THE CANCER LETTER

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RALL SAYS NTP MUST HAVE NEW POSITIONS TO SPEND EXTRA $23 MILLION ON TESTING MORE CHEMICALS

The National Toxicology Program will be able to spend the extra $23 million it received as decreed by Congress only if it also gets the 28 additional positions demanded by the House Appropriations Committee, NTP chief David Rall told *The Cancer Letter.*

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In Brief

GEORGETOWN PROFESSOR HEADS CANCER THERAPY EVALUATION PROGRAM; NCI-VA BRANCH ABOLISHED

JOHN MACDONALD, associate professor of medicine at Georgetown Univ., is on the job as director of the Cancer Therapy Evaluation Program in NCI's Div. of Cancer Treatment. He replaces Franco Muggia, who left for the position of director of the Div. of Oncology at New York Univ. . . . **JOHN MOXLEY,** vice chancellor for health sciences at the Univ. of California (San Diego), who chaired the NIH consensus meeting on treatment of primary breast cancer last June, has been named assistant secretary of Defense for health affairs. Moxley, 44, has been dean of both the UCSD and Univ. of Maryland medical schools, once worked as an investigator at NCI. . . . **NATIONAL NAVAL** Medical Center in Bethesda and NCI have agreed on a "general memorandum of understanding" in which the two agencies will conduct a cooperative research program in cancer treatment. Although the Naval Medical Center and NIH are across the street from each other, this is their first collaborative clinical program. John Minna, chief of the NCI-VA Medical Oncology Branch in the Div. of Cancer Treatment, will be chief of the NCI-Navy Medical Oncology Branch. NCI is ending a similar agreement with the Veterans Administration, and the NCI-VA Medical Oncology Branch is being abolished. DCT investigators will have hospital and lab space at the naval center, and the center's cancer patients will have the opportunity of participating in clinical trials. . . . **THE POSITION** of special assistant for scientific coordination to DCT Director Vincent DeVita is still open, and DeVita is looking for candidates. The job was left vacant when Daniel Rubin moved over to the National Heart, Lung & Blood Institute. Contact DeVita or Jane Henney, DCT, NCI, Bldg. 31 Rm 3A52, Bethesda, Md. 20014. . . . **SYMPOSIUM** on antiestrogen therapy for hormone dependent tumors is scheduled for Sept. 29 in Sorrento, Italy. Contact Lois Trench, Stuart Pharmaceuticals, Wilmington, Dela. 19897, phone 302-575-2284. . . . **"ADJUVANT THERAPY** of Cancer II," the papers presented at the Second International Conference on the Adjuvant Therapy of Cancer last March in Tucson, is now available in hardback. It was edited by Stephen Jones and Sydney Salmon of the Univ. of Arizona, may be ordered from Grune & Stratton, 111 Fifth Ave., New York 10003, $29.50.

SOME REORGANIZATION ("FINE TUNING") DUE FOR NTP; MAY BE REMOVED FROM DCCP

(Continued from page 1)

The extra money, which doubled the amount originally budgeted as NCI's contribution to NTP, was put into the FY 1980 appropriations bill at the insistence of Congressman David Obey. The Wisconsin Democrat had noted that the budgeted amount, $22 million, would not even permit the NCI Carcinogenesis Testing Program (absorbed into NTP) to finish tests on 70 of the 195 compounds in the program, much less add any new chemicals.

Obey had hoped that the extra money would permit NTP to complete the existing tests and add 80-100 new compounds. But Rall, who is also director of the National Institute of Environmental Health Sciences, said that without the additional positions, NTP would not be able to spend the $23 million on routine bioassays.

At the insistence of the General Accounting Office, some congressmen and other critics, the Carcinogenesis Testing Program is phasing out the prime contract with Tracor Jitco, through which the company managed the program. Rall commented that with the government assuming those management tasks, it was absolutely necessary to have the additional positions.

There are two problems which must be overcome in making use of the positions. First, the Office of Management & Budget must implement the congressional directions and give the positions to the program. OMB has not always followed congressional instructions in such matters. Second, Rall and Carcinogenesis Testing Program Director Richard Griesemer must recruit people to fill those positions. NCI has had considerable difficulty in getting the right people for those jobs in the past.

Rall was optimistic on that point. "I feel we can recruit them if we get permission," he said. "If we get the extra money and the 28 positions, we can do exactly what we have been asked to do, and do it very well."

It has been less than a year since then HEW Secretary Joseph Califano established NTP by taking components from four of his department's agencies—NCI, NIEHS, the Food & Drug Administration and the National Institute of Occupational Safety & Health—and placing them under Rall's overall direction. Rall reports to an executive committee consisting of the heads of those four agencies plus the chiefs of three regulatory agencies located outside HEW—the Environmental Protection Agency, Occupational Safety & Health Administration, and Consumer Product Safety Commission. Each program committed to NTP would remain with its present agency but still report to Rall.

It was a weird setup which even Califano indicated could run into administrative difficulties. He commented at the time that the structure would be reviewed after a year to see how it was working, with further changes to be made if necessary.

Rall believes it is working well. "It is as healthy a nine month old as I have ever seen," he said. But he agreed it "needs some fine tuning of the system, and we are in the process of doing that."

Neither Rall nor anyone at NCI would say for the record what that fine tuning might consist of. It was obvious from the start, however, that a group of government employees who get their pay and promotions from one agency but must follow the orders of another was headed for trouble.

Rall would not say so, but it is understood that he feels he must have more authority over the program and its staff. NCI executives, on the other hand, feel that if Rall does get additional authority, NCI should be relieved of further responsibility for the program and results or lack of results it may achieve.

One proposal currently under consideration is to remove the Carcinogenesis Testing Program completely from the Div. of Cancer Cause & Prevention, leaving it as a separate program but still within the administrative housing of NCI. This would remove one layer of management through which Griesemer would have to report. Putting it another way, it would give Rall direct access to Griesemer without having to worry about the formalities of going through DCCP.

Some NCI staff members feel that both NTP and NCI would be better off if Griesemer's operation were to be moved entirely out of NCI, either to NIEHS or to whatever disposition HEW would make with NTP. "It isn't realistic and it isn't fair either to Rall or to Griesemer and his staff to make them work through this multihead setup," one NCI executive said. "Why the hell not let Rall have the whole thing?"

"It is also rather silly for Congress to give us the money intended for NTP and then require us to turn it over to them," said another. "It just muddies things up."

But Rall said he thinks it is important "to keep an affiliation with NCI." He said some of the problems may be related to the fact that his base at NIEHS, at Research Triangle Park, N.C., is 280 miles from NCI headquarters in Bethesda, where Griesemer and his staff are located. He suggested that it would not be necessary to move the Carcinogenesis Testing Program to North Carolina but said it is possible some of the staff might be asked to make the move.

The White House also is concerned about NTP's organizational status.

OMB Deputy Director John White called the issue to the attention of new HEW Secretary Patricia Harris in a letter dated Aug. 20. White wrote:

"I am writing to request your participation and that of your colleagues in the National Toxicology

Program in the preparation of a management analysis and operating plan through FY 1981.

"The zero base budgeting analysis of toxic substances research activities that was a part of the preparation of the 1980 budget made clear the need for greater issue identification and coordination among the agencies concerned with toxic research and control. The requested management analysis and operating plan should provide a critical assessment of NTP efforts to date and lay out a comprehensive multi-agency program for NTP actions through FY 1981. A similar effort has also been requested for the Inter-agency Regulatory Liaison Group by separate letter.

"I believe it is important for the agencies involved in the NTP to determine how well the current arrangements are working and to identify what improvements must be made. If these efforts are not satisfactory, we will need to consider other arrangements for establishing the needed priorities and coordination. I hope we can count on your personal support for this effort to make the NTP a fully effective mechanism to accomplish its objectives.

"The requested analysis and operating plan should take into account, but need not be limited to, the following concerns:

"—What are the participating agencies' assessments of NTP progress to date? Is the NTP annual plan for FY 1979 satisfactory to all the agencies concerned? If not, what are its shortcomings? What changes in research/toxicology procedures have resulted from the dialogue that the NTP has established between the regulatory and research agencies?

"—What are the areas which have not been fully addressed by the NTP to date, and what actions will be taken to assure progress in these areas?

"—What are the specific operational objectives for this initiative in FY 80 and 81, particularly in such areas as prioritization of substances to be tested, testing procedures, dissemination of results? What changes in the NTP responsibilities, functions, and resource levels are essential for accomplishing these objectives?

"—How will each agency assure the fulfillment of these objectives? Provide an inventory and inter-agency ZBB ranking of agency resources (staffing and funding) to be devoted to NTP efforts in FY 80 and 81.

"Please plan to provide us with a briefing on the status of this effort by Sept. 7, 1979, and with the completed assessment and operating plan by Oct. 5, 1979. The completed plan should be as specific as possible and should include, for each of the NTP objectives, a statement of proposed accomplishment, a timetable for implementation and a specified allocation of responsibility to each of the participating agencies. It will be necessary, in developing this analysis, to assure that no components are included unless they are a part of the agency 1981 budget submissions and, as such, are identifiable within that material."

It is obvious that OMB intends to closely monitor NTP and any changes made in it.

(An unrelated but interesting sidelight is the fact that White, whose position does have a lot of clout in the Administration but who nevertheless is among the midlevel White House functionaries, is issuing orders to the HEW secretary over his own name. It isn't likely that would have occurred if Califano were still on the job, which is one reason why he isn't.)

Rall said he is in the final stages of establishing the NTP Board of Scientific Counselors. The Board "will peer review the research, and will discuss ideas on how we can peer review the end product," Rall said. "We're also looking for ways to get reports into reviewed archival journals, so scientists will have easy access to them."

Lawrence Fishbein, of the National Center for Toxicologic Research in Pine Bluff, Ark., from which FDA's contribution to NTP is derived, is chairman of the program's Chemical Selection Committee. The committee receives nominations from each of the agencies represented on the Executive Committee, and the Executive Committee makes the final decisions on which compounds are tested. NCI's Chemical Selection Working Group is still in operation and is a major contributor to the nominations.

The first annual plan for the program, commenting on chemical selection, noted:

"The development of lists of chemicals to be tested is a most important task if the resources available to the NTP are to be effectively utilized. Each agency represented on the Executive Committee was asked to propose testing initiatives and to participate in the ordering of chemicals. The principles for selection of these compounds included such factors as estimated or known extent and intensity of human exposure, estimated or known severity of toxicological effects, and the scientific needs to compare testing methodologies and to study structure activity relationships. The NTP is concerned about its appropriate role in government sponsored testing as it relates to the responsibility of the private sector to bear the burden of chemical testing as mandated by specific federal laws or statutes. The NTP is in the process of developing a set of principles for selecting chemicals that will incorporate the previously listed factors and concerns.

"The selection of a chemical does not a priori commit it to testing by NTP. It does commit the NTP to ascertain the specific toxicologic and regulatory concerns, evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories, and then propose and conduct specific tests that are needed.

"A single focus for this activity has been established to insure the future provision of a standard

base of information on each chemical nominated. This standard base of information will include chemical name, Chemical Abstract Series (CAS) No., commercial formulations, and adequacy of relevant toxicologic data and specific areas of needed toxicologic research. Once a chemical has been selected for testing, this group will provide the pertinent science information for proper design of the test protocol. Existing data resources will be utilized for these activities."

The plan notes that the $B_6C_3F_1$ mouse and Fischer 344 rat will continue to be the principal test species. "Animal production resources will continue to be developed and maintained to provide animals to chemical testing laboratories. Basic standards for husbandry and care as they specifically relate to toxicology testing are also being developed. A standard controlled, open formula test diet is to be selected and incorporated into the test protocols.

"Although the current NTP strains provide meaningful toxicology and carcinogenicity data, the test animal is such a vital selection in experimental design that an evaluation of the continued utility of these or other rat and mice strains is planned. The $B_6C_3F_1$ mouse and Fischer 344 rat are genetically uniform (isogenic) strains which is a desirable trait for toxicity testing. It has been proposed that the use of several isogenic strains in a bioassay would provide a better extrapolation base than the use of a single strain. The statistical power of data developed in several isogenic strains appears to be equivalent to, and may exceed, current practices of using single strains. A course of study to develop and validate a series of experimental designs using multiple isogenic strains is planned."

The report states that the carcinogenic potential of a chemical is currently being determined by lifetime bioassay in rodents.

"The NTP does not propose alternative methods but acknowledges a need in the longer term to develop or validate less expensive and more rapid methods that may in some instances supplant the need for lifetime bioassays.

"Mammalian cell transformations are potential short term assays that indicate carcinogenic potential of a chemical. Transformation assays being evaluated include BALB/c 3T3, Fischer rat embryo (RLV infected), hamster embryo, and C3H 10T½.

"The results of salmonella assays will be considered in prioritizing the order in which a chemical may be tested in lifetime bioassays. Other assays, once validated, that will augment the microbial assays, include cell transformation, or other in vitro and in vivo assays described in the mutagenesis segment of the annual plan.

"A substantial body of literature exists related to short term in vivo carcinogenicity testing, but no model is sufficiently validated to be applied to the routine testing of chemicals. One model, the mouse lung adenoma system, is sufficiently developed to be selected for in depth validation. During FY 79 a validation protocol will be developed for contract award and initiation. Seventy-five to 100 chemicals will be selected, giving preference to those chemicals for which adequate lifetime bioassay data exist, or are in progress, with selections balanced to insure a broad representation of chemical classes. The results of this study, along with in vitro microbial mutagenesis data and findings of lifetime rodent bioassays, will be compared in evaluation of the mouse lung adenoma system.

"Rat liver assay systems will also be reviewed in order to determine what specific areas of methods development need to be pursued.

"A literature search and analysis will permit comparison of the results of animal bioassays and mutagenesis tests with results of mouse lung, skin painting and subcutaneous assays. Particular attention will be given to: a) the concordance of in vitro fibroblast transformation and subcutaneous sarcoma formation, and b) to skin tumor production in Syncar versus non-Syncar mice. The results of this analysis will be considered in developing NTP initiatives for FY 80.

"There are different viewpoints as to what constitutes the best design of lifetime bioassays. Areas of differing opinion include choice of species and strain, age at exposure, route of exposure, number of doses tested, dose levels, and of methods used in analysis. An NTP priority is to review and possibly revise the current lifetime bioassay design consistent with the projected use of the bioassay results.

"Carcinogenicity testing traditionally begins with young adult animals (typically six-week-old rodents). Human chemical exposures may include the period of in utero development and infancy as well as continued lifetime exposure. These exposures occur through exposure of pregnant workers, use of drugs, and long term accumulation and persistence of certain chemicals in the mother's body with secretion in milk. The adequacy of lifetime bioassay methods versus methods that also include prenatal and neonatal exposures is being evaluated. Four chemicals will be tested: polychlorinated biphenyl (Arochlor 1254) and phenytoin have been selected with two additional chemicals to be selected and testing started in FY 79.

"The carcinogenic potential of chemical combinations has been described, the conversion of heterocyclic secondary amines to nitrosamines in the presence of $NO_2(N_2O_4)$ being a recent example. The ubiquity of NO_2 and the widespread distribution of heterocyclic amines prompt the hypothesis that some neoplastic diseases may be a consequence of in vivo interaction with these chemicals. A test of the hypothesis is planned in an animal bioassay using NO_2 exposure by inhalation and heterocyclic amine (2,6 dimethylmorpholine) exposure by the oral route.

"Lifetime inhalation bioassays for carcinogenicity usually involve a duration of exposure that is arbitrarily determined. The specialized facilities required for inhalation studies are expensive and commit limited technical manpower and resources for extended periods of time. A study with rats, mice and hamsters is in progress that uses a design that varies the age of animals exposed and the duration of exposure to vinyl chloride, a known carcinogen. The objective of the study is to provide data that permit a species comparison of tumor response and an analysis of the exposure regimens that provide a predicted carcinogenic response. The data may indicate that a period of exposure of less duration than is currently employed will provide a meaningful bioassay result. These studies are projected for completion in FY 80.

"The National Toxicology Program assumed responsibility for 147 chemicals being tested for carcinogenic potential in lifetime rodent bioassays. Draft reports on 13 of these chemicals are expected to be completed in FY 79 and formally issued in early FY 80. An additional 106 chemicals have been selected for extensive toxicologic and carcinogenic evaluation. Resources will permit testing to commence on 60 of these chemicals in FY 79 with testing of the remaining chemicals scheduled for FY 80. There are 104 chemicals that have been nominated for testing which will be evaluated for selection. Chemical nomination and selection is a continual process."

NTP also carries out teratology and mutagenesis testing plus toxicologic characterization in such areas as neurobehavior, fertility and reproduction, immunotoxicology, renal toxicology and respiratory function. When extensive toxicologic efforts are conducted, dose related data on absorption, disposition and metabolism is collected.

One of the justifications offered for combining the various HEW toxicity testing efforts was that it was wasteful not to look for all adverse health effects when testing a chemical. Rall insisted that data on a variety of toxicities in addition to carcinogenesis, along with pharmacokinetics and metabolic studies "can be meshed into a standard two year study, and it can be done very nicely."

Whatever the organizational setup is, the spector hanging over NTP is that of the infamous "backlog" which was eliminated, after heroic effort, earlier this year.

That backlog was created by rushing great numbers of new chemicals into test in 1972-73 without full appreciation of the time required and difficulty involved in analyzing results. When the tests were completed, the staff was not available to do the pathology and write the reports.

NCI initiated the prime contract with Tracor Jitco to help manage the program, but that wasn't enough to do the job as quickly as had been hoped. The job finally was accomplished with the help of additional staff members Obey obtained through an appropriations bill and forced NCI to take into the testing program.

With even more pressure now on NTP to add more chemicals to the program, another horrendous backlog could be in the making. The prime contractor approach now has been foreclosed; if those 28 additional positions are not made available and filled, we may see a rerun of history.

HEW FINALLY MOVES ON DISTRIBUTION OF CHEMICALS TO ALL INVESTIGATORS

The long struggle to gain equal treatment for NCI grantees with contractors in the distribution of NCI supplied reference chemicals is almost over. HEW has completed the formalities of delegating the required authority to NIH; all that remains is for NIH to pass that authority on to NCI.

Contractors have always been able to tap NCI's repository of chemicals, but due to an oversight in the National Cancer Act of 1971, NCI could offer biological materials to grantees at no charge but not chemicals.

When the Act was renewed last year, a section was added permitting NCI to distribute chemicals as well as biologicals to any investigator with a legitimate use for them. But that authority was granted to the HEW secretary, along with a variety of other new authorities. HEW had to go through what turned out to be a tedious process of developing regulations for delegating the authorities to the appropriate agencies.

It has now been a year since the renewal was signed by the President, which seems to be an inordinate amount of time to complete a relatively simple bureaucratic process. It still has not been completed, although the authority could be passed on to NCI by NIH momentarily.

One of the hangups was what to do about the language in the renewal bill which specifically permits agencies to charge for materials they have been giving away. That raised the possibility that the effort to get equal treatment for grantees would be in vain if everyone started selling those items.

That is probably not going to happen, however. HEW has passed the word that there will be no uniform policy established on payment for research materials and that agencies will be permitted to distribute items at no charge if they so desire. Those which have been requiring payment (as NCI does for certain materials) may continue to do so.

ETHICS BOARD TO CONSIDER COMPENSATION ISSUE; AACI ASKS CANCER REPRESENTATION

The HEW Ethics Advisory Board will discuss at its Sept. 14-15 meeting in Washington whether it will take up the issue of compensation for subjects injured while participating in clinical research. If the

Board does decide to take it on, the controversy that has been simmering for four years could be quickly brought to a boil.

The EAB is an advisory body to Secretary Patricia Harris. Any decision it makes would be in the form of a recommendation to Harris, who could then proceed to implement it or not.

An HEW task force recommended in 1975 that the department consider requiring institutions which carry out clinical research supported by HEW funds to compensate patients who are injured as a result of that research. No action on that recommendation has been taken, except that HEW last year put into effect a regulation which requires institutions to notify research subjects whether compensation is available if they are injured.

Any compensation requirement would have serious implications for cancer clinical research, and various organizations have expressed concern. The latest expression is a letter from Roswell Park Director Gerald Murphy, representing the Assn. of American Cancer Institutes. The letter was sent to Charles McCarthy, EAB staff director. Murphy wrote:

"As president of the Assn. of American Cancer Institutes, I would like to address myself to the proposal for compensation of patients involved in clinical therapeutic investigations. My viewpoint represents those from the 63 major cancer centers in the USA who are members of AACI.

"The proposal for compensation of research subjects experiencing excess injury during clinical therapeutic investigations is based on the premise that society gains by such studies and must compensate for injuries incurred. Also, such proposals assume that the survival rates of untreated cancer patients are known. There is very little data available to substantiate the support of this assumption.

"It must be realized that the situation in clinical research involving cancer patients poses a different set of circumstances from the usual setting. Cancer without treatment is inevitably fatal and in addition often a patient experiences considerable discomfort. There is no completely standard therapy for cancer of any kind today. A recognized need exists to improve the results of treatment with currently available methods and to bring new modalities in as they become available through preclinical research.

"Clinical research offers the cancer patient the best available treatment in a setting in which new information can be gained. The cancer patient is the principal beneficiary of this treatment, which often is associated with some risk because of the nature of the surgical procedure, radiotherapy, and chemotherapy used.

"It has been demonstrated that the risk of injury during clinical therapeutic investigation is greatest for the cancer patient. We feel strongly that any consideration of the matter of compensation for injured research subjects should have knowledge provided by an investigator experienced in clinical research for cancer. Furthermore, we would urge that the Ethics Advisory Board chairman, James Gaither, be provided with ad hoc members experienced in clinical research, particularly when this subject is under discussion. At some time in the future, we also advise that an experienced clinical investigator be appointed to the permanent Board. We think this action will be most helpful and appropriate.

"The implications of the compensation issue for continued clinical research for cancer patients is serious in our opinion and needs careful review as to its appropriateness and consequence of implementation," Murphy concluded.

Gaither is a San Francisco lawyer. Other Board members, who are appointed by the HEW secretary, include consumer, labor and other lay group representatives, and these members of the medical profession—Donald Henderson, dean of the Johns Hopkins Univ. School of Hygiene & Public Health; Robert Murray, Howard Univ. geneticist; Mitchell Spellman, dean of medical services at Harvard; Daniel Posteson, dean of the Harvard Medical School; Eugene Zweiback, an Omaha physician; and David Hamburg, who is vice chairman of the Board and is president of the Institute of Medicine.

At its September meeting, the Board will only consider whether it will take on the question of compensation. If it does, a public hearing will be held at a later date.

The meeting will be held in Room 800 (the Penthouse) of the Hubert H. Humphrey Bldg., on Independence Ave. in Washington, starting at 9 a.m. both days, all open. McCarthy said that the compensation issue probably will not come up on the agenda until after 10 a.m. Sept. 15.

GAO SUGGESTS NO LIMIT FOR INDIRECT COSTS BUT CEILING ON TOTAL COSTS

Paul Rogers, who was then a congressman and chairman of the House Health Subcommittee, became concerned two years ago about the increasing amount of NIH funds which were being paid out for indirect costs. He asked the General Accounting Office, the congressional investigative agency, to look into it.

Rogers noted that in FY 1976, NIH paid $316 million, averaging 42% of direct costs, to 611 institutions, and that 38 institutions received indirect cost awards in excess of $2.5 million each.

The GAO investigation has been completed. The report (HRD-79-67, available from US GAO, Distribution Section, Rm 1518, 441 G St. NW, Washington DC 20548, no charge for single copies) recommends that:

• Since significant differences exist among grantee institutions on how indirect costs are arrived at, the government should not attempt to place limits on just the indirect cost of health research.

• Rather, if Congress should desire to further limit federal participation in research projects, it should be done through a formal ceiling on reimbursement, perhaps by requiring minimum mandatory grantee participation in total costs.

A summary of the GAO report follows:

Indirect costs are costs for goods and services which cannot be identified readily with specific projects. For this reason, accountants have devised methods, based on estimates, to distribute these common costs among individual projects. Depending on circumstances, one organization could charge an item of cost directly to projects; another might choose to charge the same item indirectly.

For many years federal reimbursement of grantees' indirect costs was limited to a specific percentage. Since 1966, appropriation act language has provided that the federal government will not reimburse a grantee the entire cost of a research project. Cost sharing continues to be required on research grants and no limits have been reimposed on indirect cost reimbursement.

Federally sponsored health research has increased from $1.6 billion in 1973 to an estimated $2.7 billion in 1978. Indirect costs associated with this research are taking a greater share of each research dollar.

GAO asked NIH 1977 grantees what caused the greatest increase in their indirect research costs. Responses from 444 grantees showed that the most frequently mentioned factors were utilities and compliance with government mandated programs and administrative requirements. GAO's work at 14 of the larger grantees supported utilities as a cost-increasing factor. Lack of specific records prevented GAO from determining the extent of the effect of complying with government requirements. Indirect costs for supplies and materials, books and periodicals also have increased greatly in recent years.

Comparing indirect cost rates among institutions is not meaningful for measuring the relative efficiency of research activities. Many factors, such as the age and type of facilities used, accounting system differences, the type of research performed, and a host of other considerations, cause wide variations in indirect cost rates.

Various sets of federal guidelines have been promulgated which set forth cost principles and negotiation instructions to be used for reporting and recovering research costs under grants and contracts. Government wide guidelines have been issued for educational institutions and for state and local governments. The Office of Management & Budget is in the process of developing guidelines for nonprofit research institutions. The Dept. of Health, Education & Welfare issued its own guideline for hospitals and another for nonprofit research institutions. The Dept. of Defense has incorporated the OMB guidelines for educational institutions and state and local governments into the Defense Acquisition Regulation, but it is silent on nonprofit research institutions and hospitals.

Cost principles are not always consistently stated among the various guidelines. For example, the basis that can or must be used for determining the indirect cost rate varies among the guidelines currently in effect. Also, there are many instances where the principles are ambiguous and contain editorial variations which can lead to differing interpretations on the allowability of certain costs.

OMB has recently revised its guideline applicable to educational institutions. These revisions will be a significant improvement over those previously used. The revisions provided more specific principles on distribution methods, identification and assignment of indirect costs, and standards for selected items of costs. However, inconsistencies with cost principles in other guidelines still exist.

GAO's review at 14 institutions having large health research activities showed significant differences in the extent of audit coverage requested and/or actually performed, and the methods used to negotiate indirect cost proposals. Questionnaire responses from 444 NIH grantees suggest that differences in audit frequency and negotiation methods occur often.

The Defense Contract Audit Agency has a significantly higher frequency of indirect cost proposal audit coverage at grantee institutions than does the HEW Audit Agency. Although negotiators consider the results of audit reports in negotiating indirect cost rates, the benefits of these audits are not compiled and their cost effectiveness is uncertain. GAO is therefore unable to conclude whether Defense Contract Audit Agency audits of indirect cost proposals are too frequent or HEW audits are not frequent enough from the standpoint of maximizing return on audit resources.

Agency negotiation officials generally negotiate indirect cost rates on an annual basis. Significant differences, however, were noted in the methods used to negotiate indirect cost rates. Some negotiators relied on their own desk reviews of institutions' proposals, others performed their own onsite audits, and still others relied on federal audit agency reviews. Since GAO did not evaluate the quality of the indirect cost data submitted to negotiators by grantees, it did not evaluate the adequacy of the negotiation actions.

RECOMMENDATIONS TO AGENCIES

GAO recommends that:

—The director of OMB should require that there be a consistent presentation of principles in the guideline for educational institutions (Circular A-21), the guideline for state and local governments (Federal Management Circular 74-4), and the proposed guideline for nonprofit research institutions.

—OMB should work with HEW to encourage that the principles in its guideline for hospitals be brought into conformity with OMB guidelines.

–The Secretary of Defense should require that the Defense Acquisition Regulation incorporate the cost principles in HEW's guidelines for nonprofit research institutions and hospitals. Since HEW has issued guidelines for these organizational types, DOD should adopt them until such time as OMB establishes government wide guidelines.

–The OMB director should add a provision to its guidelines which would allow grantees to use a cost accounting system disclosure statement approach to identify accounting methods and changes made to them. Once grantees have established specified accounting practices and auditors and negotiators have determined them to be acceptable, subsequent reviews could be limited to system changes. GAO believes that this would allow already limited audit resources to be more effectively directed.

–The secretaries of Defense and HEW, either jointly or separately, should analyze current practices for auditing indirect cost proposals related to research grants and contracts to identify the benefits derived. The results of the analyses would provide a basis to establish dollar thresholds for audit. When coupled with the "disclosure statement" approach recommended above, this could enhance the effectiveness of audit resources.

RECOMMENDATIONS TO THE CONGRESS

If the Congress should desire to further limit federal participation in research project expenditures beyond the present legislative restriction, GAO recommends that this be achieved through some formal ceiling on federal reimbursement, such as by requiring minimum mandatory grantee participation in total costs, rather than by limiting reimbursement on just the indirect cost portion of research. A reimbursement limitation imposed in this way would be more equitable among different institutions, since indirect cost rate comparisons are not meaningful and reflect a variety of accounting practices and other differences. Further, limiting federal reimbursement in this manner would avoid the possibility of costly accounting system changes to increase direct cost classifications which might result of limits were imposed on the indirect cost portion of total research expenditures.

Institutions where GAO did detailed audit work in its study were Albert Einstein College of Medicine, California Institute of Technology, Johns Hopkins Univ., State Univ. of New York (Albany), Univ. of California (Berkeley), Yale Univ., Scripps Clinic and Research Foundation, Sloan-Kettering Institute for Cancer Research, The Salk Institute, Wistar Institute of Anatomy and Biology, Children's Hospital Medical Center (Boston), Sidney Farber Cancer Institute, Massachusetts General Hospital, and New York State Dept. of Health.

AGENCY COMMENTS

Agency officials generally agreed with GAO's conclusions and recommendations, but a few concerns were expressed.

While OMB believed the disclosure statement approach recommendation may have merit, it wanted to explore the matter further with the federal agencies involved and with the universities because of additional paperwork that might be generated. The Committee on Governmental Relations of the National Assn. of College and University Business Officers endorsed the disclosure statement concept and offered to work with OMB to field test it.

DOD's Defense Contract Audit Agency stated that the disclosure statement will facilitate the audit process, but it should not be construed as a cure-all.

HEW agreed with GAO's recommendation to analyze current auditing practices to identify the benefits derived. DOD's Defense Contract Audit Agency stated that its present frequency of audit carefully considered the extent of risk and available resources and suggested that GAO delete its recommendation for a joint HEW/DOD analysis of practices for auditing indirect cost proposals. However, GAO found that the Defense Contract Audit Agency headquarters does not have information centrally compiled to show the cost/benefit of such audits. Accordingly, GAO believes that its recommendation to analyze current auditing practices to identify the benefits derived is appropriate.

NCI CONTRACT AWARDS

Title: Prototype Comprehensive Network Demonstration Project in Breast Cancer, one-year renewals

Contractors: Institute for Cancer Research/Fox Chase Cancer Center, Philadelphia, $71,385; Albany Medical College, $149,395; and Georgia Cancer Management Network, Atlanta, $80,706.

Title: Prototype Comprehensive Network Demonstration Project in Head & Neck Cancer, one-year renewal

Contractor: Univ. of Wisconsin, $46,590.

Title: Breast Cancer Detection Demonstration Project, one year renewal

Contractor: Good Samaritan Hospital, Portland, Ore., $257,560.

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