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## Investigators Unlocking Drug Resistance Secrets, NCI Study, Bristol-Myers Meeting Reports Show

Although drug resistance is the most frequent cause of cancer treatment failure, research on mechanisms of drug resistance has not been much in the spotlight and little progress reported--until recently. The report this week on the hypothesis developed by Charles Myers of NCI and his colleagues, that anticancer drug resistance and resistance to chemical carcinogenesis may be a similar cellular response, follows on the heels of reports from the ninth

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*In Brief*

## Beatrice Mintz Appointed To Pontifical Academy; Three Americans Asked To Help Shanghai Group

**BEATRICE MINTZ**, senior scientist at Fox Chase Cancer Center, was named by Pope John Paul II to the Pontifical Academy of Sciences. She joined Maxine Singer, of NCI's Div. of Cancer Biology & Diagnosis, in induction ceremonies at the Vatican last month (Singer's appointment had been previously announced--**The Cancer Letter**, Sept. 19). Mintz has achieved world renown for her pathbreaking experiments on developmental biology of mammals. . . . **SHANGHAI COMMITTEE** of Science & Technology has invited author-activist Rose Kushner, Roswell Park's Thomas Dao and Henry Pennypacker of the Univ. of Florida to that city next spring. They've been asked to help establish a breast cancer education program. . . . **FDR'S SPEECH** at NIH dedicating what is now known as Building One or the Shannon Building, delivered on Oct. 31, 1940, was recorded on wire and preserved in the NIH historical files. A portion of that speech was played at the ceremonies last month marking the start of NIH's centennial year. The firm of Grupenhoff, Maldonado & Fenninger, which represents a number of cancer societies among others, reproduced President Roosevelt's talk in its entirety on cassettes. . . . **JAMES BOWEN**, vice president for academic affairs at M.D. Anderson Hospital & Tumor Institute, has been chosen to receive the Distinguished Alumnus Award from the American Assn. of State Colleges & Universities. Bowen received his BS degree from Midwestern State Univ., his master's and doctorate from Oregon State. . . . **JOHN LEAVITT**, of the Armand Hammer Cancer Research Center-Linus Pauling Institute, has been appointed to the Scientific Advisory Board of the International Foundation for Ethical Research.

## Drug Resistance Caused By Natural Defense Mechanism, Group Reports

(Continued from page 1)
annual Bristol-Myers Symposium on Cancer Research which presented a superb update on investigations in drug resistance.

Myers, who is chief of the Clinical Pharmacology Branch in the Div. of Cancer Treatment, reported his findings in the Nov. 25 issue of "Journal of Biological Chemistry." They suggest that cancer cells may be resisting drugs by some general defense mechanism that allows the body to protect itself against natural toxins.

Cells made abnormal by carcinogen exposure may protect themselves from other carcinogens by detoxifying a wide range of toxic chemicals, the report notes. Certain cancer cells, when undergoing drug treatment, appear to act in a similar way--by detoxifying a wide range of drugs.

When treated with any one of a number of anticancer drugs derived from natural products, cancer cells become resistant to a broad range of other drugs to which they have never been exposed (pleiotropic drug resistance, or PDR). These drugs have no common structure or mechanism of action, but they are all natural products that are toxic to human cells.

To test their hypothesis, the investigators found a model in the literature indicating that mammalian cells handle toxic substances in the same way that cancer cells with PDR handle drugs. The model, proposed by Emmanuel Farber and coworkers in 1973, works like this:

--After exposure to a carcinogen plus some manipulation to cause cell growth, some liver cells develop hyperplasia. Farber postulated that these hyperplastic cells are ultimately likely to develop into cancer and become resistant to the toxicity of the carcinogen.

Subsequent work by Farber and others has shown that both of these changes occur independently of each other. In addition, as long as the carcinogen to which the cells are exposed is also a toxin, the hyperplastsic cells will be resistant not only to that carcingoen but also to a wide range of other carcinogens and toxins markedly different in structure and function from the carcinogen that originally induced the hyperplasia. Thus, in both cancer development initiated by chemical carcinogenesis and in pleiotropic drug resistance, exposure to a single chemical results in resistance to a wide range of unrelated toxins and drugs.

Since most common cancers also appear to be initiated by carcinogens, researchers suspect that the cellular signal that warns the body that it has been exposed to carcinogens may already be turned on in these cancers before drug treatment is even started. Thus, when drug treatment is started, the cellular machinery, incapable of distinguishing between the toxicity of the carcinogen and that of the anticancer drug, responds to drugs just as it does to carcinogens.

Myers and hs coworkers have developed a biochemical method to explore the hypothesis that anticancer drug resistance and resistance to chemical carcinognesis may be a similar cellular response. They are looking inside drug resistant human cancer cells for elevated protein levels that may be biochemical markers of how human cells detoxify chemicals in general. Others in the field have been examining some types of human and animal cancer cells for elevated levels of specific protein markers in the cell membranes and increases in the number of copies of certain genes. While these strategies differ from that of Myers and his coworkers, these mechanisms may ultimately prove to be interrelated.

With his biochemical method, Myers has found, in a human breast cancer cell line that developed multiple drug resistance after exposure to adriamycin, the same major changes that Farber found in his chemical carcinogenesis model:

1. A decreased net accumulation of the toxin or drug within the cell.

2. A lack of various enzymes, such as aryl hydrocarbon hydroxylase, known to activate many carcinogens and toxins.

3. A marked increase in various enzymes such as glutathione transferase (GST) and glucuronyl transferase, which detoxify carcinogens and toxins.

The increased levels of glutathione transferase may possibly be only an expression or product of the role of a still more critical substance: a regulatory protein known as protein kinase C. Regulatory proteins direct the production of substances that perform cell functions. Cell functions require more product than regulatory substance.

In drug resistant cancer cells, the product (GST) levels are approximately ninefold higher than protein kinase C levels,

which in turn are about fivefold higher than normal. The difference in levels between these two substances leads the scientists to speculate that protein kinase C may possibly regulate GST production. This possibility is strengthened by evidence indicating that protein kinase C regulates many biochemical events in cells progressing to cancer.

If the response mechanism to toxin/drug exposure is so general, perhaps it can be inhibited simply by inactivating the regulatory protein suspected of triggering the chain of events leading to resistance. Myers and his colleagues are currently testing this hypothesis by searching for various biochemical markers in drug resistant cells and trying to confirm that protein kinase C or another agent may be the regulator of events leading to resistance. They hope to develop inhibitors of these biochemical markers, particularly to the potentially ultimate, regulatory protein that may be turning on the switch for drug resistance.

Coauthors of the report, with Myers, are Gerald Batist, Montreal General Hospital Research Institute; and Anil Tulpule, Birandra Sinha, Aspandiar Katki and Kenneth Cowan of NCI's Clinical Pharmacology Branch.

**Variety of Approaches**

The Bristol-Myers symposium, organized this year by the Vincent T. Lombardi Cancer Research Center of Georgetown Univ., featured investigators who are approaching the drug resistance problem from a variety of directions. Paul Woolley, associate director of clinical research at the Lombardi center, and Kenneth Tew, head of pharmacology at Fox Chase Cancer Center, were cochairmen.

Excerpts from some of the presentations:

**Robert Schimke**, professor of biology, Stanford Univ.--Laboratory studies at Stanford show that the overproduction of genes in a cell, gene amplification, can cause drug resistance. "For example, when cells are exposed to methotrexate in the laboratory, the gene that produces the proteins to which methotrexate binds can be present in quantities 1,000 times its normal numbers. Although patients treated with methotrexate are exposed to much lower doses of the drug, their tumors can show resistance when the gene amplifies itself only five to 10 times within the cell.

"When active DNA synthesis is slowed down, the cell begins to overproduce DNA. Some of this extra DNA is forced back into the chromosomes, where it results in gene amplification and uncontrolled growth, even in the presence of drugs."

Schimke's group is experimenting with a number of ways to stimulate gene amplification, including depriving the cell of oxygen and exposing the cell to ultraviolet light.

"By understanding what processes are involved in enhancing gene amplification, we can learn how to prevent the development of drug resistance," Schimke said.

**Emil Frei**, director and physician in chief of Dana-Farber Cancer Institute--By looking into whether the mechanism of drug resistance is the same for different types of cells and drugs, "we are finding that resistance is heterogeneous and consquently not predictable. Cells are very adaptable at developing resistance."

Frei zeroed in on resistance to alkylating agents. In his conclusion, he said, "In contrast to other antitumor agents, the production of drug resistance in alkylating agents is difficult, requires sustained exposure and only low levels of resistance can be produced. While there is variation among the alkylating agents and among the tumor cell lines, in general the maximum degree of resistance that can be achieved ranges up to 20 fold. This contrasts sharply with nonalkylating antitumor agents, wherein many logs of resistance can be induced by selection pressure. It more closely resembles x-irradiation, where tumor cell resistance occurs minimally or not at all.

"The dose response curve for the alkylating agents, whether examined in vitro or in vivo, is steep. Autologous marrow transplantation allows a five to 30 fold increase in the clinical dose. In an experimental model, superdoses, 10 plus fold in excess of the $LD_10$ dose, maintained a first order dose effect. These experimental data support the proposition that high dose alkylating agent therapy with appropriate patient support may provide a substantial improvement in tumor cytroreduction. . .

"Human tumor cells with low levels of resistance to MTX often have multiple mechanisms of resistance even within the same clone. This provides an explanation for low levels of cross resistance among the alkylating agents and has major therapeutic implications. In addition, alkylating agents have not been cross resistant to nonalkylating agents."

**Woolley**, reporting on use of colon cancer

cells to study drug resistance. "It is reasonable to think cells that exist in toxic conditions such as those present in the colon are more likely to withstand the effect of anticancer drugs. Colon cancer cells are naturally resistant, and increased resistance emerges quickly when they are exposed to drugs or combinations of drugs that can damage the DNA and kill the cell."

**Alton Meister**, chairman of biochemistry at Cornell Univ. Medical Center--In some cases, it may be possible to make resistant cells sensitive again by lowering levels of the peptide, glutathione. "Glutathione is present in all human cells. It is of special interest to cancer investigators because it protects cells against toxic compounds, including anticancer agents. A cell with a low glutathione level is susceptible to damage by anticancer drugs, while a cell with a high glutathione level is resistant to drugs.

"Tumor cells seem to have a natural mechanism to raise glutathione levels. We are experimenting with administering the drug, buthionine sulfoximine, to interfere with the manufacture of glutathione within cells. By lowering the glutathione level in malignant cells, we hope to make the cells more susceptible to treatment."

Buthionine sulfoximine appears to have no harmful side effects when given as a single drug in animal tests. Tests in women with ovarian cancer are expected to begin soon.

"This is not the only drug that will lower glutathione levels," Meister continued. "We are now doing animal experiments with other drugs that may lower the level of glutathione in malignant cells."

Meister's group is also looking at ways to raise glutathione levels to protect normal cells from the effects of anticancer agents. "Our goal is to develop a treatment that would raise the glutathione levels of normal cells without raising the levels of glutathione in tumor cells. Then we would be able to administer a compound that is potentially toxic to all cells, but would destroy tumor cells without harming the normal ones."

**Tew**, at Fox Chase, is studying a series of enzymes that are linked with glutathione and are known as the glutathione transferases. These enzymes allow cells to detoxify chemicals like anticancer drugs.

"We find differences in both the amount of glutathione transferase enzymes and in the different types of the enzymes present in cancer cells that are resistant to drugs," Tew said. "This may be quite important, because cells with high levels of these enzymes, such as colon cancer cells, show greater natural resistance to anticancer drugs than others. We would like to be able to determine if a patient will respond to chemotherapy by checking glutathione transferase levels before giving treatment."

**Leonard Erickson**, associate professor of medicine and pharmacology at Loyola Univ. in Chicago, said that drug resistance may also be overcome by inhibiting the cell's natural ability to repair damage to DNA, the cell's primary genetic material.

"A number of antitumor agents kill tumor cells by inflicting DNA damage," Erickson said. "Tumor cells that survive anticancer treatments may do so because of the cell's ability to withstand DNA damage. To increase the number of tumor cells killed, we are focusing on the use of drug combinations that prevent the cell from repairing DNA."

Erickson pretreats the cells with drugs that interfere with the DNA repair system and make the cells more vulnerable to the use of anticancer agents. "The use of the sensitizing agent in combination with the anticancer drug has a complementary effect, resulting in three to four times greater efficiency than either drug used alone. This has not been achieved before with other approaches."

Erickson is working primarily with colon cancer cells. "These are particularly resistant tumors that don't respond to many drugs, so it is somewhat of a worst case scenario. If we can get positive results with colon cancer cells, it should be encouraging for more treatable tumors."

**Victor Ling**, professor of medical biophysics at the Univ. of Toronto, said, "Despite the fact that drug resistance is quite complex and extremely variable from tumor to tumor, we have found one protein that is constant among many tumors. That factor is P-glycoprotein, a gene that is present in all cells but more abundant in malignant cells."

For the first time at a scientific symposium, investigators from several research groups confirmed that proteins they independently identified as the cause of multidrug resistance are, in fact, the P-glycoprotein discovered by Ling, and that the P-glycoprotein is the cause of multidrug resistance in cancer cells. P-glycoprotein, also known as P170, was first identified by

Ling in 1976 and has been under independent investigation by several research groups since then.

Ling said that investigators are now examining ways to either inactivate or control a cell's production of P-glycoprotein.

**Susan Horwitz**, cochairman of molecular pharmacology at Albert Einstein College of Medicine, discussed continuing research on the role of the antitumor drug in determining the structure of P-glycoprotein. "One of the real problems in cancer treatment is the fact that essentially all tumors eventually become resistant to drugs, so our ability to understand how cells become resistant will allow us to alter chemotherapy or actually devise drugs that will perform against resistant cells."

Horwitz is studying the effects of three drugs--taxol, colchicine and vinblastine--on the P-glycoprotein levels and subsquent gene overproduction in resistant mouse cells. "Although each of the cell lines showed increased P-glycoprotein levels, each one is slightly different depending on the drug that was used," she said. "This suggests that, although all multidrug resistant cells have P-glycoprotein, the specific anticancer drug used in treating the patient has a role in determining the form of P-glycoprotein."

Ling is studying how P-glycoprotein counteracts the effects of chemotherapy in human ovarian carcinoma, sarcoma and leukemia. He is also experimenting with verapamil, a calcium channel blocker, that may be able to effectively act on multidrug resistant cells.

**Michael Gottesman**, chief of the section on molecular cell genetics in the Laboratory of Molecular Biology of NCI's Div. of Cancer Biology & Diagnosis, also discussed verapamil as the kind of an agent that might be able to reverse drug resistance by blocking the ability of P-glycoprotein to bind to and then transport a chemotherapeutic agent out of a cell. "Cells don't become resistant by blocking uptake of the drug but by increasing the flow of the drug out of the cell. Anticancer drugs affected by multidrug resistance can get into the cell, but they are pumped right out again."

Gottesman's studies with Ira Pastan and Marilyn Cornwell involve using calcium channel blockers and other agents to prevent drugs from being pumped out of the cell. "Working with Dr. Igor Roninson at the Univ. of Illinois College of Medicine, we have been able to isolate the DNA for a complete P-glycoprotein," Gottesman said. "We discovered that one section of this molecule is very similar to bacterial proteins involved in transporting materials through the cell membrane.

"We can also use the isolated DNA sequence for the P-glycoprotein as a probe to determine whether a patient has a tumor that is likely to be drug resistant. Knowing that patients would not benefit from certain treatments would spare those patients the toxic side effects they unergo during therapy that proves unsuccessful."

**Lee Nadler**, associate physician at Dana-Farber, announced for the first time publicly his findings on treating lymphoma patients with bone marrow transplantation and monoclonal antibody. Thirty nine have undergone the procedure successfully and none has suffered significant complications, Nadler said.

"When a patient fails conventional chemotherapy because tumor cells are resistant to the drugs used, effective treatment can still be administered by using high doses of chemotherapy and radiation," Nadler said. By removing the bone marrow from the patient, treating it with monoclonal antibodies and freezing it, the patient can receive high doses of radiation and chemotherapy that would otherwise be lethal to the marrow. The marrow can then be returned to the patient disease free.

Nadler and his colleagues at Dana-Farber have used this procedure in patients with non Hodgkins lymphoma. "Our patients were given a very poor prognosis for survival. The bone marrow transplantation procedure sent them into remission and their tumors disappeared. Sixty five percent are disease free and our first transplant patients are doing well almost four years after the first treatments."

Treatment can be completed in less than four months. Nadler said there have been no instances of graft vs. host disease or graft failure.

Naler, Jerome Ritz and their staff at Dana-Farber have been treating the bone marrow with the monoclonal antibody, T-12.

**John Lazo**, associate professor of pharmacology at Yale Univ. School of Medicine, reported on laboratory tests showing that genes can be inserted into marrow cells, making them resistant to anticancer drugs

and allowing high doses of chemotherapy to be given without destroying the marrow.

Several methods are now available to insert genes into human cells, Lazo described the technique of using electroshock. "About 2,000 volts of electricity are delivered to cells over a very short period of time. It temporarily makes the cells very porous. We are still not able to direct the genes to the correct location in the cell." So far, this technique has been used only in laboratory research.

**Carl-Wilhelm Vogel** and his colleagues at the Lombardi center, Reinhard Bredehorst, Mounanandham Panneerselvam and Carole Spangler, reported on the use of monoclonal antibody-drug conjugates to prevent drug resistance.

"The targeted delivery of anticancer drugs by means of monoclonal antibodies or other macromolecular carriers may represent a mechanism to prevent the development of drug resistance. This is particularly true in the case of drugs for which the cellular target is in the cell membrane. In our laboratory we are concerned with a cell surface effect of adriamycin--the enhancement of complement susceptibility of human melanoma cells. We have recently shown that melanoma cells resistant to the cytolytic action of an antimelanoma monoclonal antibody and human complement rapidly inactivate C3b on their cell surface. Pretreatment of the cells with adriamycin prevented the rapid degradation of C3b and converted the cells into complement susceptible cells.

"Adriamycin covalently coupled onto an insoluble support matrix also showed this complement enhancing effect. The immobilized adriamycin was even more effective than the free drug. In addition, immobilized adriamycin was no longer cytotoxic for the melanoma cells. We subsequently exposed drug sensitive but complement resistant cells for six months to immobilized adriamycin. We observed that the cells did not develop adriamycin resistance; they remained susceptible to the complement enhancing activity of free and immobilized adriamycin and to the direct cytotoxic activity of the free drug. In contrast, a cell line made resistant to adriamycin by long term exposure to the free drug was resistant to both the direct cytotoxic activity and the complement enhancing activity of free or immobilized adriamycin.

"In conclusion, immobilization of adriamycin which prevents the cellular uptake of the drug did not affect its membrane mediated effect of enhancing the complement susceptibility while preventing the development of drug resistance. Currently, we are attempting to replace the insoluble support for adriamycin by a biocompatible carrier which also prevents the cellular uptake of the drug in vivo. Specific targeting of such an adriamycin carrier by an antitumor monoclonal antibody may be a promising approach for immunotherapy of melanoma."

## Rosenberg Starts New Study With Tumor Infiltrating Lymphocytes

The first patient has started treatment at the NIH Clinical Center with Steven Rosenberg's new tumor infiltrating lymphocyte therapy. Rosenberg has described the procedire as "from fifty to a hundred times more potent than LAK cells in antitumor activity in mice."

FDA approved the treatment protocol approximately two weeks ago. Rosenberg revealed that the phase 1 study had started during a presentation at an NIH sponsored meeting on "Progress in Cancer Treatment: Impact on Nursing."

Rosenberg, updating his results on patients treated with LAK/IL-2 at the Clinical Center, had the same figures he presented last month to the Div. of Cancer Treatment Board of Scientific Counselors (**The Cancer Letter**, Oct. 24). As of Oct. 1., a total of 104 patients had been treated. There have been seven complete responses, 15 partial responses and 10 minor responses.

The NCI surgery chief has just started collaborative studies with scientists from the National Institute of Neurological & Communicative Disorders & Stroke to look at LAK/IL-2 treatment of brain tumors. "Because of the capillary permeability and the acute swelling that exists, it's quite dangerous to admininister this kind of therapy to patients who have brain metastases, that is, systemic administration. But we're looking at ways to implant directly LAK cells into a resected tumor bed in patients with gliomas, with the installation of interleukin-2 directly into that tumor bed as well. We've treated two patients with that approach during the last several months."

The treatment involves resecting a tumor to allow a reservoir in place. The investigators can then directly install LAK cells

and IL-2 into the tumor bed "to prevent the recurrence that occurs in virtually all patients who have gliomas resected."

Noting the work is just beginning, he said it "is something that we will be pursuing vigorously in the months to come."

Another new phase 1 NCI trial under way involves the administration of monoclonal antibodies and bombesin in patients with small cell lung cancer. Gregory Curt, deputy director of the Div. of Cancer Treatment, reported that one patient has been treated.

"Although it is not known whether this patient has responded, the one interesting thing is that the monoclonal antibodies which were labeled with indium did localize to the patient's chest," he said. "So that in this particular patient, the monoclonal antibodies did what they were supposed to do, target themselves to the tumor. We'll have to see in the next few weeks, whether they have the same response that they had in the animal model."

The growth of small cell lung cancer was inhibited in nude mice who received the monoclonal antibodies to bombesin.

**There has been some confusion over the cost of the LAK-IL-2 extramural trials.**

The Div. of Cancer Treatment Board of Scientific Counselors last February gave concept approval to new phase 2 studies using modification's of Rosenberg's regimen and to phase 3 clinical trials. The phase 2 studies were grouped at two levels of effort, depending on the toxicities expected at the time the studies were to be initiated, with research costs estimated at $4 million and $6 million, respectively. The Board's approval included the estimated total of $10 million over three years. Those figures were reported by **The Cancer Letter** (Feb. 14).

In presenting the concepts, DCT also listed estimated patient care costs, which for the two levels totaled $29.6 million, which was also reported by **The Cancer Letter**. The total of almost $40 million, coupled with DCT Director Bruce Chabner's statement that if additional funds could not be obtained elsewhere to support the LAK-IL-2 studies, other DCT resources might have to be tapped, led some to believe that too much emphasis was being given to the procedure.

Further, the phase 3 trials approved by the Board would total an estimated $17 million in research costs over five years. Estimates on patient care costs for the phase 3 studies ranged from $56 to $75 million.

The totals all together, including patient care costs, for the phase 2 and 3 studies reached the mind boggling figure of $100 million. But while those cost estimates were valid for the work proposed, that kind of a bite into NCI's budget was never really a threat, and in fact, the current cost estimates are only a fraction of what they appeared they might be. Here's why:

*In the first place, NCI never had any intention of paying patient care costs. They were a concern, given the reluctance of third party payers to pick up patient care costs in research protocols and the intensive care required by the LAK-IL-2 protocol. However, so far patient care costs have not been a problem. Some are being picked up by third parties, some by the institutions and some by the patients themselves.

*DCT has reduced the scope of the phase 2 studies. At the current level, the research cost is estimated at only $4.5 million over three years.

*Finally, the phase 3 trials have been placed on hold. "We feel that randomized phase 3 trials now are not justified, considering the level of toxicity and effectiveness," DCT Director Bruce Chabner told **The Cancer Letter**. Eventually, if the procedure can be improved, with less toxicity and improved response rates, phase 3 studies probably will be undertaken.

Meanwhile, the trials at six instituions attempting to duplicate Rosenberg's results with his regimen, suspended since August because of hepatitis A contamination, probably will be resumed in January. The contamination occurred in sera in which LAK cells are cultured.

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

Risk Assessment: The Evolving Process--Dec. 3, Vista International Hotel, Washington DC. Contact Suzanna Paulovkin, American Industrial Health Council, 1330 Connecticut Ave. NW, Suite 300, Washington DC 20036, phone 202-659-0060.

Gastrointestinal Oncology 1986--Dec. 4-5, Memorial Sloan-Kettering Cancer Center, New York. Contact CME Conference Planning Office, Box 458, MSKCC, 1275 York Ave., New York 10021, phone 212-794-6754.

Cancer Centers Support Grant Review Committee--Dec. 4-5, Crown Plaza Holiday Inn, Rockville, MD, open Dec. 4 8:30-9:30 a.m.

Cancer Therapeutics Program Project Review Committee--Dec. 4, Crown Plaza Holiday Inn, Rockville, MD, open 8:30-9 a.m.

New and Future Technology in Cancer Treatment--Dec. 5-6, Cleveland. Contact Center for CME, Cleveland

Clinic Educational Foundation, 9500 Euclid Ave., Rm TT3-301, Cleveland 44106, phone (local) 444-5696; (Ohio) 800-762-8172; (elsewhere) 800-762-8173.

National Cancer Advisory Board--Dec. 8-10, Memorial Sloan-Kettering Cancer Center, New York. Annual program review, all open.

Cancer Clinical Program Project Review Committee--Dec. 10, Sir Francis Drake Hotel, San Francisco, open 8:30-9 a.m.

AIDS and the Nervous System--Dec. 11-12, San Francisco. Contact Extended Programs in Medical Education, Univ. of California, Rm 569-U, San Francisco 94143, phone 415-476-4251.

Obtaining and Using Information on Smoking in Occupational Epidemiologic Studies--Dec. 15-16, Hyatt Regency Hotel, Bethesda, MD. Sponsored by NCI and the National Institute for Occupational Safety & Health. Contact Mary Clark, Birch & Davis Associates, 8905 Fairview Rd Suite 300, Silver Spring, MD 20910, phone 301-589-6760.

President's Cancer Panel--Dec. 15, Univ. of Chicago Cancer Research Center, Dora DeLee Hall, 9 a.m., open.

Frederick Cancer Research Facility Advisory Committee--Dec. 16, FCRF, Bldg 549, open 8:30 a.m.-noon. Rescheduled from Nov. 21.

Acrylonitrile Study Advisory Panel--Dec. 17, NIH Bldg 31 Rm 7, 9 a.m., open.

International Symposium on Breast Cancer--Jan. 1-4, New Delhi. Contact Dr. I. Mittra, Organizing Secretary, Tata Memorial Hospital, Dr. Ernest Borges Marg, Parel, Bombay 400 012, India.

Colorado Cancers: Medical and Legal Implications--Jan. 14-16, Marriott Mark Hotel, Vail. 21st annual Midwinter Cancer Seminar. Contact Jiri Tvrdik, BSN, Professional Education Director, American Cancer Society Colorado Div., 2255 S. Oneida, Denver 80224, phone 303-758-2030.

UCLA Symposia--Jan. 17-23, Park City Utah. Growth regulation of cancer and steroid hormone action. Contact Molecular Biology Institute, UCLA, Los Angeles 90024, phone 213-206-6292.

Chromosomes in Solid Tumors--Jan. 18-20, Arizona Cancer Center, Tucson. Second international workshop. Contact Mary Humphrey, Conference Coordinator, Arizona Cancer Center, Univ. of Arizona College of Medicine, Tucson 85724, phone 602-626-6044.

Div. of Cancer Prevention & Control Board of Scientific Counselors--Jan. 22-23, NIH Bldg 31 *rm 10, 8:30 a.m., open.

Gastroenterology Update: 1987--Jan. 24-31, Lion Square Lodge and Conference Center, Vail, CO. Contact Jeanne Ryan, Office of Continuing Education, Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 22, Baltimore 21205, phone 301-955-6046.

Recent Advances in Leukemia and Lymphoma--Jan. 25-31, Keystone, CO. Contact Molecular Biology Institute, UCLA, Los Angeles 90024, phone 213-206-6292.

Focus on Melanoma--Jan. 31, Cleveland. Contact Barbara Guy, Ireland Cancer Center, Lowman Bldg 211, University Hospitals of Cleveland, 2074 Abington Rd., Cleveland 44106, phone 216-844-7856.

## FUTURE MEETINGS

American Society of Preventive Oncology--March 11-13, Cathedral Hill Hotel, San Francisco. Annual meeting. Topics will include cancer in minorities, prostate cancer, cancer prevention and the primary care physician, role of the media in cancer prevention and controversies in preventive oncology--dietary fat and cancer. Contact Richard Love, MD, ASPO, 1300 University Ave.-7C, Madison, WI 53706, phone 608-263-6919.

1987 Joint Annual Meeting--April 25-30, Grosvenor House, London. Joint meeting of the Society of Surgical Oncology, Society of Head and Neck Surgeons, British Assn. of Surgical Oncology and Assn. of Head and Neck Oncologists of Great Britain. Contact DDO/SHNS, 13 Elm St., Manchester, MA 01944, phone 617-927-8330.

Carcinogenic and Mutagenic N-Substituted Aryl Compounds--April 25-28, Hyatt Regency Hotel, Dearborn, MI. Contact Charles King, PhD, Dept. of Chemical Carcinogenesis, Michigan Cancer Foundation, 110 E. Warren Ave., Detroit 48201, phone 313-833-0710.

Management of Clinically Localized Prostate Cancer --June 15-17, Magnuson Clinical Center, NIH. NIH Consensus Development Conference. Contact Nancy Cowan, Prospect Associates, 1801 Rockville Pike, Suite 500, Rockville, MD 20852, phone 301-468-6555.

Freestanding Cancer Centers: Their Role in Cancer Treatment and Research--July 8-9, Philadelphia. Topics will include the surgeon's role in FCCs, new technologies appropriate to outpatient settings, marketing implications for self referral patients, demand for second opinion clinics, clinical trials in FCCs, operations and research data requirements and hospital inpatient unit/FCC relationships. Sponsored by Fox Chase Cancer Center in conjunction with CDP Associates and InterCommunity Cancer Centers of America. Phone 404-391-9872.

## RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda MD 20892. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring MD, but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

### RFP NCI-CM-67888-72

Title: Operation of an animal virological diagnostic laboratory

This RFP which was issued last March (**The Cancer Letter**, Feb. 28) has been modified. NCI is still seeking organizations with the capabilities and facilities for performing viral serological testing on rodents. Serological testing will include the following viruses: PVM, Re03, polyoma sendai, MVM, electromelia, M.Ad., LCM, MHV, GD VII, KRV, H-1, RCV/SDA, SV5, K, and LDHV.

The revised estimated total number of viral serological tests to be performed annually is reduced from 95,000 to 37,000. All interested organizations may request copies of the amendment to the RFP.

Those organizations that previously requested the original RFP will be considered and need not request another.

The incumbent contractor is Microbiological Associates.

Contract Specialist: Jacqueline Ballard
RCB Blair Bldg Rm 224
301-427-8737

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

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