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P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

## FDA Committee Okays High Dose Methotrexate, Mitoxantrone In ANL; Reverses Breast Cancer Vote

The Food & Drug Administration's Oncologic Drugs Advisory Committee recommended approval of two new drug applications, including a supplemental indication for the familiar old

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*In Brief*

## John Tampas New ACR President; Stanley Order ASTRO President Elect; Cairoli Heads Training

**JOHN TAMPAS**, chairman of radiology at the Medical Center Hospital of Vermont, is the new president of the American College of Radiology. Other officers are John Gwinn, Univ. of Southern California, vice president; Carl Bogardus, director of radiation therapy at the Univ. of Oklahoma Medical School Health and Sciences Center, secretary treasurer; Thomas Meaney, chairman of radiology at the Cleveland Clinic, chairman of the Board of Chancellors; Franklin Angell, chief of radiology at Mercy Hospital, Baltimore, vice chairman of the Board; Murray Janower, St. Vincent Hospital, Worcester, MA, speak of the Council; and Milton Gallant, General Hospital, Passaic, NJ, vice speaker . . . . **STANLEY ORDER**, Johns Hopkins School of Medicine, is president elect of the American Society for Therapeutic Radiology & Oncology. That office was omitted from the list of new ASTRO officers which appeared in the Nov. 20 issue of **The Cancer Letter**. . . . **VINCENT CAIROLI**, program director in the Organ Systems Section of NCI's Div. of Cancer Prevention & Control, is acting chief of the Cancer Training Branch. He replaces Barney Lepovetski, who is heading up NCI's new Office of Technology Development (see **Cancer Economics**, this issue). . . . **APPROVED HOSPITAL** cancer programs (approved in the program operated by the American College of Surgeons Commission on Cancer) now total 1,196. ACOS has agreed with the concept of surveying and approving nonhospital based cancer programs, such as those in free-standing cancer centers. . . . **SAMUEL WELLS** has been elected chairman of the ACOS Executive Committee, with **Robert Janes** as vice chairman. Other committee chairmen are Hugo Villar, Cancer Liaison; Glenn Steele, Patient Care & Research; John Niederhuber, Cancer Management Course; Edward Gray, Approvals; and Morton Wilhelm, Education. . . **JOAN HARTMAN** Moore, former staff member of the NCI Office of Cancer Communications, has moved from Nancy Low & Associates to the Assn. of American Medical Colleges as director of education.

## FDA Committee Reverses Decision On Mitoxantrone For Breast Cancer

(Continued from page 1)
drug, methotrexate, in high doses in combination with other drugs for treatment of osteosarcoma.

The committee also recommended approval of mitoxantrone (named Novantrone by its sponsor, Lederle Laboratories) in combination with approved cytotoxic drugs for treatment of acute nonlymphocytic leukemia.

In a reversal that gave FDA staff a solid victory and cut the ground from under one of NCI's arguments in the recent confrontation of the two agencies, the committee voted against approval of mitoxantrone for treatment of advanced metastatic breast cancer.

The committee previously had voted 9-2 in favor of mitoxantrone, proposed as a substitute for adriamycin in various combinations against breast cancer. FDA refused to approve the drug despite the recommendation, and that refusal was cited by Bruce Chabner, director of NCI's Div. of Cancer Treatment, and NCI Director Vincent DeVita, as an example of FDA staff unreasonably keeping good anticancer drugs off the market.

Robert Temple, director of the FDA Office of Drug Research & Review, defended the decision on mitoxantrone when he appeared with FDA Commissioner Frank Young at the DCT Board of Scientific Counselors meeting in October (**The Cancer Letter**, Oct. 9). He said new information would vindicate that position.

That information was presented at the committee's meeting this week: mitoxantrone's response rate of 14.8 percent is about 50 percent of that of adriamycin; survival is significantly less with mitoxantrone (median 188 days vs. 315 days); and even the quality of life issue was unclear.

Lederle representives and those of the Southwest Oncology Group who discussed the study acknowledged mitoxantrone's relative lack of effectiveness. But they pointed to its significantly less nausea and vomiting and alopecia, among the severe toxicities seen with adriamycin. Those sometimes cause women to refuse treatment, which prompted committee member George Canellos to comment that treatment with a less effective but less toxic drug may be better than no treatment at all.

However, Canellos said, "My enthusiasm for this drug, for this indication, has waned."

The cardiovascular toxicity frequently seen with adriamycin was perhaps the most important side effect which had been a possible advantage for mitoxantrone. But Lederle admitted that it also produced cardiotoxicity, although at much higher doses than adriamycin.

Even with the established reduction in toxicities, mitoxantrone did not seem to have an advantage in quality of life over adriamycin, according to a study presented to the committee. Moreover, FDA staff member Gregory Burke said, "Quality of life is an issue only for those treatments that are effective."

The SWOG studies did indicate that mitoxantrone might be closer to adriamycin in effectiveness for certain subsets of low risk patients. Canellos urged that "properly constructed" trials of low risk patients be carried out. "More less noxious agents are badly needed."

Committee member Charles Moertel said that when the application was recommended for approval by the committee, "the evidence then simply was not clear and compelling. FDA was tarred and feathered for that decision, on one occasion very publicly [the DCT Board meeting]. FDA staff showed their wisdom in that decision. We should cheer them on for not giving in to heavy pressures."

The vote on approval was 7-3 against, with Teresa Vietti abstaining. Canellos, committee Chairman Martin Abeloff and Robert Capizzi voted for approval, primarily on the basis that patients should have a choice of a less toxic agent.

### First Line Treatment

The committee made two recommendations on mitoxantrone in the treatment of ANL. It voted 7-2, with Moertel and Elaine Smith opposed and with two abstentions, for approval as first line treatment in combination with cytosine arabinoside. It then voted unanimously against mitoxantrone as a single agent or in combinations for treatment of ANL relapses.

Lederle presented results of two studies which it said demonstrated that mitoxantrone was at least as effective as daunorubicin when combined with Ara-C, considered the standard for induction therapy of ANL. There were small differences in complete responses and in duration of remission, none of them statistically significant. Almost no differences were seen in toxicity.

Zalmen Arlin, New York Medical College,

who discussed one study, said that "the hope is that when a replacement is found for Ara-C that is less toxic, then the full benefits of mitoxantrone will become apparent."

Stephen Saletan of Lederle discussed a phase 3 international trial conducted to confirm the smaller trial reported by Arlin. There were few differences in results between the mitoxantrone and daunorubicin groups. One difference, Saletan noted, was that 85 percent of the mitoxantrone patients who achieved complete remission did so after one cycle; only 56 percent of those achieving complete remission with daunorubicin did so after one cycle.

The median followup in the international study was only 18 months. "I'm not too enamored of short term results," Moertel said. He suggested that after further follow-up, the mitoxantrone survival "could be zip" while the daunorubicin survival rates plateaued at about 25 percent.

Moertel said that if after another 18 months of followup the survival patterns remained the same, he would agree that equivalency existed and would vote for approval.

Vietti disagreed with Moertel, noting that the patients had been off therapy for a year or more. "To think the curves will drop off now is not realistic."

**The Osteosarcoma Controversy**

Approval of high dose methotrexate for use in combination with other drugs for treatment of osteosarcoma ended another chapter in one of the more controversial stories of cancer chemotherapy.

After Isaac Djerassi demonstrated in the late 1960s that methotrexate could be given in very high, lethal doses when administered properly and followed with leucovorum rescue, it was used by Norman Jaffe at Harvard and Gerald Rosen at Memorial Sloan-Kettering in combination with other drugs to treat osteosarcoma. Until then, survival at two years was less than 20 percent. The combination drug regimens increased, or appeared to, long term survival to about 50 percent. Other studies had similar results, although it was becoming clear that other factors may have played a role in survival improvement.

Those studies all used historical controls. In 1976, the Mayo Clinic initiated a trial of high dose methotrexate vs. concurrent surgery only controls. The result: At eight years median followup, survival was 45-50 percent in both groups. Moertel, then director of the Mayo Comprehensive Cancer Center, has frequently cited that study in attacks on the value of historical controls. He argued that the Mayo study demonstrated at least the possibility that improved survival seen by Jaffe and Rosen was not the result of chemotherapy but rather to improved surgical techniques, more aggressive treatment following relapse, and possibly earlier diagnosis.

The Pediatric Oncology Group in 1982 initiated a study using a combination of bleomycin, cyclophosphamide and dactinomycin followed by high dose methotrexate, adriamycin and cisplatin (this and the other studies were briefly reviewed for the committee).

Patients were randomized to chemotherapy or no chemotherapy following surgery, with 18 evaluable patients on each arm. Accrual ended in 1984. At four years median followup, 58 percent of those receiving chemotherapy are alive; only 17 percent of the surgery only patients survive.

An additional 77 declined randomization; 59 received chemotherapy, 18 observation only after surgery. Twenty one of the 59 failed, compared with 15 of 18 failures in the untreated group.

Robert Justice, FDA medical officer, said he was willing to recommend approval of high dose methotrexate if used in combination with other drugs. He said the Mayo study did not have enough patients (20 on chemotherapy, 18 surgery only) "to resolve the question, while there are enough other studies that do."

Canellos said the POG study "is striking." He noted the "poor results" from surgery only, and the ability to salvage patients with chemotherapy following relapse. "It's comforting to know you can do it but is not a substitute for adequate chemotherapy at the start." He acknowledged that it "is difficult to appreciate methotrexate's role per se."

Moertel said he would vote for approval "because I have to." But he wanted to go on record that he was not voting for the principle of historical controls. He also said he was not convinced that methotrexate added anything to efficacy of the regimens.

Explaining why he "had" to vote for approval, Moertel later told **The Cancer Letter** that high dose methotrexate is being widely used anyway, since because of approval for other indications it is a prescription drug. However, it is available only in smaller vials, making it more expensive and more difficult to formulate into doses. "It's simply a practical matter," he said.

## Organ Systems Backers Go On Offense In Defending Program's Status Quo

Members of the National Cancer Advisory Board's Committee on Organ Systems Programs met last week to hear presentations on NCI Director Vincent DeVita's proposals for drastic changes in the program.

"We're here to listen and not to debate the issues now," Committee Chairman Bernard Fisher said.

The committee heard an earful.

Donald Coffey, chairman of the OSP's Prostate Cancer Working Group, pointed to what he said was "the absurdity of the situation. We get 12 to 14 people to meet [to discuss the research that should be done but which is not being done and translate that into recommendations for NCI requests for grant applications or program announcements--the primary mission of the Organ Systems Program].

"We come down on the three or four hottest ideas," Coffey continued. "We have brought in the top people in the field, to make sure we're not just talking to ourselves. These are the brightest people in the business. Then we take these ideas to the NCI Executive Committee, not one of which up to and including Dr. DeVita has ever published anything on prostate cancer. And to a board of scientific counselors, not one member of which has ever published anything on prostate cancer. None of them have the foggiest idea what we're talking about."

That is why, Coffey said with more than a touch of sarcasm, he favors going along with DeVita's suggestion that the Organ Systems Coordinating Center (now at Roswell Park Memorial Institute) be abolished and the work it does moved to NCI. "Take it inside. But NCI should have a Div. of Solid Tumors, with its own board of scientific counselors."

Coffey had some words for the NIH Div. of Research Grants, where many organ systems grants are reviewed. "Why don't they have a study section for organ systems?"

Coffey concluded, "Unless they get on the stick and do these things, there's not a prayer in hell of reaching the Year 2000 goals."

DeVita's other suggestions for changes in the Organ Systems Program included dispersing the portfolio of grants now managed in the Organ Systems Section, located in the Cancer Centers Branch, Centers & Community Oncology Program of the Div. of Cancer Prevention & Control. Those could be better managed if handled by program directors in the four program divisions, DeVita said.

Under DeVita's plan, the Organ Systems Section, headed by Andrew Chiarodo, would then be free to take over the Organ Systems Coordinating Center's duties of administering the working groups, organizing workshops, and handling the various other communication activities. It has not been made clear whether there would even be an Organ Systems Section under that plan.

William Shingleton, chairman of the OSCC Advisory Committee, presented that committee's alternative proposals. One of them was, rather than downgrade the role of the program at NCI, the Organ Systems Section should be elevated to program status.

That suggestion probably will not go anywhere, but the committee's other suggestions may fare better. Shingleton, director emeritus of the Duke Comprehensive Cancer Center and a member of the NCAB when the Organ Systems Program was initiated, said the committee reached a consensus that:

*"The present arrangement whereby the OSCC is located in a major cancer center has worked very efficiently and provided the working groups with excellent support to meet their objectives and has disseminated effectively the results of the meetings of the groups to the general scientific community. It was not clear that moving OSCC would reduce the financial cost of operation of the center. The advisory committee recommends, therefore, that OSCC be maintained in a major cancer center outside of NCI.

*"An enhanced visible focus of OSP and improved communication with components of the OSP activities to the scientific community will most likely occur if the OSP grants portfolio resides in the NCI component of the OSP rather than dispersed to divisions of NCI.

The committee also suggested that ad hoc committees reviewing grants generated by OSP RFAs be broadened to include multidisciplinary expertise, and that the approval process for RFAs and program announcements be shortened.

James Karr, who heads the OSCC as principal investigator for the cooperative agreement that funds it (and whose salary, incidentally, is paid entirely by the New York State Dept. of Health) made these points regarding the grants portfolio:

"In order to function efficiently, the

working groups must be kept informed on the focus and progress of current research activity. If the working gorups are to be regular provided with a comprehensive overview of basic and clinical research that is targeted to or which is relevant to a specific cancer site, there must be a central source and mechanism for handling such grants activity, and dispersal of the portfolio does not seem to be an approach that would serve this purpose."

After recounting the myriad of tasks performed by the OSCC, Karr said, "Given all that the OSCC does, it is hard to imaging how the Organ Systems Program can be strengthened, say nothing of maintaining it, without an external coordinating center. The coordinating center is now headquartered at Roswell Park, but there are many other capable institutions in this country which could successfully operated an OSCC. This will only be known if the recommendation is made to issue the RFA calling for a nationwide recompetition for the OSCC."

Karr noted that "there are certain obvious advantages to having an external coordinating center." Among them are:

--OSCC was given departmental status at Roswell Park and therefore cannot become diluted or side tracked with non-organ systems activities.

--The staff is nontransferable. "No one can come to me and say I want to use this or that person for some purpose unrelated to organ systems.

"In contrast, most of us are aware that the Organ Systems Section within NCI has lost Dr. Vincent Cairoli, who was program director for the Large Bowel and Upper Aerodigestive cancer programs. Dr. Cairoli's recent transfer to the Cancer Training Branch has created a tremendous void and the 25 percent reduction in professional staff that this represents has put the Organ Systems Section under a tremendous burden, because I can assure you that there has been no compensatory cutback in the activities of the OSCC and the working groups."

Bradford Patterson, a member of the OSCC Advisory Committee (with Walter Lawrence, Peter Magee, Willet Whitmore, James Cox and Sidney Winaiver, said he has been "particularly impressed that there is a minimum of bureaucratic makework" in the program. "This seems to me to be a nuts and bolts program.

"If these impressions are correct, why should we change it?" Patterson asked. "I don't see it as inefficient or wasteful. The boards of scientific counselors have approved almost all the submitted concepts and the track record of approvals has been equivalent to those emanating from other committees.

I can imagine that the NCI directors are concerned about the possibility of severe budget cuts in the near future and are therefore constrained to look at every program with an eye to prioritization, but I would hate to see the Organ Systems Program cut back in order to protect another program which is not as well focussed on those cancers which cause 40 percent of our cancer deaths annually.

"Another obvious reason for the institute to change this program would be a reluctance on the part of NCI leadership to have this many dollars not allocated by initiatives which were developed within the institute. As budgets are cut back, institutes try to exert greater control over the spending of any remaining dollars. Shrinking budgets make all of us reach for the purse strings to tighten them up. But I do not see how the objectives of the Organ Systems Program could be sought more efficiently or effectively from within the institute. I want to assure Dr. DeVita that these monies are being efficiently and effectively spent."

The committee will meet prior to the next meeting of the NCAB, scheduled for Feb. 1-3. The full Board will make its recommendation then; DeVita has said he will accept it.

*Other comments at the meeting, including those by NCI staff members, will appear in the next issue of* **The Cancer Letter.**

## Final Issue of 1987; Next, Jan. 1

This issue of **The Cancer Letter** is the 48th and final one of the year and of volume 13. The next issue will be Volume 14, No. 1, dated Jan. 1, 1988.

**The Cancer Letter** office will be staffed most of the time through Dec. 24. After that, phone calls will be answered by the tape machine, and messages will be returned when the office reopens Tuesday, Jan. 5.

Because of a malfunction which (hopefully) has been corrected, some calls left on the tape during Thanksgiving week and possibly on one other occasion were erased before they were monitored. To those who have not had responses to their calls, please accept our apologies and try again.

From all our staff members, best wishes for the holiday season and the New Year.

## Feasibility Study To Increase CIS Cost Sharing Okd By DCPC Committee

Plans for a feasibility study of how to increase cost sharing by local Cancer Information Service contracts by asking them to limit the amount of overhead have been approved by members of the Cancer Control Science Committee of NCI's Div. of Cancer Prevention & Control.

The committee suggested that DCPC pursue feasibility studies of limiting the amount of overhead to a fixed percentage, while developing a long range plan for further cost sharing. The members unanimously agreed that the system should ideally achieve full coverage at some point in the future.

DCPC staff member Kate Duffy outlined two options to increase cost sharing by CIS offices: one, to limit overhead, and the other to require sponsoring organizations to assume 25 percent of total costs.

NCI currently funds 16 CIS offices, with another nine offices independently operating without any NCI funds. The nine independent offices represent "a precedent for cost-sharing," Duffy said.

If NCI decided to fully fund CIS offices, it would require approximately $14 million to fund 32 offices. The current budget for the CIS program amounts to about $5.7 million.

Under current procedures, CIS offices are flat funded, with the salaries of principal investigators donated.

Noting that costs have increased for the offices, Lillian Giglotti said "these offices have been continuing on a flat budget for five years. So it's a stifling budget we've been imposing on them" already, she acknowledged. Giglotti is DCPC associate director and director of the Cancer Control Science Program.

Committee member Donald Hayes suggested that NCI pursue the feasibility of the first option to limit overhead. Member William Darrity suggested that NCI explore the combination, and "see what responses you get. I really want to see this program expanded," he said. "We really have to get more money."

Although Darrity and Hayes suggested that NCI could consider combining both options, Giglotti warned that it could be difficult to take both actions at this time, adding that while NCI can legally limit overhead, some contractors might challenge the limitation.

Committee Chairwoman Virginia Ernster said, "I'm inclined not to give them a double whammy at this point." Hayes proposed that DCPC pursue feasibility studies to limit overhead, and establish an advisory committee to develop a long range plan for cost sharing. He also suggested that the institute consider soliciting a proposal from small businesses to set up a model CIS office with reduced overhead.

Duffy presented the results of a CIS marketing research plan and a recently completed survey of CIS offices and cancer information coordinators. Noting that nine CIS offices continued without funding from NCI, she said the offices have found that being affiliated with CIS holds advantages for them. CIS offices "continue to be the largest users of PDQ," NCI's computerized Physician's Data Query information system, and are extremely capable of handling calls and inquiries from the local media when major cancer related events occur.

"Substantial portions of the country" remain underserved, however, she said, noting that 17 states and the District of Columbia have no local CIS offices.

The committee also approved two CIS related concepts to solicit proposals under the Small Business Innovative Research program.

The first SBIR concept would solicit proposals for the automation of CIS data collection procedures. Proposals would be sought to enable each CIS network office to input data directly to a national system and access their local data separately from the national data. Mechanisms for assuring consistency of the data entered will be included.

Phase 1 proposals would result in the development of the system design, with specifications for equipment and computer software to be provided. In phase 2, the contractor would be expected to design and conduct pilot tests, coordinate full scale implementation of the system for the entire network, and design and perform monitoring and evaluation plans for the system.

Ernster suggested that the solicitation should also include quality control issues, since the automation of the system will eliminate review by supervisors.

Another SBIR concept would solicit proposals for the development of systems to route inquiries to the most appropriate and efficient response. Systems may include a combination of response mechanisms including CIS staff and automation response systems.

Phase 1 would include an analysis of the current system and result in a design for routing inquiries. The plan should include recommendations for communications and computer technology needed.

In phase 2, the contractor would be responsible for the design and conduct of pilot tests, full scale implementation of the system for the entire CIS network, and the design and conduct of evaluation of the system, including a user satisfaction survey evaluation.

Both concepts will go before DCPC's full Board of Scientific Counselors at its meeting the second week of January.

## Cancer Control In Special Populations Concepts OKd By DCPC Committee

The Cancer Control Science Committee of the Div. of Cancer Prevention & Control has approved a concept for cancer control developmental research in special populations. If approved by DCPC's full Board of Scientific Counselors, the concept would result in a program announcement to encourage studies in the areas of needs assessment or instrument validation; intervention evaluation; and developmental intervention.

The major goals and objectives of the studies would be: a) to assess cancer prevention and control needs in communities with large special populations (i.e., blacks, native Americans, Hispanics, Asian Americans, low income groups, blue collar workers and the elderly; b) to identify barriers to cancer prevention and control in special populations; c) to validate the use of existing intervention methods (e.g., dietary modification, health services patterns) as applied in special populations; d) to develop and pilot test unique intervention methods sensitive to the needs of special populations; and e) to develop and validate assessment instruments to measure the cancer control related needs of special populations and to evaluate the effectiveness of intervention methods in special populations.

The committee also approved a concept that could result in an RFP for cancer control research in native Americans. If approved by the full DCPC board, NCI could fund up to six five year awards, at least one targeted to each population group (American Indian, Alaska native, and native Hawaiian) for each RFP issued. Funding for each award would begin at $150,000 per award district in FY89, increasing to $250,000 in fiscal years 1990 through 1993.

The goals and major objectives of the projects would be to characterize the cancer prevention and control needs of native american populations; identify innovative approaches that address excessive cancer risk through intervention research in native Americans; and to develop, implement and evaluate long term cancer control intervention in native americans.

The committee approved with proviso a concept for an interagency agreement with the Indian Health Service for cancer control research in American Indian and Alaska native populations. The three year agreement is expected to have total annual costs of $1 million. The project is intended to: stimulate cancer prevention and control research with the Indian Health Service; develop specific intervention research projects to be implemented within the Indian Health Service; and address the cancer control needs of American Indian/Alaska native populations.

The committee asked that DCPC officials provide more information on primary prevention of cancers in the Alaska native population in order to justify the proposed agreement.

In addition to primary prevention, the agreement would be expected to include secondary prevention of cancer in an IHS facility; tobacco use intervention; and health services research/pattern of care studies in American Indian cancer patients to focus on the adequacy and quality of early detection and treatment services provided by IHS and its contract care facilities.

The committee also approved a concept for a "Prescribe for Health" project intended to improve the routine office practice of selected preventive services by primary care physicians. If approved by the full DCPC board, the concept would result in an RFP for three six year awards--two for intermediary organizations, and one for an evaluation unit. Estimated costs for the awards would be $612,825 in FY88, rising to $1.15 million in FY89, with outyear funding ranging from $706,185 in FY92 to $1.15 million in FY91.

## NCI Advisory Group, Other Cancer Meetings For Jan., Feb., Future

DCPC Board of Scientific Counselors Committee on Prevention--Jan. 6., NIH Bldg 31 Rm 2, I p.m., open.

DCPC Board of Scientific Counselors Committee on

Centers & Community Oncology--Jan. 6, NIH Bldg 31 Rm 7, 7 p.m., open.

DCPC Board of Scientific Counselors--Jan. 7-8, NIH Bldg 31 Rm 10, 8:30 a.m. both days, open.

Third International Conference on Prevention of Human Cancer: Chemoprevention--Jan. 12-15, Arizona Health Sciences Center, Tucson. Contact Mary Humphrey, Conference Coordinator, Arizona Cancer Center, Tucson 85724, phone 602/626-2276.

Biological and Molecular Aspects of Atrial Peptides--Jan. 17-23, Steamboat Springs, CO. Contact UCLA Symposia, 103 Molecular Biology Institute, UCLA, Los Angeles 90025.

Occupational Health in the 1990s: Developing A Platform for Disease Prevention--Jan. 21-23, Washington DC. Contact Ellen Marks, Conference Coordinator, New York Academy of Sciences, 2 East 63rd St., New York 10021, phone 212/838-0230.

Transitional Cell Carcinoma of the Urinary Tract--Jan. 23-24, New Hyde Park, NY. Contact Ann Boehme, CMP Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park 11042, phone 718/470-8650.

Mechanisms and Consequences of DNA Damage Processing--Jan. 24-31, Taos, NM. Contact UCLA Symposia, 103 Molecular Biology Institute, UCLA, Los Angeles 90025.

Symposium Annuel d'Oncologie Pediatrique--Jan. 25, Paris. Contact L. Saint Ainge, Organisation des Reunions Scientifiques, Institut Gustave-Roussy, 39, rue C. Desmoulins, 94805 Villlejuif Cedex, France.

Session de Formation a l'Activite Pluridisciplinaire en Oncologie--Jan. 25-30, Toulouse, France. Contact Le Centre Claudius Regaud, 20-24, rue du Pont Saint-Pierre, 31052 Toulouse Cedex, France.

Care of the Patient with Cancer--Jan. 27-29, London. Contact Institute of Oncology Marie Curie Memorial Foundation, 28 Belgrave Square, London SW1X 8QG, UK.

Management of Hematologic Malignancies--Jan. 30, Cleveland. Contact Barbara Guy, PhD, Assistant to the Director, R. Livingston Ireland Cancer Center, Univ. Hospitals of Cleveland/Case Western Reserve Univ., 2074 Abington Rd, Cleveland, OH 44106, phone 216/844-7856.

Technological Advances in Vaccine Development--Jan. 30-Feb. 6, Park City, UT. Contact UCLA Symposia, 103 Molecular Biology Institute, UCLA, Los Angeles 90025.

B Cell Development--Jan. 31-Feb. 7, Taos, NM. Contact UCLA Symposia, 103 Molecular Biology Institute, UCLA, Los Angeles 90025.

National Cancer Advisory Board--Feb. 1-3 (?), NIH Bldg 31 Rm 6, open Feb. 1, 8:30 a.m.-adjournment; closed Feb. 2 for grant review. A decision on whether the Board will meet Feb. 3 is pending. Committee meetings will be announced later.

Diagnostic Cytopathology for Pathologists--Feb. through April, Home Study Course A, Johns Hopkins Univ. School of Medicine. In residence Course B is scheduled for April 25-May 6. Contact John Frost, MD, 604 Pathology Bldg, Johns Hopkins Hospital, Baltimore, MD 21205.

Monoclonal Antibody Immunoconjugates for Cancer--Feb. 4-6, Inter-Continental Hotel, San Diego. Third international conference. Contact Office of Continuing Education, Univ. of California (San Diego) School of Medicine, La Jolla, CA 92093, phone 619/534-3940.

Gene Transfer and Cancer Therapy--Feb. 6-12, Tamarron, CO. Contact UCLA Symposia, 103 Molecular Biology Institute, UCLA, Los Angeles 90025.

Cancer Control in Developing Countries--Feb. 8-9, Bangalore, India. Precongress workshop. Contact Dr. Krishna Bhargava, Director, Kidwai Memorial Institute of Oncology, Hosur Road, Bangalore, India.

Indian Society of Oncology--Feb. 10-12, Bangalore. III Biennial Congress. Contact Dr. Bhargava, address above.

Liposomes in the Therapy of Infectious Diseases and Cancer--Feb. 16-20, Lake Tahoe, CA. Contact UCLA Symposia, 103 Molecular Biology Institute, UCLA, Los Angeles 90025.

32nd Symposium on Endocrinology--Feb. 17-20, Hamburg, German. Contact M. Dietel, Institute of Pathology, University Hospital Eppendorf, Martinistr 52, 2000 Hamburg 20, Federal Republic of Germany.

Div. of Cancer Treatment Board of Scientific Counselors--Feb. 18-19, NIH Bldg 31 Rm 10, 8:30 a.m. both days. Closed Feb. 18, 4:30 p.m.-adjournment (tentative).

Neoadjuvant Chemotherapy--Feb. 19-21, Paris. Second international conference. Contact Prof. Claude Jacquillat, SOMPS, Hospital de la Salpetriere, 47 boulevard de l'Hospital, 75651 Paris, Cedex 13, France.

Ninth GDR Cancer Congress--Feb. 22-25, Leipzig. Contact Dr. K. Schauer, Organizing Committee, University Clinic of Surger, Leibigstr 20A, 7010 Leipzig, German Democratic Republic.

Div. of Cancer Etiology Board of Scientific Counselors--Feb. 25-26, NIH Bldg 31 Rm 10, open Feb. 25, 1 p.m.-adjournment and Feb. 26, 8:30 a.m.-adjournment.

Intracavitary Chemotherapy--Feb. 25-27, U.S. Grant Hotel, San Diego. Second international conference. Contact Office of Continuing Medical Education, M-017, Univ. of California (San Diego) School of Medicine, La Jolla, CA 92093, phone 619/543-3940.

22nd Annual Clinical Symposium--Feb. 26-27, Memphis. Contact Joseph Simone, Director, St. Jude Children's Research Hospital, Box 318, Memphis, TN 38101.

Cancer in Women: Diagnosis and Management--Feb. 27, Cleveland. Contact Barbara Guy, PhD, R. Livingston Ireland Cancer Center, University Hospitals of Cleveland/Case Western Reserve Univ., 2074 Abington Rd, Cleveland, OH 44106, phone 216/844-7856.

## FUTURE MEETINGS

Drug Treatment of Cancer Pain in a Drug Oriented Society: Adequate or Inadequate?--March 16-18, Houston. Contact Office of Conference Services, HMB Box 131, M.D. Anderson Hospital & Tumor Institute, 1515 Holcombe Blvd, Houston 77030, phone 713/792-2222.

Leukemia: Molelcular Alterations and Cellular Proliferation--March 16-19, Hotel Inter-Continental, New Orleans. fourth national symposium. Contact Louise Toglia, Leukemia Society of American, 733 Third Ave., New York 10017, phone 212/573-8484.

AIDS: Defining the Progress--March 24-26, Hilton Hotel, Daytona Beach, FL. Fifth annual oncology conference sponsored by Halifax Medical Center and the Regional Oncology Center, Herbert Kerman, director. Contact Educational Services, PO Box 1990, Daytona Beach 32015.

American Radium Society--April 16-20, Four Seasons Olympic, Seattle. 70th annual meeting. Contact Suzanne Bohn, Administrative Director, American Radium Society, 1101 Market St., 14th Floor, Philadelphia, PA 19107, phone 215/574-3179.

**The Cancer Letter** _Editor Jerry D. Boyd Associate Editor Patricia Williams

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Cancer Economics

## ACCC To Help JCAH Formulate Clinical Indicators For Oncology

The Assn. of Community Cancer Centers will help the Joint Commission on Accreditation of Healthcare Organizations formulate ongoing clinical indicators for oncology.

The project, which could have profound implications on the way cancer care is delivered in the United States, will involve the use of a computerized national data base to formulate organizational indicators and severity/case complexity adjusted clinical indicators.

CHOP-DS, the database, is maintained by ELM Services Inc., a management firm run for the association. ELM is owned by Lee Mortenson, who is also the ACCC executive director.

The database encompasses 370 hospitals in 29 states and includes approximately 10 percent of all U.S. cancer patients.

According to ACCC, the database and ELM staff are being made available to the Joint Commission without charge.

ACCC has formed an advisory committee with representation from:

--American Society of Clinical Oncology.

--American Society of Therapeutic Radiologists.

--Assn. of American Cancer Institutes.--College of American Pathologists.

--Memorial Sloan-Kettering Cancer Center.

--National Surgical Adjuvant Breast & Bowel Project.

--National Tumor Registrars Assn.

--North Central Cancer Treatment Group.

--Oncology Nursing Society.

--Southwest Oncology Group.

--Society of Surgical Oncology.

The project will attempt to identify and select valid and acceptable indicators of clinical structures, processes and outcomes with specific application to oncology.

(Continued to Page 2)



## NCI, NIH Implement Law Increasing Collaboration With Private Sector

The Federal Technology Transfer Act of 1986 (FTTA), which authorized establishment of NCI's new Office of Technology Development, "will revolutionize the way science is done in this country," according to OTD Acting Director Barney Lepovetsky.

It has certainly revolutionized the potential incomes of government scientists who are involved in development of technology that becomes commercially successful. In the past, most of the royalties or licensing fees to which the government was entitled went back to the Treasury. FTTA now permits individuals to receive a minimum of 15 percent of royalties and fees, up to a maximum of $100,000 a year. It can exceed $100,000 with concurrence of the President.

The new law also directs that the government laboratories or branches in which the technology originated share in income derived from that technology.

FTTA does far more than help make government employment more attractive to scientists. "It's a breakthrough in the direction of more efficient technology transfer," said Lepovetsky, who was appointed to the position for six months (**The Cancer Letter**, Nov. 27). He has been chief of the

(Continued to Page 7)

## JCAH, ACCC To Use Database In Formulating Oncology Indicators

(Continued from page 1)

In the first stage, each site committee will define which stages and histologies will be the major focus of their efforts.

Data from NCI's SEER program and from the CHOP-DS II National Data Base will be provided to each committee.

The criteria for selection include the potential for sample sizes sufficient for analysis, the existence of a state of the art in cancer patient management, the importance of the site and stage to an evaluation of cancer patient management.

After the clinical sites and stages are selected for initial consideration, the core committee will review the selection of sites and stages and give the individual committees feedback on possible additional selections.

The second stage of the indicator selection involves individual site committees in consideration of each selected site and includes the development of suggested indicators.

The criteria for potential indicators include their importance in clinical decision making, importance in evaluating the quality of patient management, importance in categorization of cancer patients, and importance in evaluating the outcomes of care.

The third objective of the project is to validate clinical indicator data and evaluate its availability, reliability and importance for selected cancer sites.

ACCC will ask hospitals to determine four things: Whether an indicator can be found within the medical record, whether an indicator not usually found is available from hospital sources or outside the hospital, and the cost of collection of information.

Next, indicators currently included in the CHOP system will be evaluated. ELM will perform a variety of analyses on each of these variables, including availability of data, relation of each variable to suggested outcome variables, and the relation of each variable to other possible characteristics of analysis.

The fourth objective is to examine available data on patient outcomes at various levels of analysis (patient, hospital, hospital size). The project will look at some of the problems of analysis, and differences in hospital characteristics.

The next step will be to review the evaluation of variables and develop recommendations for the presentation to the Joint Committee.

Finally, the project will monitor the Joint Committee's selected indicators and ACCC indicators and develop institutional profiles.

Using regions, hospital characteristics, and other criteria selected by the commission, cooperating institutions will be categorized and profiled.

It is possible that institutions significantly outside the normal distribution of profiles may be visited to determine why their data are outside the profile.

ACCC will review information from participating institutions on a quarterly basis and update previous assessments of the importance, validity and accessibility of clinical indicator information.

**Enck Senior Liaison**

The project organization is as follows:

Robert Enck, ACCC president, will serve as the senior liaison to the commission. Enck has served on the PTAC and has worked with the commission in a variety of roles.

Lee Mortenson will serves as senior project manager and will oversee the development of the indicators, their validation, and assure project timeliness.

Irvin Fleming will be chairman of the Core Committee.

Herbert Baum will serve as senior research scientist. He leads ELM's Research Div.

Rosemarie Clive will be the project coordinator for the various site committees and core committee meetings. She is a vice president of ELM and a director of ACCC, and a former director of the cancer department of the American College of Surgeons.

Each of the 10 major site committees are chaired by individuals from a variety of cllinical specialties. The site committees and their chairmen include:

Breast: Gale Katterhagen
Lung: Ralph Scott
Leukemia: Lloyd Everson
Ovary: John Yarbro
Prostate: Irvin Fleming
Colon/Rectum: Peter Deckers
Testis: Rodger Winn
Melanoma: Larry Nathanson
Bladder: Alan Yagoda

The appointment of a chairman for the Hodgkins and non-Hodgkins lymphoma committee is pending.

ACCC has also invited individuals from other organizations to assist in the review of clinical indicators.

"We are in the process of obtaining agreements for institutional participation in the project," the ACCC work plan said. "Since all data are institutional data, it is vital to obtain complete cooperation of the hospital participants.

"This should not be difficult, since all of the current CHOP-DS institutions have signed a participation agreement for the national data base and most have joined the system because of its extraordinary capabilities for comparative research.

"While this would be sufficient for some of the analyses, we will require cooperation from participating institutions for supplemental information and for use of the hospital characteristic data."

The database to be used in the project includes:

--Patient demographic information: Age, sex, race, place of birth and patient contact information.

--Cancer information: Topography, morphology, stage, staging system, tumor size, number of nodes positive and examined, class of case, and tumor grade.

--Diagnostic information: Pretreatment and site specific diagnostic tests and findings, clinical and pathological staging, and ICD9-CM coding.

--Treatment information: Site specific therapies including surgery, radiation therapy, immunotherapy, biological response modifiers, hormone, chemotherapy, residual tumor, quality of survival, radiation dose and fields, chemotherapeutic agents, and routes of administration.

--Referral information: Hospital referred from and to, ZIP code at diagnosis, current address, primary care physician, and attending physician.

--Survival information: Length of survival, disease free interval, sites and types of recurrence, cause of death, place of death, patient and tumor status, and subsequent therapies.

--Site specific clinical indicators: Key family history, pathology, diagnostic tests, consultations, and treatment data.

--Financial information: DRG coding, primary and secondary diagnostic information, charges, costs, reimbursement, and inpatient and outpatient billing.

--State required data sets: Information required by state governments.

--Institutional information: Hospital size, number of cancer patients, oncology unit, inhouse or freestanding radiation therapy unit, region of the country, medical director, levels of staffing, competition.

--ACOS required data items: All of the basic data items of the American College of Surgeons.

--Severity of illness: Provision has been made for the gathering of severity information for each admission.

The data base is also linked to several other data bases which may prove useful in the evaluation process:

--OSCAR: ELM's outpatient data base includes information on patient care outside the hospital in medical oncology offices. This data base is being developed in conjunction with 100 CHOP-DS hospitals and 30 medial oncology practices and is expected to accrue between 24,000 and 30,000 matched/combined inpatient and outpatient cancer records a year. The combined OSCAR/CHOP-DS data base is sponsored by grants from Bristol Myers.

--CFIS: ELM's CHOP-DS is becoming the standard for the Voluntary Hospitals of America, a group of 750 major hospitals. Preliminary plans to link CHOP-DS and VHA's CFIS system are now under discussion.

## Franciscans, Fox Chase Establish Regional Cancer Center in PA

The Franciscan Health System of Chadds Ford, PA, and Fox Chase Cancer Center of Philadelphia announced plans to establish the Bucks County Regional Cancer Center, the region's first community based comprehensive cancer treatment center, on the campus of Saint Mary Hospital in Langhorn.

The hospital was selected as the site for the $3.5 million cancer center because of the its extensive array of regional medical services and its central location, officials of both institutions said.

The 251 bed nonprofit hospital also has plans to develop a dedicated inpatient oncology unit, which officials said will complement the new center.

The 14,000 square foot regional cancer center will contain advanced radiation therapy and chemotherapy services, physician offices and treatment rooms, and the full range of support services, including social services, pastoral care, nutritional counseling, pharmacy and rehabilitation services.

Officials of the Franciscan Health System and Fox Chase estimate the Bucks County center will open during the summer of 1988.

During a groundbreaking ceremony last month for the facility, Fox Chase President John Durant and Franciscan Health System Chairman Sister Corda Marie Bergbauer said the new program will build on the strengths of both institutions in bringing cancer care to the region.

"We believe that this partnership between a comprehensive cancer center and a leading community hospital system will aid in the effective transfer of technology as it applies to modern cancer care," Durant said.

"Traditionally, there have been barriers between specialized medical centers and community hospitals," Sister Bergbauer said. "But we have overcome them in order to develop a program that we believe is a model for others to follow."

Durant noted that more than 80 percent of all cancer patients in the U.S. are treated in community hospitals. "It is critically important for all patients to have access to state of the art care, delivered by a multidisciplinary team and based on the latest medical research," he said.

Radiation therapy equipment in the center will include an 18 MEV linear accelerator with simulator and dual energy capabilities, and a computer to design the optimum treatment for each patient.

Stuart Packer, a medical oncologist on the staff of Saint Mary Hospital, has been appointed medical director for the new center. Barbara Schlager, a radiation oncologist at the hospital, will be head of radiation therapy.

The Bucks County facility is the first of several in the Delaware Valley that Fox Chase will develop with community hospitals, officials said.

As part of its role in the center, Fox Chase will provide a system of computer based cancer management guidelines to provide recommendations for each major cancer site and stage of disease.

*FINANCIALS*

## Biotherapeutics 1988 Forecast: "Lower Revenues, Higher Expenses"

**Biotherapeutics Inc.** of Franklin, TN, lost $2.2 million during the second quarter ending Oct. 31, four times the loss for the second quarter of 1986.

Gross revenues were $1.4 million, up from $839,000 for the same period last year. According to the company, the loss can be attributed to expenses from research and development costs and the expansion of satellite laboratories.

The company's cash position was reported at $24.3 million, and book value was $31.3 million.

"Though revenues continue to increase, they have not kept pace with anticipated growth," said Louis Berneman, company president.

"Factors contributing to slower growth include a slower than expected transition of our satellite laboratories from the agreement phase to an operational status, longer than anticipated education phase for referring physicians, delays in FDA approvals of new clinical investigators and FDA limited expansion of current laboratory services.

"Revenues anticipated to be booked for the monoclonal antibody/immunoconjugate program remain deferred due to the complicated science of bringing a new conjugation technology to clinical trials."

"The company now anticipates lower revenues and higher expenses for fiscal 1988 than originally expected."

The firm has corporate laboratories in Franklin and Memphis, TN, Plantation, FL, and La Jolla, CA. Satellite laboratories are operating in Newport Beach and Los Angeles, and new laboratories are ready to operate in San Francisco, Dallas, Sioux Falls, SD, and Birmingham, AL.

During the past quarter agreements were executed with Arlington Memorial Hospital, San Francisco, Saint Johns Hospital of Santa Monica and Nu-Med Sherman Oaks Hospital of Van Nuys, CA.

Letters of intent to establish laboratories and affiliated clinical programs have been reached with hospitals in Greenwich, CT, Springfield, IL,and Miami, company officials said.

**Repligen Corp.** of Cambridge, MA, lost $788,000 in the second quarter ended Sept. 30, down from a $1.4 million loss for the same period last year.

The revenues were $1.7 million, up $435,000 from comparable period last year. The increase in revenues primarily reflects fees from Repligen's collaboration with **Merck & Co.** and from fourfold increase in sales of rProtein A, company officials said.

The firm also reported a $25 million reserve.

In May, Repligen signed an agreement with Merck to work on development of an AIDS vaccine. Under the agreement, Merck made a $7.5 million up front payment to Repligen, company officials said.

"This agreement, in combination with our scientific advances, has thrust us into the forefront of the race to develop an AIDS vaccine," Sandford Smith, Repligen president, said at the company's annual meeting Aug. 19, 1987.

**Scientific Leasing Inc.** of Farmington, CT, has launched a program to provide what officials said is a unique financing package for Philips Medical Systems Inc. of Shelton, CT, to assist prospective purchasers of its mammography system.

The program is run by Scientific Leasing's Program Sales Group, which is targeting vendors, manufacturers and distributors of medical and related equipment to provide specially designed financial products.

The company completed a mailing to more than 30,000 doctors, clinics, practice groups and hospitals describing the program.

Scientific Leasing also reported profits of $339,000 for the quarter ending Sept. 30, up from $165 in the same period of 1986, and total revenues of $13.37 million, up from $12 million last year.

In September the company completed its first major financing of securitized equipment lease receivables totaling almost $20 million. Officials said the transaction was particularly significant as an indication that the quality of the firm's lease portfolio continues to enable it to obtain good financing terms.

**Xoma Corp.** of Berkeley, CA, has disclosed that it is being sued by **Sanofi**, a French pharmaceutical.

The suit alleges infringement on a Sanofi owned U.S. patent involving immunotoxin technology. The French pharmaceutical claims that several Xoma products use technology covered by the patent.

"We deny any infringement and the suit is without merit," said Xoma Chairman and Chief Executive Officer Steven Mendell. "Xoma has been aware of this patent for several years, and the patent has been analyzed in depth by outside patent counsel and by our scientific staff.

"We have concluded, and have received patent counsel's opinion, that the patent is invalid based on obviousness and prior invention. Xoma will vigorously defend its rights to use its technology."

**Vestar Inc.** of Pasadena, CA, announced a loss of $845,000 for the third quarter ending Sept. 30. Last years, the third quarter loss was $1 million.

Revenues were $665,000, up form $177,000 last year. According to the company, revenue increase is attributed primarily to collaborative agreement revenues and increases in interest income.

The interest income comes from investment of the $11 million proceeds of the company's initial public offering in November 1986 and $10 million of secondary public offering in June 1987.

Vestar specializes in liposome products.

During the third quarter, the company entered a collaborative agreement with **City of Hope National Medical Center** of Duarte, CA, under a $2 million contract from the **National Institute for Allergy & Infectious Diseases.**

The firm and the hospital will perform research into drug therapies and drug delivery systems targeted to the AIDS virus.

**Biogen N.V. and Hoffmann-La Roche & Co. Ltd.** of Basle, Switzerland, last month announced an agreement under which Roche has acquired Biogen's worldwide rights to B-cell growth factors and related small molecules and inhibitors.

Under the same agreement, Hoffmann LaRoche has purchased a Biogen research laboratory in Ghent, Belgium. The laboratory will be integrated into the organization of **Produits Roche S.A.** of Brussels, a Belgian subsidiary of Hoffmann-La Roche.

Biogen will receive cash and royalties from the sales of products resulting from research conducted at the laboratory. The two firms will also share marketing and associated manufacturing rights.

Financial terms of the deal were not disclosed.

**Applied DNA Systems Inc.** of New York reported a loss of $514,000 for the third quarter ended Sept. 30. Last year, the company's third quarter loss was $105,000.

The company attributed $464,000 of that loss to losses incurred in redemption of mutual fund shares, company officials said.

Donald Bachmann, chairman and chief executive officer said that while the investment loss is a temporary disappointment resulting from "extraordinary circumstances,"

the company's capital position remains strong.

Total capital was reported at $5.8 million. The firm's lead product is an in vitro chemosensitivity assay. The company hopes to be able to process up to 100,000 such assays in 1989, officials said.

In September, ADNA obtained rights to joint venture Oxyrase, a nontoxic antioxident.

**Liposome Technology Inc.** of Menlo Park, CA, announced a net loss of $2.5 million for the year ended Sept. 30. Last year, the firm lost $1.3 million.

Total revenues for fiscal 1987 were $4.2 million, up $300,000 from last year. Research and development expenditures for fiscal 1987 were $5.3 million, about 30 percent more than last year.

**80% To R & D**

"The increase in losses for the year is attributable primarily to the 30 percent increase in staff size," said Nick Arvanitidis, president and chief executive officer.

"We continue to devote approximately 80 percent of our resources to research and development," he said.

In the fourth quarter, the net loss was $1.1 million, up from a $716,000 loss last year. Revenues were $664,000, down from $894,000 last year.

The company, which uses its liposome based drug delivery technology to develop pharmaceutical products, ended the year with $23.5 million in cash and short term investments.

Arvanitidis said key accomplishments for the year include significant progress in advancing products to clinical trials.

The firm's bronchodilator and dry eye products entered U.S. clinical trials. Phase 1 studies were initiated in England for LTI's liposome based anticancer formulation.

LTI earlier began sponsoring a phase 1 evaluation of its anticancer formulation in Israel.

**Cytogen Corp.** of Princeton, NJ, lost $1.1 million for the third quarter ended Sept. 30, up from a $229,000 loss for the same period last year.

Gross revenues were $4 million, more than double the $1.7 million in the third quarter last year.

The sale of research services under contract and milestone payments was $3.3 million.

Those sales were made to **Eastman Kodak** and **Farmitalia Carlo Erba.** Interest income was $711,000 and the cash balance $40.6 million.

**Unimed Inc.** of Somerville, NJ, posted a $524,000 loss for the fiscal year ended Sept. 30, down from last year's loss of $759,000.

Revenues were $4.2 million, a 63 percent increase from last year's $2.6 million. Revenues from the company's pharmaceutical segment nearly tripled to $1.7 million from $623,000 last year.

Fourth quarter earnings were $33,000, up from $274,000. Revenues were $1.3 million, up from $685,000.

"Fiscal 1987 was a successful one for Unimed," said Paul Bollenbacher, chairman and chief executive officer.

"We signed one of the most important international licensing agreements in our history for our promising low toxicity cancer chemotherapy pharmaceutical, G-6-M.

"We also began to see significant acceptance of our antinausea pharmaceutical, Marinol, among doctors and their cancer chemotherapy patients."

*PRODUCTS*

## BioGenex Markets Test To Use With Monoclonal, Polyclonal Antibodies

**BioGenex Laboratories** of Dublin, CA, has released StrAviGen 1-2-3 for use with over 140 monoclonal and polyclonal antibodies, including CEA.

The CEA 1-2-3 test, besides greater ease of use, provides the most specific staining of the carcinoembryonic antigen, the company said.

**PEOPLE**

## Edgar Haber Named President Of Squibb Medical Research Institute

**Edgar Haber,** chief of cardiology at Massachusetts General Hospital in Boston and Higgins Professor of Medicine at Harvard Medical School, has been named president of the **Squibb Institute for Medical Research** and a member of the board of the **Squibb Corp.** The appointment becomes effective Jan. 1.

Haber will succeed George Mackaness, who will retire after 12 years as president of the institute.

**Judith Rice** has been named director of marketing at **Roswell Park Memorial Institute.**

She will direct the institute's communi-

cations programs and will develop a marketing plan for the institute's clinical and research services.

Rice previously was vice president of William Collins Associates, and was director of public affairs at the Children's Memorial Medical Center in Chicago.

**Cytogen Corp.** has announced five clinical investigations and research appointments:

**Wesley Church,** formerly a senior research scientist at Collaborative Research Inc., was appointed principal research scientist for biochemistry.

**Steven Gilman,** who was manager of the inflammation section of the experimental therapeutics division of Wyeth Laboratories, was named assistant director for clinical investigations.

**Marjorie Messick,** also of Wyeth Laboratories in regulatory affairs and project planning, was appointed project manager for strategic research planning.

**Joseph Nardo** was named senior research scientist for Cytogen. He previously worked in the E.I. DuPont Medical Products Division.

**Roberta Thompson,** who was senior clinical research coordinator at Johnson Cardiovascular Inc., was appointed manager for clinical research assistants.

**Intermagnetics General Corp.** announced that **Edward David,** president of the consulting firm **EED Inc.,** was elected to the board of IGC. David serves on a large number of boards for industry and government, including the White House Science Council.

IGC also has appointed **Joseph Vacca** to the newly created position of marketing manager. He has held various management positions in the GE-Medical Systems Magnetic Resonance Program.

## NCI, NIH Implement Law Increasing Collaboration With Private Sector

(Continued from page 1)

Cancer Training Branch in NCI's Div. of Cancer Prevention & Control. His long experience in biomedical science and the fact that he also holds a law degree makes him uniquely qualified for a job that will require him to, in the words of NCI Director Vincent DeVita, "assess technology development by means of a complex analysis using scientific, technological, legal, economic and managerial skills in determining whether a particular technology should be developed, whether any resultant intellectual property could and should be protected and by what means, and whether both commercialization of the invention and the public interest would be served through licensing."

OTD also will advise DeVita in matters relating to technology management, proposing new or revised policies intended to promote the best use of cooperative agreements and the best means of protecting intellectual property and promoting its commercialization for the public good, DeVita said. It will also advise him as to what position NCI beneficially might take on questions arising from its generation of inventions and their commercial interest.

FTTA and the law which it amended, the Stevenson-Wydler Technology Innovation Act of 1980, "create a new environment in which government, academia and industry can collaborate in developing technology by means of a new instrument, the cooperative agreement, which greatly simplifies the process of research and development contracting, and by means of a liberalized process of licensing intellectual property and rewarding the inventors," DeVita said.

Licensing and royalties are only part of what Lepovetsky referred to as a revolution. FTTA also encourages collaborations by government scientists with academic and industry laboratories. Those arrangements permit private sector investigators to work in NIH labs and vice versa. Industry is now permitted to contribute directly to the support of collaborative projects at NIH. This could lead to vastly increased investment by industry in federal government research efforts.

"OTD will manage the intellectual property generated by both the extramural and intramural research programs," DeVita said. "It participates in identifying and protecting the value of such property and in its development and transfer.

"It must assure the property's timely commercialization as well as the protection of both the government's and the inventor's interests.

"It will determine whether an invention or writing should be protected or copyrighted or whether the public's best interest would better be served by placing the material in the public domain through publication or registration with the patent office for public use, whether intellectual property should be assigned to the inventor or to another organization, and whether it should

be exploited through exclusive or nonexclusive licensing.

"To do all this, OTD must participate in all situations which may lead to a cooperative agreement and/or the issuance of licenses. In meeting its responsibilities, the staff of OTD will work closely with the division directors, laboratory and section chiefs and scientists, as well as staff of the Public Health Service, NIH and other institutes, the National Technical Information Service, and the office of the general counsel. OTD will represent the Institute before other agencies, both public and private, in matters of NCI's technology development program."

OTD also will work with the new NIH Div. of Invention Development, which is being established to implement provisions of FTTA. The division is headed now by Philip Chen, who is NIH associate director for intramural affairs.

When a permanent director is recruited for DID, he will report to Chen.

DID's role is to coordinate all NIH patent and licensing matters, and also may do so for the Alcohol, Drug Abuse & Mental Health Administration, "depending on the resources they make available to us," Chen told **Cancer Economics**.

NCI is the only institute to establish a technology development office. Chen said he is encouraging the other institutes to at least name a liaison person to work with DID.

All NIH patent and licensing matters will go through DID, which has a Patent Policy Board that meets monthly. Chen is chairman, and other NIH employees are members, with liaison members from the HHS asssistant secretary for health, Centers for Disease Control, ADAMHA, the Food & Drug Administration and NTIS, which is part of the Dept. of Commerce. NTIS does the actual work involved in licensing and patents.

A subcommittee of the Patent Policy Board, for Collaborative Research and Development Agreements, reviews all NIH licensing and patent matters before they are sent on to NTIS. Richard Adamson, director of NCI's Div. of Cancer Etiology, is chairman of the subcommittee.

FTTA delegates to the individual institute directors the authority to executive patent and licensing agreements, without going through NIH, HHS or anywhere else. However, Chen said "it would be chaos" without some central oversight at NIH. The law permits the director of NIH to take up to 30 days to review submissions.

Here's how FTTA breaks down the royalty and fee revenues received by NIH:

--15 percent of gross revenues to the inventor.

--25 percent of the first $50,000 to the inventor.

--20 percent of the second $50,000 to the inventor.

--15 percent of everything over $100,000 to the inventor.

From what is left, NTIS will be reimbursed for its costs involved in the process, and the rest will be divided between NIH and the institute involved. At least 51 percent of that will go to the institute.

The law spells out what NIH and the institutes may spend that money on, primarily efforts to further technology transfer including education and training. Some funds will be used to develop foreign patents.

Among the first in line when the money is distributed will be scientists, engineers, technicians and others involved in the development of that particular invention.

Also, one item Lepovetsky feels is especially important, is payment to basic scientists who may have contributed to the development indirectly but whose names were not included on the patent.

NIH is receiving several million dollars a year now through licenses and royalties previously established, most of it from the Gallo AIDS patents and a hepatitis vaccine, Chen said. Until FTTA took effect, the inventors received a relatively small amount, and the rest went to the Treasury. Neither biomedical research nor technology transfer benefitted from those funds.

"I think it is important that we not let the emphasis go too much to applied research at the expense of basic research," Lepovetsky said. "The program will help us keep many scientists who otherwise might take higher paying jobs elsewhere, and we should see to it that the income of basic scientists is supplemented."

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Editor: Paul B. Goldberg
Associate Editor: Jerry D. Boyd

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# AIDS update

*News • Policy • Research*


## AIDS Clinical Trials Cooperative Groups Formed From ATEUs, CSGs

The National Institute of Allergy & Infectious Diseases is forming a large AIDS cooperative group to be made up of its existing AIDS Treatment Evaluation Units and Clinical Study Groups. Although the final name of the group has not yet been decided, the move is part of an effort to improve the institute's clinical trials program.

Other measures include plans to speed protocol development and increasing the number of new drugs being tested in clinical trials.

The plans were explained in an interview with Daniel Hoth, recently named acting director of the institute's AIDS Program.

Hoth is former chief of the Investigational Drug Branch in the Cancer Therapy Evaluation Program within NCI's Div. of Cancer Therapy, and at one time served as acting director of CTEP.

Many of the changes are based on recommendations from a Clinical Trials Advisory Committee appointed last June by NIAID Director Anthony Fauci to review the status of the institute's clinical trials program. The committee's report is still in draft form, but Hoth said, "I'm not waiting for the [final] report--I'm already implementing many of their recommendations." The committee was chaired by Robert Couch, a professor in the department of microbiology and immunlogy at Baylor College of Medicine.

Hoth noted that the existing ATEUs already share many of the features of a cooperative group because "they are multiple centers sharing and participating in common protocols with a central collection system," and have committees that focus on major scientific areas.

NIAID plans "to formalize that by making explicit the role of committees, and by establishing quarterly meetings where all of the investigators in the ATEUS and the CSGs

(Continued to page 2)



## HIV "Runs Ahead" Of Immune System In Unsuccessful Chimp Vaccine Trials

Results of challenge trials with chimpanzees immunized with an experimental AIDS vaccine suggest that HIV "is running ahead of the immune system" and that by the time the immune system makes antibodies against one isolate, the virus has evolved ahead, PHS AIDS Coordinator Peter Fischinger told the National Cancer Advisory Board.

Fischinger, who was deputy director of NCI and director of the Frederick Cancer Research Facility prior to his recent appointment as AIDS coordinator, told the board of two challenge experiments with chimpanzees conducted at FCRF.

One trial involved a native gp 120 subunit vaccine. Two chimps were immunized with the product, then challenged with a dose of HTLV-3 that was the 100 percent infectious dose "times 10."

The two chimps developed a type specific neutralization response against the virus, which "shifted from a type specific response within several weeks to a group specific response which only improved in time." The animals also showed good antibody dependent cell mediated immunity responses.

When the HIV virus was isolated from the challenged chimpanzees weeks later, however, investigators found that the virus was different in terms of type specific neutralization.

Tests conducted six weeks post challenge found that the virus isolate could not be

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Supplement to the Cancer Letter

## Trials Group Committee Meetings To Include All Group Investigators

(Continued from page 1)
will meet to review the progress of ongoing studies, and to decide on an agenda of new studies, as well as to exchange scientific information." The new group will be very similar to NCI cooperative groups, he said.

The quarterly meetings will include "not only the principal investigators, but other involved professionals, particularly the physician staff."

NIAID will invite up to six people from each of the institutions to the first meeting. "The key concept is that each member institution will be attending these quarterly meetings," he said.

ATEU investigators currently are organized into subcommittees, in such areas as antiviral, opportunistic infections, and pharmacology. The groups include representatives from several, but not all of the ATEUs.

"Our proposal is to have these committees meet quarterly, and it is the meeting of all these committees that is the 'cooperative group meeting.'"

NIAID is in the process of appointing the group's executive committee, which will set overall policy for the group, such as membership policy. The institute is making initial appointments of the executive committee and the chairs of the various committees. "After that, however, we expect the executive committee to decide how it should go, whether they wish to make it appointive or elective," he said. "That will be up to them."

Committee meetings will be open to members of the ATEUS and CSGs, "so there will be opportunity for any investigator to propose a protocol to the committee."

The scientific committees will review the progress of ongoing studies, develop an agenda for new studies, and identify which studies are to be done. After prioritizing the proposed studies and deciding which studies should be done, the committees will appoint protocol teams to write the protocol. The committees "will make the major decisions about which studies will be done, together with input from NIAID staff," he said.

"The emphasis on this is to create a notion that this is a community of investigators with a framework provided by NIAID, so we're providing a superstructure for them, in which they collectively are doing the most important AIDS clinical research as a group, as a collective body."

Cooperative group investigators are not limited to clinical studies involving a group protocol. For example, if a pharmaceutical company wishes to conduct a study with investigators at one of the treatment units, "that's fine," Hoth said. "There's no monopoly here."

Although cooperative group investigators don't even "have too talk to us about" a study conducted with a pharmaceutical company, they would be required to have to the protocol approved by one of the group's committees in order to receive credit for the study under the ATEU program.

Hoth emphasized that the changes represent only a "midcourse correction" in the clinical trials program that has grown so rapidly in recent months.

"It's an impressive accomplishment to establish a complex network of institutions to perform clinical trials in the space of 16 months," he said. "To me, it is unprecedented that such a system has been established so quickly.

"My summary of where we are is that an excellent job has been done, [but] it has experienced some growing pains. And what we are now doing is taking on a midcourse correction to improve the system."

The focus that NIAID is putting on the clinical trials system "is to improve the speed of protocol development, to foster and improve the collaboration with the pharmaceutical industry, and to increase the role of the investigator in the clinical trials units."

In addition to organizing the institute's clinical trials effort into a cooperative group and formalizing the structure of committees, "protocol development is being defined very clearly."

The goal of protocol development "is to increase speed and to achieve high quality research," he said. "This is a critical point."

NIAID plans to "define the procedures so that the methods for getting a protocol developed are clear. We have methods, but we are disseminating them widely to the group."

The institute is also "increasing the resources devoted to protocol development" and adding more staff to assist with development of protocols. The AIDS Program is currently recruiting physicians and research nurses for the effort. "The key to making

faster protocols is to have people who are experts in writing protocols work with the investigators to write the protocol."

NIAID also hopes to speed protocol development and clinical trials by better defining its relation with pharmaceutical companies.

"The goal is to define the procedures through which the pharmaceutical industry can have access to the cooperative group," Hoth said. "Our overall goal with respect to the pharmaceutical industry is partnership."

In the area of drug development, "it is essential to translate that goal into reality by working closely with the industry." Noting that NIAID has been working with the pharmaceutical industry since its AIDS Program began, he said, "Again, this is sort of a midcourse correction.

"Because we deal with dozens of companies, we feel that it's very important to write down a set of guidelines for industry and NIAID interactions." Hoth and other NIAID officials will hold a meeting with senior representatives of the pharmaceutical industry after the first of the year.

In addition to forming an AIDS cooperative group, one of the most important changes in the clinical trials program will be "to increase the number of drugs in clinical trial to the capacity of the group. We should be testing any therapy with promise."

The program looks for laboratory or clinical evidence of effectiveness of drugs in three broad classes: antivirals, opportunistic infection therapies, and anticancer drugs. "The key point is that there has to be data," either clinical or laboratory, of effectiveness.

NIAID's AIDS Clinical Drug Development Committee, composed of representatives from industry, academia and NIH, selects candidates for clinical studies. After recommending a drug for trial, the committee then assigns a high or low priority to the agent. AIDS Program staff then "work down the priority list" and bring the drugs to the ATEU scientific committees for a recommendation.

"My goal would be to have any drug that is recommended by the committee be tested up to capacity of the system," Hoth said. "Dr. Fauci has asked us to attach a higher priority to putting as many, if not all, of the recommended drugs into clinical trial."

Hoth pointed out that the plan to increase the number of drugs going into clinical trials "doesn't represent so much of a policy change, as much as a priority emphasis."

NIAID officials hope that by formalizing the entire clinical trials process, "all of that system of doing business is clearer to everyone," investigators, industry, the media and the public.

Discussing NIAID's interactions with the extramural research community, Hoth said the staff informally interacts with outside scientists "all the time" by attending meetings, reading the scientific literature, and by talking with and soliciting advice from outside investigators.

In addition, many people from outside of NIH write to program officials with suggestions for further research. "Anyone is free to write us at any time and say, 'I think that such and such an area needs further research.'

"Working in NIH in a senior position, you're constantly the recipient of letters like that--it's exciting--that's what we're here for--to help make good ideas happen."

NIH will also sponsor workshops with outside experts to address a new area of research when necessary, he said.

"We are constantly keeping an eye out, surveying the field of AIDS research, and seeing where are the areas of scientific opportunity, what are the most promising areas of research, or what are the gap areas. That's really our job.

"The most important job I have is to allocate resources, to identify gap areas, then to stimulate research in gap areas. Our job is to help set national priorities and to allocate resources. We do that" with input from the outside, he said.

## Broad Neutralizing Antibody Cellular Immunity Needed For Prevention

(Continued from page 1)
neutralized by the serum collected at the same time.

At 30 weeks after challenge, "it seems that that serum now is able to neutralize what we call the early virus," Fischinger said.

The new viruses isolated from the chimps, however, "are nowhere near as susceptible as the parental virus, and with time, if anything, these viruses get even less susceptible," he said.

"The virus that comes out of the infected animal on reisolation sure doesn't look the

same as the input virus, so you have to think of a number of possibilities as to what could have happened along the way."

Fischinger said NCI officials had not wanted to talk about the unsuccessful experiments before because "the data weren't in, and even just now we're beginning to see what we think has happened."

He noted that the viruses isolated from both the chimps "are not susceptible to the immune responses the animal is generating."

The investigators believe that the virus may be able to "by selection change adapt and run ahead of the immune system. As the immune system catches up and makes antibodies and cellular immunity against the one isolate, the virus is already evolving further ahead.

"This seems to be the most simplistic explanation, but it's something that these data suggest may be happening in vivo in these infected animals as well."

Investigators first speculated that immune pressure changed or shifted the virus. When they looked at control animals, they found that the control animals "also exhibited changed isolates weeks later."

**"We're Not Successful"**

Speaking about the trial's implications for vaccine development, Fischinger said, "It's obvious to us that what we probably are going to have to do if we're going to consider primary prevention, we will have to start out with an extremely broad neutralizing antibody, extremely broad ACC, ADCC, and cellular immunity and this may be the way to do it.

"So far in terms of type specific response, we're not successful."

Maintaining a note of optimism, however, Fischinger said he believes the viruses are susceptible. "They are not magical viruses here, but I think they are running ahead of the immune system."

The first chimp experiment using a vaccinia infectious recombinant vaccine with LAV isolates "was not successful in preventing primary infection," he reported.

The investigators also conducted an experiment in two goats in an effort to see if vaccination with two different vaccines could broaden the response in order to produce a neutralization for a series of other viruses as well.

"Unfortunately, this is not the case," he reported. "If you get a specific antibody response...it is highly type specific." In the goats that received dual immunization, first with HTLV-3b, then with rf gp 120, "it looked like it had a group response because both of them were neutralized," he said. "But when we tested the serum of these goats against the mn, and a series of other viruses, all you could show was that you got two type specific responses, not a group specific response, so this is not the answer so far."

Fischinger also posed the question of when a candidate vaccine should be considered for clinical trial in humans.

"It is quite clear that gp 160, which is now in human trials, does give type specific immunity, and it seems to be a reasonable titer, but I think that certainly before you want to increase the activity and volume of patient trials, you may want to repose that question. Do you need actual data from chimpanzees to show whether or not you have actual protective immunity occurring in the homologous virus and later the heterologous virus?

"If you get failure of protection in one instance, you want to increase the titer, certainly cell mediated immunity, specifically using the t specific epitopes. You may want to alter the presentation, change adjuvants, and so on and hopefully get a better response."

Fischinger also described six different approaches to vaccine development. "It seems that probably the most reasonable first line approach is to get some subunits--to get the native, to get some benchmark studies, but really to consider the genetic engineered material is probably one of the highest priorities.

"The second highest priority, coequal, is to get infectious recombinant virus, that is to take a virus of estimable safety record, put the genome of interest into it, and let it replicate, like in a vaccinia virus. Together with getting an immune response against vaccinia, you also get an immune response against the viral protein of interest."

Other approaches include peptides, and killed inactivated HIV. While Fischinger believes that a killed inactivated vaccine "is feasible," he warned of potential dangers with the technique. "When you purify this virus, it's immensely dirty. There's no way of cleaning up this virus that I know of, and in terms of nonpathogenic infectious agents, [NIAID investigators have shown] that when such agents are actually constructed, they

could revert back to pathogenicity. Obviously the long term effects of viral nucleic acids...is something you will have to worry about in terms of long term ramifications."

The use of ISCOMS (immune stimulating complexes) is useful in some animal models and could be an effective strategy.

The majority of researchers are currently focusing on envelope proteins, with some looking at core proteins as well.

Fischinger advised that "nonstructural genes may be of interest, and eventually we may have to look at all of these to determine whether these are going to important as a target for vaccine intervention."

One of the major problems facing the development of an AIDS vaccine is the choices to be made regarding the number of targets available for vaccine intervention.

"When you have that many targets, you have to make choices, you have to look at a whole series of antigens and epitopes, you have to ask in terms of numbers of adjuvants, routes of inoculation, and testing in various species. This will give you safety, immunogenicity and focus."

Investigators also have to consider the kind of responses in testing in higher species, such as reactivity, neutralizing antibody, and various forms of cellular immunity. "Once you have that, you can consider a challenge matrix.

"This is a multidimensional matrix--you're dealing with literally thousands of possibilities." He also advised that investigators "have to be extremely circumspect" in testing in higher primates because of the limited supply of chimpanzees.

Intrinsic problems in developing an effective AIDS vaccine to prevent primary infection include the virus' heterogeneity, cellular association, and the lack of an animal model for the disease.

## St. Jude Children's Hospital Announces AIDS Research Effort

St. Jude Children's Hospital has announced plans to launch an intensive multidisciplinary research effort to find a cure for AIDS in children.

The hospital's new pediatric AIDS research program will be headed by Walter Hughes, chairman of the hospital's infectious diseases department. Hughes pioneered the use of trimethoprim-sulfamethoxazole to treat pneumocystis carinii pneumonia in patients with acute lymphocytic leukemia more than a decade ago at St. Jude. Prior to the use of the therapy, PCP was the major cause of death in patients with ALL.

The new AIDS research program will involve a multidisciplinary approach of clinical and laboratory research involving eminent physicians and scientists from the fields of hematology/oncology, virology, psychology, neurology, pharmacology, pulmonary and infectious diseases.

St. Jude expects to begin accepting patients to the pediatric AIDS program in July 1988. The researchers will identify and test combinations of drug therapies, including AZT, in an attempt to find a treatment plan to kill the virus and return the child's immune system to normal.

The hospital's approach will parallel the approach used to find a cure for childhood leukemia, and establish a "total therapy protocol" for children with AIDS. The institution is already involved in AIDS related research that "covers the array of opportunistic diseases, hematological disorders and cancers associated with AIDS," Hughes said.

The hospital expects to establish its research protocols in the spring.

St. Jude plans to significantly expand both the research team and the amount of monies devoted to AIDS in the coming year, and will add research staff members with specific expertise in AIDS.

Hughes anticipates that the hospital will need only 10 to 20 patients, mostly outpatients, the first year for its research. The number of patients needed for the program will be reevaluated in subsequent years.
Children with AIDS will need to be referred by a primary care physician.

He believes that a large portion of St. Jude's research results "will be directly applicable to adults," although dosages of drugs will differ substantially.

The hospital announced its plans during the recent ground breaking for a five year, $100 million building expansion program, which will double the size of the Memphis based institution. The hospital was established by actor Danny Thomas 25 years ago in order to combat catastrophic diseases in children.

"St. Jude's well established basic and clinical research expertise in childhood catastrophic diseases gives us a unique capability to handle all aspects of pediatric

AIDS within one institution," Hughes said. "Many other centers or institutions address mainly adult AIDS with much smaller efforts in children.

"Having treated more than 10,000 patients in the past 25 years, we have more experience than any other institution in the country in dealing with already ill children whose immune systems have been impaired by drug and radiation treatments," Hughes said.

## RFAs Available

### RFA 88-NS-07

Title: Research centers for AIDS dementia and other retrovirus associated neurological disorders
Application receipt date: Feb. 12, 1988

The National Institute of Neurological & Communicative Disorders & Stroke expects to establish up to four research centers, each for five years. Awards for the centers will depend upon availability of funds. Support is expected to be given to centers with major thrust on the neurological aspects of AIDS in children and in adults, as well as on the clinical neuroscience of other retroviral diseases in man and in animal models.

The research centers will be established for the investigation and elucidation of the etiology and pathogenesis, natural history, epidemiology, pathology, definition of the diagnostic criteria, and prevention and therapy of AIDS dementia and other retrovirus associated neurological syndromes. Proposals focusing on AIDS dementia and encephalomyelopathy in children and infants are particularly encouraged.

While the principal stimulus for establishment of the centers is concern for the involvement of the central nervous system in AIDS, appropriate studies in relevant fundamental neurobiological areas will be acceptable within the center's mission, e.g., basis for the predilection of some retroviruses for the nervous system, as well as studies of retrovirus associated neurological diseases, other than AIDS, such as tropical spastic paraparesis in humans and visna in animals.

The number of people, including children and infants, affected by the AIDS retrovirus, HIV, is growing and the associated neurological syndromes are recognized with increasing frequency. Neurological involvement may be apparent before severe immunodeficiency is recognized. The neurological disorders associated with AIDS are of particular concern to NINCDS.

Dementia is one of the more common and devastating neurological complications of AIDS, with as many as 60 percent of AIDS patients developing dementia that cannot be attributed to opportunistic infections. The dementia may occur at any stage; it is often manifested very early in the clinical course of the illness.

Other neurological manifestations associated with HIV infection are spastic paraplegia and ataxia, sensory and motor neuropathies, multiple mononeuropathies, developmental abnormalities in children with loss of cognitive ability and progressive long term signs, and a dysmorphic syndrome due to intrauterine infection with HIV.

The clinical features, course and pathology of these conditions require elucidation and clarification. An understanding of the etiologies and pathogeneses may provide a rational basis for the development and evaluation of prophylactic and therapeutic strategies.

Multidisciplinary approaches are encouraged. Investigations appropriate to the RFA are broad and limited only by the creativity and ability of the applicants to exploit leads from basic studies in virology, molecular neurobiology, immunology, biochemistry, neuropathology, and clinical neurology. Fundamental scientific approaches consonant with the RFA may range from investigations of the peculiarities that predispose to persistent retrovirus infection in the central nervous system to the effects of the dysimmune state on the developing and mature nervous system. Studies leading to the identification and development of animal models of retrovirus infection with predilection for the mature and immature central and peripheral nervous systems are particularly solicited.

To qualify for consideration, an appropriate population of clinically well defined patients with AIDS and ARC sufficient in number to meet the objectives of the research plan is essential. A well established neuropathological research program and a broad, fundamental neuroscience capability are prerequisites for successful applications.

Any United States academic medical center, school of public health, research institution, profit making organization, or consortium of cooperating institutions may submit a proposal. Applicants must demonstrate the ability to marshall the requisite expertise needed for all functions of the research plan, including neurological, neuropsychological, and behavioral assessment of AIDS patients; neuropathological confirmation of diagnosis; biometry; epidemiology, and clinical data management; and fundamental neurovirological and immunological research. Prospective applicants are encouraged to consult with the staff of the Div. of Demyelinating, Atrophic, & Dementing Disorders early in the planning stage.

A copy of the complete RFA, which provides background information, research goals and scope, terms and conditions, review procedures and criteria, and the NINCDS guidelines for preparation and submission of clinical research center proposals may be obtained by contacting the program administrator: Dr. A.P. Kerza-Kwiatecki, Program Administrator, Div. of Demyelinating, Atrophic & Dementing Disorders, Federal Building, Room 702, NINCDS, Bethesda, MD 20892.

The National Institute of Mental Health also supports research centers on the assessment of the central nervous system effects of the AIDS virus, such as dementia, cognitive impairment, and neuropsychiatric disorders. A more detailed announcement of NIMH interests will be published in the near future. Potential applicants should contact: Dr. Ellen Simon Stover, Deputy Director, Div. of Basic Sciences, NIMH, Room 11-103, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857, phone 301/443-3563.

### RFA 88-DK-02

Title: Genitourinary tract manifestations of the human immunodeficiency virus
Letter of intent: Jan. 15, 1988
Application receipt date: Feb. 10, 1988

The National Institute of Diabetes & Digestive & Kidney Diseases expects to award 15 to 20 grants for up to five years for research on the effects of infections with HIV on the genitourinary tract. The support mechanism for the program will be the traditional individual research project grants (RO1s) only. Current plans for FY1988 include $3 million for the total costs of the program. Funding of applications submitted in response to the RFA is contingent on the actual availability of funds and receipt of

applications deemed worthy of support by the NIH peer review procedure. The specific amount to be funded will depend on the merit and scope of the applications received. Applicants should request a start date of Sept. 30, 1988.

The RFA notes that significant progress has been made in understanding the molecular biology and the clinical presentations of HIV infections, and that it has been established that the genitourinary tract plays a major role in the transmission of the virus. Further information is needed to better understand the behavior of the virus in the GU tract, the site(s) of virus replication, and factors influencing transmission of the virus from an individual to another.

It notes that in addition to blood, semen of HIV infected individuals has been demonstrated as a very effective vehicle for transmission. The T lymphocyte has been proposed as the agent responsible for transporting the virus throughout the body, and probably from host to host. Although the T lymphocyte in the semen may be an effective means of transmission of the virus, other mechanisms are possible.

NIDDK is seeking proposals that deal with the HIV infections in the genitourinary tract, the specific organs and cells in which the virus resides and/or replicates, and the mechanisms of transmission from host to host. Particular encouragement is offered to investigators well trained in pertinent technologies who currently may be pursuing other research interests.

The GU tract is a focal point in the transmission of HIV from host to host. Although the mode of transmission from the male is proposed to be via the semen, the mechanism from female to male is not well understood. It is also unclear whether the virus in the GU tract resides and replicates in cells other than the T lymphocytes. Nor has there been a clear definition of the specific organs in the GU tract where the virus resides and replicates. Conditions in the GU tract that promote or hinder transmission of the virus need to be explored. Finally, very little is known of the effect of specific therapy directed against the virus, such as AZT, on the structure and functions of organs and cells of the GU tract. A major objective of this initiative is to encourage collaboration between individuals in the basic and applied fields of medicine to study the needed mechanisms of viral replication and transmission through the GU tract.

For more information and a copy of the complete RFA, contact: Lawrence Agoda, M.D., Director, Clinical Studies, Div. of Kidney, Urologic & Hematologic Diseases (DKUHD), NIDDK, NIH, Westwood Building, Room 625, Bethesda, MD 20892, phone 301/496-7571.

## RFA 88-DK-03

Title: Effects of HIV infections on the kidney, and in dialysis and renal transplant patients
Letter of intent: Jan. 15, 1988
Application receipt date: Feb. 17, 1988

The National Institute of Diabetes & Digestive & Kidney Diseases expects to award 20 to 25 RO1 grants for up to five years, for research dealing with the effects of HIV infection on the kidney; and the implications of such infections in patients on dialysis and/or with renal allografts. Current plans for FY1988 include $4.5 million for the total costs of the program, although funding will be contingent on the availability of funds and receipt of applications deemed worthy of support. The specific amount to be funded will depend on the merit and scope of the applications received.

The major goal of the program is to encourage investigators with diverse interests and expertise to work together to improve understanding of the pathophysiologic mechanisms involved in HIV infections and kidney disease, and the effect on dialysis and renal transplant patients, and management of these patients.

HIV type 1 infection is a leading cause of renal failure in the U.S. The clinical course of the renal syndrome is that of a fulminant progression to end stage renal disease in a relatively short period of time, with a probable specific histologic appearance of the kidneys. It also has been shown that renal manifestations in individuals with antibodies to HIV may precede any other clinical manifestations of the syndrome.

Patients with ESRD on dialysis are relatively immunosuppressed, therefore, progression from onset of infection to the development of ARC or AIDS may be sufficiently altered, compared to the non renal disease individual. However, it has been observed that dialysis patients who develop AIDS follow a more rapidly fatal course with generalized wasting.

There also are suggestions that other relatively routine procedures related to dialysis, such as blood transfusions, vaccinations and immunizations adversely affect the clinical course of dialysis patients with AIDS.

Patients with renal allografts may acquire HIV infection by additional risk factors, such as infected graft, or through blood transfusions. Because of their unique status, such renal allograft patients may follow a modified clinical course.

Presently, a controversy exists as to whether the immunosuppression status of the transplanted patient aggravates or favorably modifies the clinical course in HIV infection.

Insufficient data are available to determine whether introduction of the renal allograft and the attendant immunosuppression accelerates or retards the development of AIDS and/or ARC in the asymptomatic individual with antibodies to HIV only.

Finally, the effect of the treatment of HIV infection, such as with AZT, on the clinical course of patients with renal disease, on dialysis, and/or with renal allograft needs to be investigated.

The program is intended to explore the effect of HIV infection on the kidney, and on the clinical course of dialysis and allograft patients. Collaboration between basic and applied science is encouraged to investigate the following areas:

* The effect of HIV infection on renal structure and function at the organ, cellular and molecular level; and the pathogenesis of the nephropathy associated with HIV infection, using state of the art technology to investigate the presence (or absence) of the virus in the renal tissue.

* The clinical course of HIV infection in the dialysis patients with specific reference to factors that modulate progression from initial infection and anti HIV antibody positivity to the development of ARC and/or AIDS; the effect of blood transfusion, immunization and vaccination, coinfection with the hepatitis virus, and treatment of anemia with recombinant human erythropoietin.

* The clinical course of the renal transplant recipient, focusing on specific issues relevant to graft and patient survival in the presence of HIV; and on factors such as immunosuppression, histocompatibility, pretransplant blood transfusion regimen, and concurrent infections.

* The effect of treatment of HIV infection, such as with AZT, on the course of renal disease, on morbidity and mortality in the dialysis patient, and on graft and patient survival as well as on immunosuppression regimen in the renal allograft patient.

Further information and copies of the full RFA may be obtained from: Lawrence Agoda, MD, Director, Clinical Studies, DKUHD, NIDDK, NIH, Westwood Building, Room 625, Bethesda, MD 20892, phone 301/496-7571.

## RFA AA-88-01

Title: Alcohol research center grant on alcohol and immunological disorders (including AIDS)
Letter of intent: Feb. 15, 1988
Application receipt date: April 1, 1988

The National Institute on Alcohol Abuse & Alcoholism is soliciting grant applications for centers to investigate various aspects of the relationship between alcohol, immune system alterations and infectious diseases, with special attention on AIDS and HIV.

Support for the program will be through the Specialized Research Center grant. Center grants are awarded to an institution in behalf of a center director for the support of a broadly based multi-disciplinary long term research effort consisting of several major research components. Each component is expected to contribute to, and be directly related to, the effects of alcohol on the immune system and alcohol as a possible cofactor in the acquisition of infectious diseases, especially as related to AIDS and HIV.

The research program should include interrelated studies focusing on problems that have the potential for producing significant scientific information related to alcohol and immunologic disorders, including AIDS and HIV. Research conducted within the center must be clearly related to problems concerning alcohol's interaction with the immune system and the role of alcohol as a cofactor in the development of infectious diseases and immune disorders.

The Alcohol Research Center Grants program is designed to complement the regular research grants program of NIAA by providing long term (typically five years) support for interdisciplinary research programs with a distinct focus on a particular theme relating to alcoholism, alcohol abuse, and other alcohol related problems. The program is intended to help attract the best scientists from biomedical, behavioral and social science disciplines to work on research problems related to alcohol abuse and alcoholism and to provide a stable environment for such persons to engage in alcohol research in a coordinated and integrated fashion. A center is expected to be a source of excellence in research, and through sustained excellence, to become a significant regional or national research resource. In addition, the applicant institution is expected to afford opportunities for training to persons from various disciplines and professions for research careers in alcoholism problems.

Application form PHS-398 (Revised 9/86) should be used. "Special instructions for preparing an Alcohol Research Center Grant Application" are available from NIAA. The signed original and four permanent legible copies of the application should be sent to: Grant Application Receipt Office, Div. of Research Grants, NIH, Westwood Building, Room 240, 5333 Westbard Ave., Bethesda, MD 20892-4500. In addition, two copies should be sent directly to: Office of Scientific Affairs, NIAA, Parklawn Building, Room 16C-20, 5600 Fishers Lane, Rockville, MD 20857.

## RFA 87-TW-01

Title: Special international postdoctoral research program in AIDS
Application receipt date: Jan. 22, 1988

This is a revision of an announcement that appeared in May. The requirements for 1) equal number of U.S. and foreign scientists and 2) full range of clinical and basic science disciplines have been relaxed. In addition, the Fogarty International Center plans to make six awards rather than two.

Applicants who submitted applications for the Sept. 15 receipt date need not reapply.

The Fogarty International Center is inviting applications from U.S. institutions with interest in developing multidisciplinary postdoctoral fellowship programs in AIDS research for U.S. and foreign scientists. Funds will be awarded to encourage basic and clinical research in all biomedical and behavioral disciplines related to AIDS. Applications received in response to this request will be reviewed and considered for funding in a single competition.

According to the World Health Organization, 100 nations from all continents have reported AIDS cases in their countries. The current doubling time of new cases reported in the United States is approximately 15 months. Until the disease can be prevented, cures are found, or an effective vaccine is developed, AIDS will continue to be an increasingly global public health problem. International cooperation is important in understanding and preventing AIDS.

The objectives of the special institutional fellowship program are 1) to support collaborative research between U.S. and foreign scientists who wish to enhance their knowledge and skills in the epidemiology, diagnosis, prevention, and treatment of AIDS and 2) to stimulate scientists from nations affected by AIDS to cooperate and to share research knowledge in combatting this global problem.

It is expected that the program director will be a recognized scientist in AIDS research, interested in both the basic and clinical aspects of the syndrome, and able to attract as preceptors basic and clinical scientists in his or her institution who are experts in other biomedical and behavioral disciplines related to AIDS.

Under the award, the program director will make fellowship appointments to U.S. and foreign scientists varying from three to 24 months. Scientists who are appointed must have an earned doctoral degree or the equivalent in a health science field, be actively engaged in AIDS research, not be employed by a for profit institution, and if foreign, have a permanent position in his/her home institution. Postdoctoral scientists at all career levels are eligible for appointment. It is expected that appointments will cover scientific disciplines related to AIDS research.

U.S. scientists from the grantee institution will be limited to collaborative study in foreign institutions only. The U.S. appointees must have a letter of invitation from the foreign hosts accepting the fellows and committing the resources foreign institutions to the research effort.

For further information and a copy of the RFA, contact: Bettie Graham, PhD, Chief, International Research & Awards Branch, Building 38A, Room 613, Fogarty International Center, NIH, Bethesda, MD 20892, phone 301/496-6688.

## Revised RFA 88-AI-01

Title: Programs of excellence for basic research on AIDS

The National Institute of Allergy & Infectious Diseases is changing the mechanism of support for PEBRAs to the program project grant mechanism. For clarification, or to obtain a copy of the full revised RFA, contact: Martin Padarathsingh, PhD, Chief, Pathogenesis Branch, AIDS Program, NIAID, NIH, Westwood Building, Room 7A-04, Bethesda, MD 20892, phone 301/496-8378.

**AIDS Update**

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Editor: Patricia Williams
Associate Editor: Jerry D. Boyd

P.O. Box 2370 Reston VA 22090

**703-620-4646**