Perspectives of Pediatric Oncology" at the National Conference on the Care of the Child with Cancer in Boston this week.

D'Angio, who is chairman of the Wilms' Tumor Study Group, called for a "newly expanded army" of epidemiologists, and related specialties for an assault on "the last and strongest bastion of our mutual enemy, cancer."

Referring to a survey by the Children's Cancer Research Center in Philadelphia of the four state region near Philadelphia included in the Greater Delaware Valley Pediatric Tumor Registry, D'Angio noted that survival of children with Wilms' tumor managed in community hospitals compares favorably with those treated in the cancer center. Of 74 patients treated in the Children's Cancer Research Center, 81% were alive after three years; of the 10 patients reported from the community hospitals, 87% were alive after three years.

In analyzing those results, Anna Meadows, who directs the Registry, found that most of the children treated in the communities either are being treated according to cooperative group protocols, or their responsible physicians are in active communication with members of the center staff.

"For the physicians in our region, then, management of patients with this tumor by the time sanctioned individual entrepreneur system is being superseded by adherence to well defined and well tested treatment regimens of proven worth," D'Angio said. "At least for the early stages of this tumor, we can assure all those concerned—parents, legislators and others—that the fruits of the latest treatment advances are being transferred to the community of the Delaware Valley, can be applied there, and are in

active use."

D'Angio said that "a rather similar conclusion regarding acute leukemia" was reached by S. Green et al for the nation at large in a population based study of referral, diagnostic and treatment pattersn published last year in the *American Journal of Epidemiology*. It was estimated that 70% of American children have access to the effective therapies, as compared with fewer than 20% prior to 1970.

"The results of our inquiries in the Delaware Valley with respect to leukemia are not quite the same as with Wilms' tumor," D'Angio said. "If one divides the patients according to prognostic factors, children with relatively low initial counts seem to fare better when treated centrally. Perhaps this is because successful management of these patients, although possible, is more complex and demanding than for Wilms' tumor where therapy is more straight forward. Leukemia often requires the more comprehensive facilities and resources of large pediatric institutions, where specialists are to be found for the care of the myriad complications—infections, hematologic crises and the like—that attend the disease. It is the prevention of these complications and their effective management when they occur, that makes for success or failure for patients of the type described.

"These disparate results within our region demonstrate that accurate triage of patients is needed. Center based physicians as well as those in the community, must constantly re-evaluate the indications for referral of children to centers and encourage the sometimes reluctant parents to make the journey when it clearly is of benefit to the patient."

D'Angio noted that more than 50% of children with leukemia survive for more than five years—"We can now speak confidently of cure—and others of the implacable killers of yesterday are being fended off with increasing success. These advances have not been made with ease. They are the results of efforts by not only clinicians, but also the biochemists, pharmacologists, radiobiologists, physicists, and other basic scientists who have helped forge the weapons the clinicians used in their battles against the malignant diseases of childhood. Individual practitioners made their contributions, but a most important instrument evolved in the process, that of the multidisciplinary team.

"Highly coordinated battle plans now are drawn up by integrated staffs of surgeons, radiation therapists and chemotherapists, each move plotted in advance and carried out with military precision. Surely, those engaged in the treatment of children with cancer can take justifiable pride in the role they have played in the development of this concept and in refining its application in practice. It was they who most often showed the way; they were among the pioneers largely responsible for the genesis of the cooperative group mechanism. New and promising drugs needed testing in the clinic; no institution, however large, could amass enough children with cancer to test the toxicity of the efficacy of the individual drugs let alone the use of multiple agents in combination.

"The acute leukemia study groups were established in order to permit such studies, and to make sure that the results would be statistically valid. There is little doubt that what has come to be called protocol management has resulted in better care for the individual patient, and has permitted more rapid advances to be made through careful study of systematic treatment regimens. These teams have their merit, whether they function within individual institutions, or whether they extend extramurally as part of official or unofficial cooperative endeavors. The basic precepts on which the cooperative program was built remain as valid today as they were at the beginning.

"In fact, large numbers and precision are needed more than ever, now that highly successful multiple modality, multiple drug treatments have been developed. This is because adding other toxic drugs or aggressive surgical maneuvers such as radical node dissections to already reasonably successful regimens, results in ever smaller benefit cost ratios as survival rates climb towards 100%. The risks of adding such therapies vs. leaving well enough alone clearly require precise and, at times, agonizing assessments.

"In no sphere in clinical medicine is the scientific approach more manifest than in these interinstitutional cooperative endeavors related to cancer. Success has gone hand in hand with the emergence of the statistician as an integral member of the team. Most oncologists—be they surgeons, radiation therapists or pediatricians—now understand the importance of careful study design, of feasibility studies, of validation tests, and the other words in the language of the biostatistician that were unheard, let alone unlearned, a few years ago.

"There is no doubt," D'Angio emphasized, "that future success of the increasingly complex treatment regimens will rest squarely on the ability of the clinicians to collaborate at every stage with their colleagues in the statistical disciplines. This is not to say that the individual practitioner or the small group cannot play an important role. On the contrary, small numbers of patients, carefully studied, often provide the leads that can then be tested through the cooperative group mechanism. The one complements the other.

"In fact, there is increasing acceptance within the larger cooperative groups of the notion that small cadres of institutions should run feasibility and toxicity trials before drugs or complex regimens are adopted group wide.

"Clusters of institutions with special expertise, or equipment, or patient populations are conducting substudies or special trials within the wider group framework. But all these are refinements and em-

New Chemical Test, Control Plan Begins

By United Press International

A new campaign by government scientists to track down and control toxic and cancer-causing chemicals in the environment was set in motion yesterday.

Joseph A. Califano Jr., secretary of Health, Education and Welfare, announced that four federal agencies have allocated $40 million for the 1979 budget of the government's new national toxicology program.

The agencies include the National Cancer Institute and the Food and Drug Admninistration.

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bellishments of the basic technique, which is now well established, and requires only constant tuning and remodelling to make it more effective."

D'Angio posed the question, "What remains to be done?" Ultimate success cannot be stated in terms of high survival figures and low complication rates, he said.

"Rather, success will have been achieved only when cancer no longer exists as a threat to the health and well being of children everywhere. Etiology, therefore, remains the last and strongest bastion of our mutual enemy, cancer. Without more understanding of the causes of cancer, means of prevention and prophylaxis cannot be developed. Battalions of basic scientists are hard at work in laboratories everywhere for these very purposes; but another and newly expanded army is needed for this last battle, and preparations must be made without delay so that it can be put into the field. It should be made up largely of epidemiologists, demographers, toxicologists, and allied scientists including that hybrid species, the 'etiologist,' to use Dr. Robert Miller's term. (Miller is chief of NCI's Clinical Epidemiology Branch). Experienced warriors on these sectors are in short supply, and the recruits to their ranks are few. What can be done?

"First, the needs must be recognized more widely. Conversations with several epidemiologists, some of them directors of training programs, indicate that graduates of schools of public health in the field of epidemiology are not numerous. These impressions are confirmed by recent surveys that show they make up but 10% of the graduating classes albeit the proportion has risen during the last several years. They almost all immediately find positions. Very few undertake advance studies, and few shift to positions outside their chosen field. These statistics are obvious indications of a shortage in the market place. Information must be gathered to define what kinds of specialists are required, and at what level of training and experience their services are in demand. . . . The problem must be met head-on today if the even greater needs of tomorrow are to be met. Career opportunities should be assured and made known to bright and enterprising young people, whether physicians or not. Positions must be established within medical schools, schools of public health, and universities for individuals at the professorial as well as the assistant-associate professor level. . . . All this takes money, and the National Institutes of Health and American Cancer Society immediately come to mind as possible sources. Well conceived funding would be catalytic. There is room for additional support, however. What an opportunity for big business. It could help provide the much needed funds through a variety of mechanisms–underwriting the program through one of the voluntary agencies, for example, or endowing chairs, and thus servings its own needs at the same time.

"The National Cancer Institute could make its contribution, not only in terms of an identified program, but also in focusing on this area when reviewing centers, specifically comprehensive cancer centers. The 10 characteristics of comprehensive centers, as they are currently defined, do not include an explicit reference to the epidemiology-etiology of cancer; yet it would seem that activities in these areas should be included as a measure of 'comprehensiveness.' Comprehensive centers certainly are in the best position to provide the necessary environment for specialists of high competence. Why not provide such centers with the means, through targeted funds to be allocated through the peer review mechanism, for senior, intermediate and junior staff faculty? Why not generously fund training programs for epidemiologists-demographers-toxicologists-environmentalists-etiologists?

"It is heartening to report that Dr. (Frank) Rauscher and his colleagues at the American Cancer Society are showing bold and forceful leadership in this regard. Their initiatives will have far reaching consequences in the struggles to conquer cancer."

FREIREICH LASHES OUT AT PREVENTION ADVOCATES, DEFENDS THERAPY RESEARCH

"We aren't making any progress in prevention that I know of. We are in treatment. We're winning there."

Emil (Jay) Freireich, head of the Dept. of Developmental Therapeutics at M.D. Anderson, challenged the popular concept that prevention is the key to substantially reducing the number of cancer deaths. Freireich chaired the session on future developments at the National Conference on Care of the Child with Cancer in Boston this week. His attack on advocates of stepped up prevention research was made at a press conference prior to the session.

"Senator McGovern goes on national television and says all we have to do to stop cancer is to eat the right food," Freireich said. "That's stupid. People will rush out to the health food stores now, buy tons of sunflower seeds and all that good stuff, and it won't help them a bit.

"I would like to say one thing to Senator McGovern. There is one major proven human carcinogen. Cigarettes are the overwhelming cause of lung cancer. Why doesn't he do something about that? More than half of all cancer is caused by cigarettes, so the President says that cigarettes are getting better every day, and so does Gio Gori."

(Sen. McGovern, chairman of the Committee on Nutrition, has criticized NCI for spending too much money on treatment research and not enough on nutrition.)

"To prevent cancer caused by cigarettes, you have to do the prevention for 20 years," Freireich continued. "What about the rest of those poor bastards who've been smoking all the time? You have to do something for them.

"What McGovern is talking about is reduction in money for treatment research. He's not asking for additional money for prevention or nutrition. He's voting for a reduction in treatment research.

"The nice thing about treatment research and the reason why it should be the first priority is that it deals with the problem."

Freireich disputed the contention by prevention advocates that prevention has been responsible for all the major victories against disease. "Look what antibiotics have done," he said. "That is treatment, and it has eliminated deaths from infectious disease. Prevention has been effective in a few major diseases—polio, smallpox, malaria, although malaria is a public health problem, not a medical problem. Treatment is the proven way to deal with the health problem. It's the way we eliminated deaths from infectious disease, and it is the way we're going to deal with cancer."

Freireich said that the cancer research community "is in the midst of a backlash. People are unhappy that we haven't cured cancer. The dramatic progress in treating childhood tumors indicates that we can have an impact on other areas.

"Cancer is our worst health problem, but it is still rare, relative to the entire population. Prevention is at an enormous disadvantage of having to be applied to everyone. There are damn few screens that work."

Referring to the NCI budget, in which NCI requested $1 billion. the President requested $130 million less, Freireich said, "The government tells us there are priorities higher than health. I've always wondered what they are. Money is the guts of cancer research. We can't operate at a profit."

Donald Pinkel, Midwest Children's Cancer Center, at the same press conference called for establishment of regional cancer centers specializing in pediatric oncology. Some of the 20 existing comprehensive cancer centers do serve their regions in that capacity, he said, "but some are not strong in pediatrics."

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 of Contract Specialist for copies of the RFP, citing the RFP number. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Their addresses, all followed by NIH, Bethesda, Md. 20014, are:
Biology & Diagnosis Section — Landow Building
Viral Oncology & Field Studies Section — Landow Building
Control & Rehabilitation Section — Blair Building
Carcinogenesis Section — Blair Building
Treatment Section — Blair Building
Office of the Director Section — Blair Building
Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NO1-CM-87213

Title: *Continue a screening resources contract to aid in the evaluation of results of the testing of new materials as anti-cancer agents*
Deadline: *Approximately Nov. 10*

The contractor will assist the staff of the screening section, Drug Evaluation Branch, DTP, DCT NCI, in reviewing the activity of compounds disclosed by the current screens used by the NCI Drug Screening Program.

Based upon the knowledge and experience in both biological activity as indicated through various in vivo systems and the criteria of selection utilized by NCI in its current screen and published protocols, the contractor will evaluate the status of compounds and make recommendations to NCI regarding the adequacy of testing and quality control procedures. To be considered for award of a contract, respondents must meet the following minimum criteria:

(1) Must demonstrate experience with large scale biomedical screening programs (2) Must have knowledge and experience with both biological activity as indicated through various in vivo test systems, as well as the criteria of selection utilized by NCI in its current screens and protocol (Last published in "Cancer Chemotherapy Reports," Part 3, Vol. 3 No. 2, Nov. 1972).

(3) Since electronic data processing is employed by NCI to report data to and from contractors, it is imperative that the organization have knowledge of the limitations and the scope of computer-stored data and its ability to change as requirements change. (4) Since compounds of a confidential nature will be reviewed, pharmaceutical companies are specifically excluded and chemical companies will be excluded, if in NCI's judgment, there may be a potential conflict of interest.

Failure of a respondent to meet one or more of the above criteria will result in elimination of the proposal from further consideration. It is anticipated that one award will be made as a result of the RFP. It is also anticipated that level of effort for the first year will be seven man-years and that follow-on years levels of effort will be the same as that for the first year.

Contract Specialist: Daniel Abbott
Cancer Treatment
301-427-8125

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