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1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

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FDA NEARLY WRECKS NCI DRUG DISTRIBUTION PROGRAM, FINALLY AGREES TO NEW GUIDELINES

The Food & Drug Administration, in its indiscriminate and heavy-handed reaction to the sins of a few, nearly wrecked the program in which NCI supplies drugs not commercially available to thousands of physicians for use on a humanitarian basis in patients with a variety of advanced cancers for which there is no alternative treatment.

FDA's crackdown last year on investigational new drug applications from NCI and clinical cancer researchers around the country was accompanied by new, stringent and prohibitive monitoring and reporting requirements for all NCI-distributed drugs. NCI's Div. of Cancer Treatment ran into a stonewall in negotiations over the issue, finally told FDA that unless some understanding could be reached, it would no longer sponsor independent investigators for those drugs.

The disclosure that at least some members of the pharmaceutical industry supplied faulty data in support of new drug applications—perhaps, in some cases, deliberately—was responsible for FDA's unreasonable restrictions on NCI.

(Continued to page 2)

In Brief

BUDGET TIMETABLE PUTS PRESSURE ON CONGRESS TO COMPLETE APPROPRIATIONS BEFORE OCT. 1

NEW BUDGET timetable for Congress goes into effect this year. The new budget committees in the House and Senate must report out their first resolutions by April 15, establishing total tax and spending targets, with functional subtotals, including one for health. Differences between the House and Senate figures must be resolved and a combined budget resolution adopted by May 15. That date is also the deadline for legislative committees to report out any new spending authorization bills for fiscal 1977. Appropriations bills must be passed by seven days after Labor Day, and Congress then has the rest of September to compare actual spending with its goals, and reconcile the two. Reconciliation bills must be passed by Sept. 25, with the new fiscal year starting Oct. 1. . . . **NEW FISCAL** year starting date has changed dates of grant reviews and deadlines for submission of applications. Check with NIH Div. of Research Grants for deadlines, review dates. . . . **WORKSHOP** on future directions in radiological diagnosis of cancer is planned for March 16 by the NCI Div. of Cancer Biology & Diagnosis. Topics include research in diagnosis using nuclear medicine, physical methods in imaging, ultrasound, clinical diagnostic radiology endoscopic imaging, and advanced automation. The entire meeting is open. . . . **YALE NEURO-ONCOLOGY** Group is offering a two-day course dealing with the biology, epidemiology, diagnosis and treatment of brain tumors. It is scheduled for May 17-18 in New Haven. Registration fee is $50. Contact George Dohrmann, 333 Cedar St., New Haven, Conn. 06510.

NCI TO CONTINUE SUPPLYING DRUGS TO INVESTIGATORS, PRIVATE PHYSICIANS

(Continued from page 1)

NCI insisted that it is unique and has demonstrated many times over its capabilities without having to prove itself with each new submission. NCI Director Frank Rauscher told the Kennedy Subcommittee last week that its drug development testing differs from that of industry because NCI contractors have no apparent profit motive; they often receive coded and known check compounds; NCI deals with them directly and monitors them directly; contractors provide raw data often on a weekly basis; NCI does the analysis and site visits frequently and unannounced; and the entire program is subject to peer review by non-federal and non-industry scientists.

To meet FDA's reporting requirements, DCT suggested new guidelines for the use of its IND approvals by independent investigators. The proposal included classifying NCI's INDs into three broad categories with respect to sponsorship of independent investigator protocols:

An incredible story of how FDA ineptness and unresponsiveness is stopping one of the nation's outstanding groups of clinical investigators from using promising new cancer therapy will appear next week in *The Cancer Letter*.

1a. Drugs, which by virtue of data accrued, publications and/or pending NDAs, are considered to be indicated in a variety of neoplastic conditions and no longer in a truly investigational stage. Because they are commercially unattractive, some of them probably will never reach the NDA stage. NCI would supply those drugs on request, on certain predetermined written indicators, without detailed review of the protocol for use to licensed physicians of a variety of persuasions, without stringent review of qualifications, for use in the treatment of malignancies in which they appear indicated. Reporting to FDA would be kept to a minimum level, to be worked out in a memorandum of understanding.

Specifically, the drugs NCI said should be on this list were CCNU, daunomycin, streptozotocin, methyl CCNU, 5-azacytidine, L-asparaginase (Erwinia), L-asparaginase (E. Coli), and BCNU.

1b. NCI also would continue to supply those drugs for investigational protocols to physicians conducting major therapeutic research, either independently or under contract or grant with DCT (the grants would be those to the Cooperative Groups).

2. Drugs in earlier stages of development, with known or suspected clinical utility, would be supplied only for established protocols for the study of the diseases in which they are of interest to investigators or institutions which may or may not be working under a DCT contract or grant. NCI might hold the IND or allow cross reference.

Those drugs at this time would include thioguanine, procarbazine, and L-PAM (commercially available but not in parenteral dose formulation); hexamethylmelamine, nafoxidine, dibromomannitol, cis platinum, VM-26 and VP-16.

3. Drugs which are currently in phase I or early phase II would be supplied only to the specified groups or institutions involved with DCT under contract or grant specifically to perform such studies.

Those drugs include at this time azaserine, cycloleucine, gallium nitrate, methyl-GAG, TMCA, 5-BUDR, streptonigrin, tubercidine, porfiromycin, chromomycin, A3, thalicarpine, phosphoramide mustard, b TGdR, aTGdR, F_3TDR, d-Tetrandrine, S-trityl-L-cysteine, camptothecin, yoshi-864, dibromodulcitol, cytembena, iphosphamide, Tice BCG, Pasteur BCG, Connaught BCG, diglycoaldehyde, dichloroallyl lawsone, dianhydrogalactitol, piperazinedione, Baker's antifol, anguidine, pyrazofucin, ICRF-159, MER BCG, cyclocytidine, ftorafur, cisclomiphene, asaley, C. parvum (B-W), acronycin, ara-A and dichloromethotrexate.

The names of 40 drugs for which the IND will be discontinued were listed.

Drugs which are commercially available would continue to be supplied by DCT to the Cooperative Groups and contract supported institutions as part of their support to perform the missions outlined in their grants or contracts.

Those drugs are methotrexate, 6-TG, 6-MP, DES, citrovorum factor, thiotepa, L-PAM, prednisone, prednisolone, fluoxymesterone, dromostanolone, testolactone, mithramycin, cyclophosphamide, provera, mitomycin C, 5-FUDR, hydroxyurea, ara-C, vincristine, calusterone, adriamycin, bleomycin, spironolactone and procarbazine.

NCI agreed that it and its contractors would follow the standard FDA reporting and monitoring procedures for conduct of clinical trials evaluating new therapeutic approaches.

NCI asked that FDA ease up on its redundant paperwork requirements, such as the requirement that NCI maintain a separate form 1573 (a statement of the investigator's qualifications) for each protocol being used by each investigator. NCI asked that a single, periodically updated form 1573 suffice for each investigator conducting therapeutic research under the auspices of a DCT IND number. Other procedural matters unique to DCT, including its development of cancer drugs in general, should be streamlined wherever possible to meet the requirements of the law while recognizing DCT's unique position in this area, NCI proposed. An example is the differing chemistry requirement for INDs of many drugs which will likely never reach the status of an NDA.

FDA finally went along with most of NCI's proposals, including the continued distribution of drugs from group 1, after a series of negotiations and after NCI agreed to:

Review with FDA in advance additions to and subtractions from the list of drugs in group 1.

Work to develop some common protocol for use of each drug by private physicians.

Keep a list of names and affiliations of physicians who receive these drugs and send it annually to FDA.

Develop a form letter to request followup information from these physicians and send to FDA only what NCI receives in return.

Provide FDA with descriptions of each Cooperative Group, including how they choose investigators, provide assurance in regard to review of protocols by institutional review committees and how they obtain proper informed consent, how they monitor studies for safety, and how they drop investigators considered not competent to use investigational drugs. NCI agreed to provide a summary update on an annual basis of studies in progress in Cooperative Groups from the minutes of Cooperative Group meetings.

As for drugs in groups 2 and 3, NCI agreed to review and approve submitted protocols of qualified investigators, obtain assurances for informed consent and institutional review for each protocol from each investigator, and obtain an annual report for each study for submission to FDA.

NCI said it would develop with FDA some check sheet type annual report suitable for service drugs; would provide FDA with a description of how it informs investigators of new information on investigational drugs; and would review with FDA the qualifications of potential contractors for the manufacture of new drugs before awarding the contracts.

Franco Muggia, director of DCT's Cancer Therapy Evaluation Program, pointed out that NCI-distributed drugs would be used in patients who "almost certainly will die without therapy. Even though the therapeutic yield with these drugs in many cases is low, experienced oncologists agree that it is untenable to leave these patients with no therapy at all. The cancer drug field is unique in that it is not commercially attractive, and few drug firms are willing to go to the expense and effort of developing them. This latter point was the prime mover behind the creation of the Drug Development Program which we feel should influence decisions of the Food & Drug Administration in regard to the role of the National Cancer Institute and supply of drugs to the community at large."

FDA CONTINUES TO HOLD UP CANCER DRUG INDs FOR BUREAUCRATIC REASONS

Meanwhile, FDA was being as obdurate as ever in blocking INDs for cancer drugs. The agency did back down a little when it gave NCI approval to use the promising new drug maytansine at the NIH clinical center although refusing to permit distribution to non-NCI investigators (***The Cancer Letter,*** Dec. 5). More recently, FDA relented and approved the IND submitted by the Sidney Farber Cancer Center for amenopterin, one of seven INDs for cancer drugs blocked when the crackdown started. But the door remains shut on the others.

NCI is continuing to attempt to solve the matter through negotiations with FDA at the staff level, so far without much progress. It may require negotiations between Rauscher and FDA Commissioner Alexander Schmidt, and if that fails, the intervention of Benno Schmidt (no relation), chairman of the President's Cancer Panel. The commissioner has the specific authority to waive any of the regulations his staff are using to hold up the INDs if he determines it is in the public interest to do so.

DCT Director Vincent DeVita has pointed out how the public interest would be served by less stringent interpretation of the regulations.

"The prior arrangement between FDA and NCI acknowledged the unique role of the NCI Drug Development Program in the cancer drug field and acknowledged the problems unique to cancer patients," DeVita said. "In the past years filing of new cancer drug INDs was facilitated by FDA and new, useful drugs were discovered, developed and made available to the public.

"To our knowledge, there has not been a single incident related to new cancer drug testing to suggest that the safety of the public has been jepardized in any way, which can account for the recent reinterpretation and tightening of requirements for IND approval for cancer drugs," DeVita said.

NCI's position is that:

- The patient population with advanced cancer, who serve as the subjects of investigation in phase I trials, is unique in that they almost certainly will die without the discovery of new treatments. No other such population can be identified.
- In view of that, requirements for IND approval should be different for cancer drugs than for a new headache remedy, a new antibiotic, or birth control pills, since the risk/benefit ratio of the subject population is enormously different than the normal public, the life span of the cancer patient is extremely short, and the clear implication in phase I trials is that no drug now exists for the treatment of that particular cancer. In addition, the yield of new drugs developed out of those tested is small. Therefore, rules and regulations developed and rigidly interpreted, quite wisely, for the protection of the normal public from potentially harmful new drugs do not apply in same way to the cancer drug field.
- The patient population with advanced cancer, because of its uniqueness, is a minority group, not truly represented in discussions and peer review of these issues by the normal healthy person or the

cured cancer patient. Consideration should be given to their viewpoint on their protection.

• That the NCI Drug Development Program is unique since it is not profit motivated, it developed the guidelines for toxicology for new cancer drug testing, and has certain inherent assumptions built into the system which must be met before drugs are considered by NCI for submission to the FDA for clinical trials. These assumptions are recognized world wide and have been recognized in the past by FDA as inherent in each new IND application. They are—any compound must have biologic activity in at least one standard animal tumor system before it will be offered for clinical trial; and the assumptions leading to the determination of the safe starting dose in a phase I trial are inherent in the master toxicology protocol which the FDA has accepted as sufficient for approval in the past. The protocols for identification of drug activity, scheduled dependency, and toxicology are published and well known, and if questioned they should be reviewed en masse and not in each individual IND application at the time of submission.

• That a plan for clinical drug development exists for each drug as part of the system of proceeding from phase I to phase III clinical trials and need not, and should not, be detailed for each compound over and over again prior to testing. The sequence of steps for each drug is influenced by data generated at each testing point. This overall plan should serve as the plan for each new cancer drug. This includes the generation of clinical pharmacology data at appropriate points but not always at the first testing of the drug or with each subsequent testing.

• That the most important safety parameter in new drug testing is batch to batch reproducibility. Since many new drugs will not ultimately show sufficient efficacy for marketing it seems unreasonable to require the same chemical standards at IND filing as at NDA filing for new cancer drugs. Since many of these compounds are selected because they are new structures, or mixtures of unknown structures, such a requirement, in and of itself, will seriously slow and damage the process of new cancer drug development. Stringent chemistry requirements should be reconsidered provided the data on batch to batch reproducibility and toxicology are sufficient to provide the necessary assurances of safety for this population of patients undergoing phase I trials.

DeVita said he feels that those points are "well within all existing regulations, would provide more than adequate safety for the patient population in question and would facilitate new drug testing by easing the filing and approval of INDs for cancer drugs."

FDA staff involved in the negotiations with NCI include Richard Crout, director, Bureau of Drugs; Marian Finkel, association director for new drug evaluation; William Gyarfas, director, Div. of Oncology & Pharmaceutical Drug Products; and R.S.K. Young, group leader, Div. of Oncology.

BIG INCREASE REPORTED IN CANCER MORTALITY TURNS OUT NOT SO BIG

The 5.2% increase in cancer mortality reported by the National Center for Health Statistics (NCHS) for the first seven months of 1975 over the same period in 1974 (*The Cancer Letter*, Dec. 12) turns out not to be true.

Leonard Chiazze, acting chief of the Biometry Branch in NCI's Field Studies & Statistics Program, told the President's Cancer Panel last week that a comparison of the final data for 1974 with the most recently published provisional estimate for the first nine months of 1975 shows a 2.8% increase.

Even that figure is probably too high, Chiazze said. "I think it is more like 2.3%."

That's quite a difference from the 5.2% increase that appeared in black headlines around the country, but is still about double the average annual increase of 1% reported since 1930.

"There is some upward trend," Chiazze said. "We feel something is going on in the NCHS estimating procedure, and they agree. We believe their data at this point is not reliable."

Chiazze explained how the errors could occur.

"A true increase of this magnitude (5.2%) would be quite startling and we are attempting to determine the components of the reported increase. However, a final determination even as to what increase may have occurred in 1975 must await final data for 1975 which will not be available for some time.

"Consideration of a sudden increase as large as that reported by NCHS must include the possibility that some portion may be due to an artifact. With the cooperation of NCHS, we are attempting to scrutinize carefully the manner in which provisional mortality rate estimates are derived. First some comments on the methodology for producing provisional estimates. To begin with, provisional data published in the Monthly Vital Statistics Report are based upon a sample of deaths reported rather than those which actually occurred for the given months.

"Exclusions are noted in the monthly report and double counting for a state can occur for a given month. Consequently, estimated death rates are not calculated in the usual fashion directly from the sample data. These provisional rates represent relative frequencies from the sample adjusted by an independent estimate of the annualized total U.S. crude death rate. The net result is that considerable variation exists from one month to the next in the provisional monthly rate. . . . The provisional mortality rate generally declines through the year as it does for all causes.

"Of considerable interest is the fact that for 1970, 1971 the cumulative pattern for cancer recurs at one level, for 1972, 1973, 1974 the pattern recurs at a higher level and for 1975 at a higher level yet. There is no clear suggestion why this may occur but the sudden jump from 1971-1972 and again from 1974-

1975 suggests that some component of the provisional data may reflect, in part, some change in the estimating procedure.

"NCHS has recalculated the estimated crude rates for the first seven months of 1975 both on the basis of deaths reported and deaths occurring during that time. In each case the data have been subjected to the 'adjustment for bias' procedures applied by NCHS to numbers of deaths by cause. In addition, sample numbers are adjusted upward to account for differences between sample and total estimates.

"A comparison of the final data for the first seven months of 1974 with the provisional data for 1975 would indicate a 4.8% increase in the estimated cancer death rate. A comparison of the final data for all of 1974 with the provisional data for the first seven months of 1975 would indicate a 4.6% increase. Finally, a comparison of the final data for 1974 with the most recently published provisional estimate (for 9 months of 1975) yields a 2.8% increase. Note that the 5.2% increase no longer exists.

"It is important to remember that in addition to dealing with overall provisional estimates, the 1975 data are not standardized for age. We have been able to look at crude and age standardized cancer mortality rates from 1968 to the present. Over the period 1968-1975, crude mortality rates from cancer based upon final data have increased 6.7% while the age-standardized rates have increased only 1.2% for the six year period. That is, up to 1974 nearly all of the increase in the total rate is accounted for by the aging of the population. With the data in hand we will be looking at greater detail.

"At this stage it seems reasonable to conclude there is an upward trend of undetermined size in something. Exactly what this means remains unclear but is indicative of the need for additional study."

NCI ADVISORY GROUP, OTHER CANCER MEETINGS SCHEDULED IN FEB., MARCH

National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis—Feb. 4, NIH Bldg 31 Room 9, 9:30 a.m., all open.

Cancer Special Programs Advisory Committee—Feb. 5-6, NIH Bldg 31 Room 4, open Feb. 5 9–10 a.m.

NIH Director's Advisory Committee—Feb. 9-10, NIH Bldg 31 Room 6, 9 a.m. both days, all open.

Chemotherapy and Supportive Therapy of Hemopoetic Malignancies—Feb. 12, Roswell Park Continuing Education in Oncology, registration required.

Cancer Control Intervention Programs Review Committee—Feb. 13, NIH Bldg 31 Room 7, open 8:30–9 a.m.

Molecular Control Working Group—Feb. 13, NIH Bldg 31 Room 4, open 9–10 a.m.

Cancer Research Center Review Committee (Clinical Section)—Feb. 16-17, NIH Bldg 31 Room 6, open Feb. 16 8:30–9 a.m.

Committee on Cancer Immunodiagnosis—Feb. 17, NIH Bldg 10 Room 4B14, open 1–1:30 p.m.

President's Cancer Panel—Feb. 18, NIH Bldg 31 Room 7, open 9:30 a.m.–noon.

Carcinogenesis Program Fourth Annual Collaborative Conference—Feb. 23-27, Carlton House, Orlando, Fla., 8:30 a.m.–5 p.m. each day, all open.

Cancer Control Grant Review Committee—Feb. 23-24, NIH Bldg 31 Room 8, open Feb. 23 8:30–9 a.m.

Virus Cancer Program Scientific Review Committee B—Feb. 23, NIH Bldg 37 Room 1B04, open 9–9:30 a.m.

Cancer Control & Rehabilitation Advisory Committee—Feb. 23, NIH Bldg 31 Room 6, 9 a.m., all open.

Clinical Trials Committee—Feb. 25, NIH Bldg 31 Room 9, open 8:30–9 a.m.

Committee on Cancer Immunotherapy—Feb. 25, NIH Bldg 10 Room 4B14, open 1–1:30 p.m.

Committee on Cancer Immunobiology—Feb. 26, NIH Bldg 10 Room 4B14, open 2–2:30 p.m.

Symposium on Modern Concepts in Brain Tumor Therapy—Laboratory and Clinical Investigation—Feb. 26-28, Sheraton Biltmore Hotel, Atlanta, sponsored by NCI Cancer Clinical Investigation Review Committee, registration required.

Cancer of the Bone, Soft Tissue and Melanoma—March 11, Roswell Park Continuing Education in Oncology, registration required.

Future Direction of the Research Program in Radiological Diagnosis of Cancer Workshop—March 16, NIH Bldg 31 Room 3A10, 9 a.m., all open.

National Cancer Advisory Board Subcommittee on Centers—March 21, NIH Bldg 31 Room 7, 7:30 p.m., open.

National Cancer Advisory Board—March 22-24, NIH Bldg 31 Room 6, open March 22 9 a.m.–1:30 p.m., March 23 1:30 p.m.–adjournment, March 24 9 a.m.–adjournment.

Additional listings for March will be published in the Feb. 27 issue of ***The Cancer Letter.***

CONTRACT AWARDS

Title: Bay Area (San Francisco) resource for cancer epidemiology
Contractor: Calif. Dept. of Public Health, $75,516.

Title: Operation of the Louisiana tumor registry
Contractor: Charity Hospital of Louisiana, $247,878.

Title: Prototype animal cage rack isolator
Contractor: Laboratory Products Inc., Garfield, N.J., $4,999.

Title: Study on the value of mammography
Contractor: Health Insurance Plan of Greater New York, $152,235.

Title: Investigation of steroid sulfation and estrogen-binding in human breast cancer
Contractor: Roswell Park, $97,000.

Title: Investigate aspects of enzyme induction of chemical carcinogenesis relative to lung cancer incidence
Contractor: Weizmann Institute, Rehovot, Israel, $693,635.

Title: Studies of carcinogenesis in organ culture of trachea and brochi
Contractor: Univ. of Vermont, $130,166.

Title: Workshop on the geochemical environment in relation to health and disease
Contractor: National Academy of Sciences, $30,000.

Title: Studies on carcinogenesis in human tissues: bronchial epithelium, pancrease, breast and colon
Contractor: Univ. of Maryland, $257,949.

Title: Development of short courses on the principles of biohazard and injury control in the biochemical laboratory
Contractor: Univ. of Minnesota, $260,204.

Title: Miscellaneous alterations to laboratory facilities at the Frederick Cancer Research Center
Contractor: Litton Bionetics, $59,496.

SOLE SOURCE NEGOTIATIONS

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

Title: Breast Cancer detection demonstration project
Contractors: Samuel Merritt Hospital, Oakland, Calif.; Iowa Lutheran Hospital, Des Moines; Good Samaritan Hospital, Portland, Ore.; and Cancer Research Center, Columbia, Mo.

FORD BUDGET WOULD HAVE DEVASTATING IMPACT, CUTTING NEW GRANTS TO 54

The impact the President's 1977 budget would have on the Cancer Program is nowhere more apparent nor devastating than on regular research grants. Combined with the Administration's determination to hold present fiscal year spending to the 1975 level, the result would be to limit new research grants to a handful for two consecutive years.

Congress included $15.7 million for regular research grants in the 1976 appropriations bill, which President Ford vetoed (At press time, the House had not yet voted on the attempt to override the veto). That would have included $101.4 million for noncompeting awards, that is, funds previously obligated for 1,526 grants and which must be continued through the commitment. That would have left $56.4 million for 655 competing grants–$20.3 million for 243 competing renewals, $24.4 million for 412 new grants, and $11.7 million for 223 supplemental awards.

The budget for fiscal 1977 acknowledges the commitment to existing grants not up for renewal and allows $112.8 million to fund 1,483. But competing awards are slashed to 177 and $21.4 million, with $13.2 million for 123 competing renewals; only $3.8 million for 54 new grants; and $4.5 million for 176 supplemental awards.

With the Administration attempting to hold 1976 spending to the 1975 level, which is essentially the same as proposed for 1977, that would mean three straight years at $687-690 million. If that does turn out to be the final figure for 1976, those amounts cited above for 1977 grants would also be approximately the same amounts for 1976, the current year, although commitments already made might force some reprogramming of funds from other categories and change the number of grants and dollar amounts somewhat.

Nearly every NCI grant program would be cut, except for fellowships, radiation development research and Cancer Research Emphasis Grants (CREG). Here's the rest of the breakdown (1976 figures are based on the vetoed congressional appropriations bill, dollars in millions):

	1976		1977	
Program	No.	Funds	No.	Funds
Centers	194	$122.6	175	$118.3
Task Forces	158	14.1	130	12.6
Res. career	139	3.2	124	2.9
Clin. Ed.	91	8.5	51	5
Rad. Dev.	17	4	17	4
CREG	59	4.3	87	6.2
Fellowships	291	12	269	14.3
Training	46	5.3	14	1.8

NCI's research and development contracts, estimated at $213.2 million under the 1976 congressional appropriation, would be slashed to $181.4 million.

Intramural research and direct operations would increase, because of inflation costs and built-in wage increases, from $127.8 million to $134.5 million.

Here's a breakdown of NCI's budget by program, comparing the 1976 figure in the vetoed appropriations bill with the 1977 Presidential budget (first figure is 1976, dollars in millions):

Cause & Prevention – $199.5, $181.6.
Detection & Diagnosis – $48.1, $44.4.
Treatment Research – $240.7, $221.2.
Cancer Biology – $124.3, $116.1.
Centers Support – $34.4, $32.3.
Research Manpower Development – $31.3, $27.8.
Construction – $25.6, $10.9.
Cancer Control – $58.7, $53.4.

Although the President's budget would severely limit new initiatives in the Cancer Program and stop cold the momentum that has been building since 1971, NCI was forced to put on a happy face about it in presenting its budget justification to Congress. This is the document the Appropriations Committees require, explaining how the money requested will be spent. Committee members accept it for what it is worth and usually give agency representatives the chance to tell them the truth, an opportunity Director Frank Rauscher has used well.

The justifications summarize by program area what NCI feels its accomplishments have been during the year and what its objectives are for the next fiscal year. They don't tell the whole story, but they are worth reading:

Cause & Prevention

Accomplishments in 1976: (1) In the carcinogenesis bioassay area a new structure for increased development and validation of a battery of cell cult-

ure methods for screening environmental chemicals has been established; (2) evidence has been found to show that viruses and chemicals can interact to cause cancer in animals; (3) a new avenue for exploitation was opened through studies of site-specific cancer deaths, 1950-1969, by county within the United States; (4) the development and evaluation of inhalation smoking machines for the bioassay of small rodents and the beagle dog were completed; (5) radioimmunoassays for the detection of minute traces of cancer causing chemicals in body fluids or foodstuffs have been developed; and (6) the association of herpesviruses, which have been found to cause cancer in primates, with tumors of the head and neck and urogenital tract have been demonstrated.

Objectives for 1977: Research efforts in this area will be continued to include: research in the search for other cancer viruses; further assessment of carcinogenic risk from environmental exposure; continued evaluation of less hazardous cigarettes; and studies to uncover dietary and nutritional determinants of cancer.

Detection & Diagnosis

Accomplishments in 1976: (1) Completion of the U.S. county-by-county survey of cancer mortality rate has provided a prospective identification of groups at high risk to cancer from environmental contaminants; (2) a prototype cell-sorting machine has been developed to screen cervical cytology specimens automatically at the rate of 15-25 per hour. This is a significant step toward the goal of automation of the reading of Papanicolaou smears; (3) the development of computer-assisted x-ray tomography has vastly improved the diagnosis of brain tumors in the clinic, easily showing the location and extent of tumors never before observable by x-ray; (4) the study of sputum cytology for detection of lung cancer in smokers without symptoms of the disease followed by fiberoptic bronchoscopy for tumor localization, has screened 20,000 individuals and found 154 cancers; and (5) a clinical test involving the estrogen receptor protein has been developed which indicates whether the tumor in a breast cancer patient will respond to removal of hormone sources (ovaries, adrenals, or pituitary). If the test indicates no response, the patient will have been spared a useless operation.

Objectives for 1977: Research efforts in this area will be continued to include: refinement of automated machines to assist in cervical cytologic screening for cancer; development of ultrasonic scanning for mammography to avoid all ionizing radiation; and investigation of new immunologic reactions of importance in cancer.

Treatment

Accomplishments in 1976: (1) In breast cancer the use of a three drug regimen in the post-operative period has led to an even more dramatic drop in the recurrence rate than was observed in earlier studies using a single drug; (2) the first effective drug combination for the treatment of advanced colon cancer has emerged; (3) the two-year survival rate for patients with osteogenic sarcoma, a tumor of the bone in young people, has been increased from 20 to 80 percent through the use of combined modality treatment; (4) advances were made in the use of biological marker substances found in the blood or urine correlating with the presence of tumor to determine the extent of breast cancer; and (5) the addition of immunotherapy to chemotherapy in patients with acute myelogenous leukemia has led to an increase in the number of persons remaining alive and free of leukemia when compared to the use of drugs alone.

Objectives for 1977: Research efforts in this area will be continued to include: studies in breast cancer research using chemotherapy after mastectomy; further emphasis on ovarian cancer, the fifth most common killer of women; and expanded surgical oncology, radiation oncology, and pathology within the Cooperative Group Program in order to begin to develop a more complete combined modality potential.

Cancer Biology

Accomplishments in 1976: (1) General differences between the membranes of normal and malignant cells have been demonstrated. Different growth characteristics of normal and transformed cells may be caused by primary membrane changes. These changes may affect the enzymes thus influencing the regulation of cell proliferation; (2) a substance extracted from the starfish has a damaging effect on cancer cells. Initial investigations are under way to identify and determine its potential as a treatment for cancer; (3) new evidence shows that only a small part of a cancer virus' genetic material directs or controls tumor growth. Isolation of that cancer gene from other genes of the virus would help in understanding the transformation of normal cells to cancer cells.

Objectives for 1977: Research efforts in this area will be continued to include: research into the mechanisms by which cancers spread. Information on those factors promoting or arresting the growth of metastases could lead to improved methods of control; continued efforts to learn more about the biological, chemical and physical properties of the cell surface membrane; and explorations into why tumor cells avoid normal body immune systems.

Cancer Control

Accomplishments in 1976: The cancer control program supported projects in many different areas of the cancer problem. Prototype studies for the education of employees and employers on industrial carcinogens are in progress in Tyler, Texas and Louisville, Kentucky. Three series of networks have been organized in breast cancer, head and neck cancer and childhood leukemia and lymphoma to develop diagnostic, treatment and rehabilitation techniques for specific cancer sites. A Communication Network (Controline) has been established through the 17

Comprehensive Cancer Centers allowing each individual in the U.S. access to what is known about cancer. At least 32 states are continuing to participate in the screening of women at high risk to cervical cancer utilizing the Pap test. Support is being continued to the 27 Breast Cancer Detection Projects jointly sponsored by the Cancer Control Program and the American Cancer Society to involve 270,000 asymptomatic women with early screening by clinical history, clinical examination, mammography and thermography.

Objectives for 1977: The cancer control program will continue to support ongoing projects in all of the intervention areas with emphasis on industrial carcinogens, breast cancer, cervical cancer and new treatment and rehabilitation techniques.

Construction

Accomplishments in 1976: In 1976 $25,577,000 will support the upgrading and construction of cancer research facilities including various comprehensive and specialized cancer centers. These funds will permit the modernization and creation of additional cancer research space which is essential to the achievement of the research and cancer control goals of the National Cancer Program. Additional renovation and modernization projects will be supported on the NIH campus as well as at the Frederick Cancer Research Center.

Objectives for 1977: Funds requested for 1977 are $10,907,000. These funds will permit new construction, alteration and renovation of existing facilities and the completion of shell space and biohazard and containment laboratories for the continuation and development of the cancer program.

Centers

Accomplishments in 1976: Currently the NCI has recognized 17 Comprehensive Cancer Centers. In 1976, 32 core grants will be supported. In addition, 32 exploratory projects will provide support in many areas of the country to determine the feasibility of establishing cancer centers.

Objectives for 1977: Core support for cancer centers will continue as in 1976 commensurate with development of the Cancer Research Centers Program. Approximately 13 exploratory projects will be supported.

Research Manpower Development

Research manpower needs in specific disciplines which are important for fulfilling the National Cancer Program are met by providing fellowships, training grants, and education awards. The National Research Service Awards Program supports research training in eight areas: carcinogenesis, tumor biology, drug development, chemotherapy, viral oncology, immunology, radiation oncology and epidemiology. The Clinical Cancer Education Program supports the improvement and expansion of cancer teaching at the undergraduate and graduate levels in schools of medicine, dentistry, osteopathy, public health, in major hospitals affiliated with medical schools and in specialized cancer institutions. The program also promotes the continuing cancer education of physicians, dentists and other health professionals. The Research Career Development Award Program provides support for young scientists who show potential for developing into outstanding independent investigators in the cancer-related sciences. The Research Career Award Program, which is being phased out, provides lifetime stipends to accomplished cancer research specialists.

The Graduate and Clinical Training Program and the Research Training Program are being phased out and replaced by the National Research Service Awards Program.

The 1977 budget estimate for research manpower development of $27,758,000 and 15 positions represents a decrease of $3,565,000 and 1 position below the 1976 estimate. The program plans will allow the awarding of approximately 305 individual and 78 institutional awards under the National Research Service Awards Program. These awards will continue to support training in the fundamental disciplines of cancer research: biology, molecular biology, biochemistry, pharmacology, hematology, embryology, pathology, physics, genetics, medical oncology, epidemiology, chemotherapy, and surgical oncology.

The Clinical Cancer Education Program will support approximately 51 institutional awards for coordinated and innovative cancer teaching in schools of medicine, dentistry, osteopathy, and public health, in major hospitals affiliated with medical schools, and in specialized cancer institutions.

Research Career Development Awards will support 115 individuals who show outstanding potential for developing into independent investigators of high quality in sciences related to cancer. Research Career awards will continue to provide stipends to accomplished cancer research specialists. Support for all programs is summarized below ($ in thousands):

	1975 Actual	1976 Est.	1977 Est.
NSRA	$10,772	$11,285	$16,184
Clinical Education	5,033	8,492	5,000
Career Development	2,524	2,958	2,618
Career Awards	282	282	282
Grad. & Clinical Training	9,736	5,323	1,764
Research Training	2,596	1,555	215
Staff and Support	952	1,428	1,695

The Cancer Letter—*Editor* JERRY D. BOYD

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