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RESEARCH EDUCATION CONTROL

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## NEW NIH CHIEF SPLITS WITH PREDECESSORS, HEW BRASS, OPPOSES "BALANCE," LIKES CANCER PROGRAM

When Sen. Alan Cranston (D-Calif.) attempted unsuccessfully to cut $100 million from the amount recommended by the Senate Appropriations Committee for NCI (*The Cancer Letter*, Oct. 3), he justified the move as an effort to achieve "balance" in biomedical research.

Cranston contended that increases in appropriations for NCI and the Heart & Lung Institute had been made at the expense of the rest of NIH. In terms of "constant" dollars since 1970, the other institutes actually had suffered a 13% decrease in funding, Cranston said. He supported his call for balance with letters from former NIH Directors James Shannon and Robert Marston.

While Shannon's letter was something less than all-out support for Cranston's amendment, Marston was unequivocal:

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*In Brief*

### INCREASING SURVIVAL THROUGH ADJUVANT THERAPY SEEN AS ADDING TO COST OF CARE

**CANCER CARE** costs now are "just the tip of the iceberg" compared to what they will be when adjuvant therapy is applied across the board, Donald Morton of UCLA predicted in a presentation to the National Cancer Advisory Board. Morton discussed the application of immunotherapy to the treatment of localized and metastatic malignant melanoma, mentioned that follow-up treatment requires patients to come in weekly or even twice weekly. "When we have more and more patients living longer and longer, bring them back every week, and extrapolate that to the major tumors, the drain on medical manpower time will be enormous," Morton said. **CANCER PANEL** Chairman Benno Schmidt did some quick figuring, then commented that those additional costs would amount to less than 10% of what cancer care costs today. "I wouldn't worry about that," Schmidt said. . . . **NCAB CHAIRMAN** Jonathan Rhoads has received the Pennsylvania State Medical Society distinguished service award. . . . **THE HOUSE HEALTH** Subcommittee has begun marking up a medical devices bill. This legislation passed the Senate overwhelmingly in the last Congress but never got out of the House committee. The bill would codify FDA regulation over devices, establish procedures for setting standards, provide for premarket clearance in certain cases. . . . **RESEARCH TRAINING** extension was scheduled to reach the floor of the House this week. No serious opposition was expected. . . . **MEETINGS:** Seminars in Cancer Involving the Skin, at Roswell Park, Nov. 19. Edmund Klein and Ole Holtermann are co-chairmen. . . . **HAROLD CHALKLEY**, who was assistant chief of NCI's Grants and Fellowships Branch when he retired in 1952, died recently in Bethesda. He was 88. One of his sons is Donald Chalkley, who heads the NIH Office for Protection from Research Risks.

## PLANNING, NOT BAD-MOUTHING CANCER PROGRAM WAY TO INCREASE HEALTH FUNDS

(Continued from page 1)

"I support the need to restore balance to funding among NIH institutes," Marston said. ". . . At the time of the enactment of the Cancer Conquest Act . . . I feared that the push on cancer would lead to over-promise and unjustified hopes. . . I think much of my apprehension has now been justified."

Fortunately for the Cancer Program, the current NIH director has no such fears. Splitting sharply with his predecessors over the issue, and also with HEW Secretary David Mathews, Donald Frederickson told the National Cancer Advisory Board that "I am not a great balance man. I expect there will be imbalances in biomedical research, based on needs and opportunities."

Later, Frederickson told ***The Cancer Letter,*** "We will never have perfectly balanced research efforts at NIH. That's just not the way science works. To assume that budget increases for all the institutes should go up regularly in the same increments across the board is incorrect."

Frederickson denied a rumor that was circulating among cancer program advocates—that the Cranston amendment was his idea and that he had promoted it.

"I was not, in any sense, responsible for the Cranston amendment," Frederickson told ***The Cancer Letter.*** "It did not originate in this office or gain its impetus here."

Frederickson told NCAB that "I am much wiser about the National Cancer Program now" than before he was appointed NIH director. "A cordial entente exists between NCI and NIH."

Cranston's amendment, in addition to removing $100 million the Senate added to the House bill for NCI, would have taken $50 million the Senate had added to the National Heart & Lung Institute budget and reapportioned it among the other NIH institutes (except NCI). Cranston justified that effort in part because, he said, "I believe that the appropriation of substantial additional funds for cancer research—and to a lesser degree heart and lung research—is and has been at the expense of adequate support for research in other areas, especially basic biomedical research."

Mathews supported Cranston in a letter, saying "I think that there is a consensus among medical researchers that the expenditure of more than $800 million for cancer research is not justified if we are to maintain a balanced biomedical research program."

That so-called consensus is more myth than fact, according to Benno Schmidt, chairman of the President's Cancer Panel. Schmidt is a member of the Biomedical Research Panel, which is taking a long, hard look at the federal health establishment and government-supported biomedical research.

Schmidt told NCAB that after listening to many hours of comment and testimony from a wide range of scientists, he feels "there is more general recognition today of the extent to which the cancer program supports basic research of the highest excellence. There is recognition in the scientific community that half the cancer budget goes into basic research."

In fiscal year 1971, before the National Cancer Program went into effect, NCI's total budget was $181 million. In fiscal 1975, NCI alone supported about $350 million worth of basic research.

Cranston argued that "there is much evidence that the benefits of expanded basic research programs at the other NIH institutes will also accrue to the understanding and conquest of cancer and heart disease."

The other side of that coin, of course, is just as valid. With the expanded NCI and NHLI programs, basic biomedical research is being supported now to a greater extent than it ever has been. More investigators have more money to work on more projects which they initiated themselves, irrespective of which NIH institute provides the funding. Many grants are being funded now by NCI which in previous years, if they were funded at all, would have received their money through the National Institute of General Medical Sciences, the National Institute of Allergy & Infectious Diseases, or one of the other institutes that is heavily involved in basic research.

The argument for a "balanced program" in biomedical research ignores the fact that, by passing overwhelmingly the National Cancer Act in 1971 and renewing it overwhelmingly last year, Congress determined that an emphasis on cancer was needed and justified. The "balance" argument is in line with the view of HEW brass (except perhaps for Asst. Secretary for Health Ted Cooper), that "there is only so much money for health, and cancer programs will have to compete with all the others for their share of that money."

Here are the facts:

In 1971, the budget for NIH excluding NCI was about $1.4 billion. NCI's budget was $181 million. NIH's total appropriation in 1976 will be about $2.3 billion.

Later in 1971, Congress passed the Cancer Act which authorized $400 million for NCI in fiscal 1972, and that authorization was progressively increased to more than $1 billion for fiscal 1977, including cancer control.

Congress did not specify that those extra funds for cancer were to come out of the $1.4 billion NIH had been getting, nor were they to be siphoned off any other HEW agency. The legislative history of the Act—committee testimony, committee reports, floor debate—in both houses made it absolutely clear that this was to be new money, an extra effort provided by the American people to conquer the disease they most dread.

But now, HEW budget makers are reaching for this new money to help solve their perennial crises, claim-

ing it belongs to the entire health establishment and should be spread around to achieve "balance."

Those authorization figures, incidentally, were not picked out of the air. They were based on the best estimates available, in 1971 and again in 1974 when the Act was renewed, of how much could be effectively spent in each of the major areas of cancer research and on basic research with relevance to cancer. Actual appropriations have never come up to authorizations, although NCI fares better in that regard than most government agencies.

A case could be made that NCI authorizations and appropriations should be revised upward. The original estimates were made five years ago, and inflation has had its effects on costs of contracts and grants. More importantly, cancer funds for the most part have been well spent. The program is gaining momentum, and new opportunities are developing that inevitably will lead to significant if not dramatic advances in treatment, diagnosis, and prevention.

Rather than attempt to cut themselves in on cancer money, health forces aligned with other disease categories would fare better if they would follow the example of cancer program advocates—take an intensive look at their own fields, develop a scientifically sound plan for attacking their problems, and present it to Congress.

That this approach still works with Congress was evident in the Senate appropriation bill. The Senate voted $50 million for the National Eye Institute, a 25% increase over the 1975 appropriation and the largest increase for any institute except NCI and NHLI. The Senate was impressed by a report, "Vision Research Program Planning," prepared by the National Advisory Eye Council.

The report "represents a major and unique effort to evaluate the state of the art of vision research in the U.S. and to assess the major research needs and opportunities in this field," the Appropriations Committee report said.

That's the way to get more money for biomedical research, not bad-mouthing the cancer program.

Pro cancer forces were dismayed by Cranston's defection. He is highly regarded by moderates and liberals in the Senate and is a good bet to become majority leader when Mike Mansfield retires. The cancer program can ill afford to lose the support of such an effective and increasingly powerful figure.

## THOSE SHUT OUT OF COMMUNITY CONTROL PROGRAM MAY HAVE ANOTHER OPPORTUNITY

NCI's decision to proceed with the Community Based Cancer Control Program left unanswered for the moment the question of what to do—if anything—about the unsuccessful bidders for the planning and implementation contracts.

With other NCI or any government contract offerings, the losers normally shrug it off and go looking for other jobs on which to bid. "This one was different," one non-government member of an NCI advisory group commented. "The RFP in both the planning and implementation phases required that someone in the community stick his neck out a mile. He had to assume, or accept, leadership, then try to organize all the disparate elements in the community on the premise that if they went along with him, the government would give them the money to help get the program started.

"But then he fails to get the contract. His failure is widely known throughout the community, he's embarrassed and furious. Even if our demonstration programs in those communities which received contracts do succeed, how can we expect those others to try to organize themselves again?"

When the National Cancer Advisory Board was considering the program recently, Board member Denman Hammond suggested that NCI might consider funding all those who submitted proposals, at least for the planning phase. The planning contracts involved only about $100,000 each, an amount Hammond said could be "enormously influential" in mobilizing those elements of a community which could play a role in the control program. Even if they did not go on to the implementation phase, Hammond suggested, "in this case planning is implementation."

There were 32 proposals submitted for the planning contracts and five for implementation. NCI eliminated nine of the planning proposals for various reasons, and the remaining 23 were site visited. Nine awards were made, leaving 14 very unhappy communities.

Five proposals were submitted for the implementation contracts, all were site visited, and two awards were made.

What about the prospect of giving planning contracts to the 17 unsuccessful proposers?

"That can't be done under federal contract regulations," Diane Fink, director of the Div. of Cancer Control & Rehabilitation, told ***The Cancer Letter.*** "That was a very specific procurement, and it would not be legal to go back and make awards now to those who had been determined, through our peer review process, as not having met those specific requirements."

The door is not closed, however. Fink said "We are rethinking the entire program. I think there will be a small but definite amount of money that will be made available to communities, to assist them in planning and organizing cancer control efforts."

Fink said the "small but definite amount" of money could be several million dollars for the new program which would be similar to CBCCP but without the specific requirements which many of the responders were unable to meet.

The new program could be funded through grants or contracts, or through the Cancer Research Emphasis Grant mechanism; that will be determined later.

## ABSTRACTS OF PAPERS FROM COPENHAGEN SYMPOSIUM ON RESEARCH ON LEUKEMIA

*The VIIth International Symposium on Comparative Research on Leukemia and Related Diseases was held Oct. 13-17 in Copenhagen. Abstracts of papers presented at the symposium appear below; others will be published in subsequent issues of* ***The Cancer Letter.*** *The International Assn. for Comparative Research on Leukemia and Related Diseases will publish the complete papers by mid-1976. Copies may be obtained by writing to David Yohn, IACRLRD Secretary General, Ohio State Univ., 1580 Cannon Dr. Suite 357, Columbus, Ohio 43210.*

**Experimental Studies With Maytansine – A New Antileukemic Agent** – ***Richard Adamson, Mary Wolpert, Susan Sieber, Richard Cysyk, Vincent Bono & David Johns, NCI***

Maytansine is a naturally occurring ansa macrolide originally isolated by Kupchan et al. We have investigated its antileukemic activity in vitro and in vivo in several experimental systems. Maytansine was active in vitro against the human lymphoblastic leukemia line CEM and against several murine leukemias including leukemia L1210, leukemia L5178Y and leukemia P388, the $ED_{50}$ for the P388 murine leukemia cells being $6 \times 10^{-10}$M. In vitro studies on the macromolecular synthetic processes indicate that maytansine inhibited DNA synthesis to a greater degree than RNA or protein synthesis. Maytansine at levels of $10^{-4}$M did not inhibit *E. coli* RNA polymerase.

Maytansine was active in vivo against several experimental tumors including mast cell P815, plasma cell YPC-1, Walker 256 carcinosarcoma and although very active against murine leukemia P388, it was not active against leukemia L1210. In addition, maytansine was inactive when evaluated against the P388 variant made resistant to vincristine.

When injected into pregnant Swiss mice on gestational day 7 or 8, maytansine induced a high rate of intrauterine death and fetal malformations at doses greater than 150 mg/kg. At doses of 200 mg/kg daily for five days, maytansine induced neurotoxicity in mice as evidenced by muscular weakness and hind limb paralysis similar to that previously reported for vincristine (R.H. Adamson, Arch. Int. Pharmacodyn. 157: 299, 1965).

In an analysis of the stathmokinetic properties of maytansine, it was found that within 12 jr of exposure to the drug at a concentration of $10^{-8}$M, the distribution of the DNA content in a population of exponentially growing L1210 cells shifted to a single peak, corresponding to cells with a $G_2 + M$ DNA content. Histologic examination of these cells revealed that the majority (approx. 60%) were arrested in metaphase, suggesting that maytansine impairs the function of mitotic spindles.

**Concepts Concerning The Origin Of RNA Tumor Virus Markers In Human Leukemic Cells** – ***David Gillespie & Robert Gallo, NCI***

RNA tumor virus markers detected in peripheral blood myeloblasts from patients with myelogenous leukemia include: reverse transcriptase; viral structural proteins; viral-related RNA; a discrete cytoplasmic particle having a bouyant density of 1.17-1.19 gm/ml and a diameter of 1000 Angstrom and capable of synthesizing DNA molecules attached to 35S or 70S RNA and with viral-related sequences; and extracellular, infectious, type-C RNA virus particles. All of these components are genetically related to analogous components from certain primate, type-C RNA tumor viruses, yet, paradoxically no viral-related sequences have been detected in the DNA of leukemic, peripheral blood myeloblasts. We consider here four hypotheses that could account for these observations.

1) The hypothesis most consistent with conventional RNA tumor virology (the "infection hypothesis") states that the viral components are acquired through infection. If this is the case, the site of infection may be a minor population of myeloblasts or another, unknown tissue. Viral nucleotide sequences become integrated into the DNA of the infected cells and these cells may produce a factor that arrests the development of myeloblasts and causes them to accumulate in the peripheral blood. Complete DNA provirus is not detected because the average number of proviruses/cell can be considerably less than one.

2) Another hypothesis (the "ontogene hypothesis") does not depend on infection of the leukemic patient by an external vector. The ontogene hypothesis states that certain genes are discarded during differentiation and among those are genes coding for RNA tumor viruses. In this hypothesis, the RNA tumor viruses are "endogenous" but few cells (possibly only germ line cells) containing DNA provirus exist in adult animals. Failure to discard the viral genes during differentiation might allow virus production by some cells and result in leukemia as proposed in the "infection hypothesis". Again the DNA provirus would not be detected.

3) Leukemic myeloblasts may contain a metabolically unstable DNA provirus. During its lifetime the DNA provirus would participate in the accumulation of viral protein and RNA components, but the provirus would then be destroyed. This model has no precedent in RNA tumor virology.

4) The virus from leukemic patients contains proteins that immunologically cross-react with proteins from primate type-C RNA tumor viruses but may yet have a genome that is too genetically distant from them to be detected by molecular hybridization using viral probes.

Notwithstanding the mechanism of RNA tumor virus origin it is proposed that the developmental arrest in leukemic myeloblasts involves an alteration

of RNA processing. A "paraprocessing hypothesis" has been put forward to explain structural features of RNA tumor virus RNA and embryonic mRNA. Paraprocessing is described as a selective mode of gene expression required for proper development and differentiation. It is viewed as a newly evolved control mechanism, prone to error; some errors can lead to an arrest of differentiation, one consequence of which may be leukemia.

**Biochemical Pharmacology Of Cytidine Analog Metabolism In Human Leukemic Cells** – ***Bruce Chabner, Ronald Stoller, C. Norman Coleman & Paul Chang, NCI***

The nucleoside analogs cytosine arabinoside (ara-C) and 5-azacytidine (5-aza-C) are effective in the treatment of acute myelocytic leukemia (AML). In order to define the relationship of intracellular drug metabolism to clinical response, the relative levels and kinetic properties of the activating and degradative enzymes as found in AML cells were studied prior to treatment.

The primary degradative enzyme for ara-C in AML cells was found to be cytidine deaminase which has a $K_m$ of 0.09 mM for ara-C and 0.43 mM for 5-aza-C. In a series of 41 previously untreated patients with AML, cytidine deaminase (D) activity averaged 540 n moles/hr/mg protein, although this activity varied over a 350 fold range and displayed great variability between patients.

The phosphorylation of ara-C was catalyzed by deoxycytidine kinase (CdR K), which had a $K_m$ of 0.026 mM. This enzyme was separable from uridine-cytidine kinase (U–C K) by hydroxylappatite chormatography. In extracts of AML cells purified by Ficoll sedimentation, CdR K activity average 13.7 $\pm$ 12.4 units/mg protein, but varied over a 28-fold range. U–C K, the enzyme believed to be responsible for 5-aza-C activation, averaged 13.9 $\pm$ 13.3 units/mg protein and ranged from less than 1 to 46 units/mg protein. There was no consistent relationship between the activities of these two enzymes in AML cells; the ratio of CdR K to U–C K varied from 0.03 to 7.9, indicating the variation in the relative ability to activate ara-C and 5-aza-C in this group of patients. In a similar manner the ratio of kinase to deaminase activity varied from 0.0016 to 1.182 for CdR K/D, and from 0.0003 to 1.351 for U–C K/D.

These results suggest that patients with AML have widely different potentials for activating and degrading two actively used antileukemic agents, and indicate that therapy in this disease might be improved by basing drug selection on pretreatment biochemical assessment.

**Oncornaviral Genes And Murine Differentiation Markers** – ***Richard Lerner & Bert Del Villano, Scripps Clinic & Research Foundation***

A number of investigators have postulated that endogenous oncornaviruses play a role in development and differentiation and that neoplasia is an unfortunate consequence of an otherwise important symbiosis. Although attractive on a theoretical basis, these concepts remain unproved. Nevertheless, it is possible to study the relationship betwéen viral gene expression and normal host functions. Recently, evidence from several laboratories has suggested that expression of endogenous oncornavirus genes may be under differentiation control in the mouse. The clearest example of this is seen in the case of gp70, the major envelope glycoprotein of the murine leukemia viruses (MuLV). Several years ago, we and others reported that a glycoprotein with a molecular size of 67,000 daltons was a component of the surface of oncornaviruses and infected cells. Strand and August purified gp70 to homogenity and in a series of important studies, they showed that this protein was coded for by the viral genome.

From the beginning, one enigma concerning gp70 was evidence of expression in normal thymocytes of a number of murine strains. Very recently, it was shown that gp70 is a constituent of the surface of normal thymocytes, even in the absence of expression of infectious virus, and other studies have shown that the lymphocyte differentiation marker $G_{IX}$ is an antigenic determinant of the same molecule. Thus, the extensive genetic studies already carried out for $G_{IX}$ were now applicable to a protein which was coded for by the viral genome and expressed as a constituent of the plasma membrane of cells following certain pathways of differentiation. With respect to the connection between $G_{IX}$ and MuLV expression it is important to recall that following oncornavirus infection, $G_{IX}$ may be inappropriately expressed in $G_{IX}$– strains of mice or even in rats.

Although, as suggested from studies of $G_{IX}$, expression of gp70 was indeed linked to cellular differentiation, its control is more relaxed than previously recognized. By immunofluorescence, we detected gp70 in a number of cell types prominent among which were lymphoid and epithelial cells. An interesting site of expression was the epithelium of the epididymis and ductus deferens where staining for gp70 was found to be concentrated along the luminal aspects of the secretory epithelium of the epididymis and ductus deferens in a number of strains of mice. Importantly, the protein was present in the 129 $G_{IX}$+ but not in the congenic 129 $G_{IX}$- mouse. Immunologic and biochemical studies of the virus associated gp70 and the molecule secreted by the male genital tract showed that they were related. The gp70 of the epididymis and ductus deferens represents up to 10% of the secreted proteins and associates with the surface of sperm.

Thus, gp70 shows biological pleomorphism in that it is a component of viruses, lymphoma cells, normal thymocytes, and now the secretions of the epididymis and ductus deferens.

**Antigenic Relationships Between Human Leukemia Associated Antigens and RNA Tumor Virus Antigens** – *R.S. Metzgar, T. Mohanakumar, W. Schafer & D.P. Bolognesi, Duke Univ.*

Antigenic relationships between known RNA tumor viruses and membrane associated antigens of human leukemia cells have been established as follows: 1) Some antisera to gradient purified mammalian RNA tumor viruses or their isolated structural components react by a microcytotoxicity technique with certain morphological types of human leukemic cells; 2) Certain mammalian RNA tumor viruses are able to absorb out the cytotoxic reactivity of nonhuman primate antisera to human myeloid and lymphatic leukemia cells. Detailed absorption and direct cytotoxicity testing studies using the approaches described above have established an antigenic relationship between human myeloid leukemia antigens and p30 and gp71 structural components of Friend leukemia virus. In addition, preliminary studies show a strong antigenic relationship between primate RNA tumor viruses, feline leukemia virus and membrane antigens of human leukemia cells which are not related to those noted with Friend virus.

**Lymphocyte Responsiveness In Marmosets, Squirrel and Cebus Monkeys Infected With *H. Saimiri* – *S.S. Kalter, W.T. Kniker, J.S. Harvey Jr., P.J. Felsburg & R.L. Heberling, Southwest Foundation***

Previous studies from this laboratory have demonstrated differences in susceptibility of nonhuman primate species to herpesvirus *(H. hominis)*. It also has been shown that the humoral and cellular immunological competence of these species differed; the baboon and squirrel monkey most closely approximating man, the cebus intermediate and the marmoset relatively incompetent. This study of immunological competence was continued using *H. Saimiri* (HVS) to infect these simian hosts. Inoculation of HVS into six squirrel monkeys resulted in no evidence of disease after 18 months, even though they were initially immunosuppressed. One of six infected cebus monkeys died at four months with a lymphoproliferative disease. All five inoculated marmosets developed typical fatal malignancy. Before and after inoculation, peripheral lymphocyte incorporation of $H^3$ thymidine in response to mitogens and HVS was studied.

At three months, results in squirrel and cebus monkeys were comparable; in each group one animal exhibited an elevated background count (viral stimulation?), two animals showed specific reactivity to HVS, and there was unimpaired responsiveness to mitogens. Marmosets were tested when terminally ill 20 days after infection. In contrast to the other species, all showed marked (20-200 fold) elevations in background counts. Concomitantly, absolute responses to all mitogens and HVS were less than the background, with transformation indices of 0.2 to 1.0. These data indicate that lymphocyte stimulators added in vitro may suppress $H^3$ thymidine incorporation of lymphocytes already intensely stimulated by virus.

**Kinetics Of Type C Virion Release From A Human Diploid Fibroblast Strain** – *Sandra Panem, Edward Prochownik & Werner Kirsten, Univ. of Chicago*

We have recently reported that a strain of normal human lung embryo cells (HEL-12) spontaneously release type C virions after in vitro propagation for 4-6 months. Spontaneous expression of virion antigens and virion release were examined in relation to the growth duration of HEL-12 cells following exposure to 2-deoxy-D-glucose (2-DG) was also monitored during serial cell propagation. HEL-12 cultures were split 1:3 every five days. Under these conditions, HEL-12 cells grew with a doubling time of 36 hours, and each subculture represents 3.3 cell generations. Virion antigens were monitored in indirect cytoplasmic immunofluoresence tests using control goat serum and immune goat serium to tween-ether disrupted simian sarcoma virus (SiSV) and tween-ether disrupted Baboon endogenous virus (BabEV). Virion production was measured by monitoring spent culture fluids for RNA-directed-DNA polymerase activity using the synthetic polynucleotide poly(rA)·oligo (dt) 12-18 as template.

Primary cell cultures of HEL-12 cells did not express virion antigens or produce virions. Low levles of SiSV-related antigens were spontaneously expressed within 10 in vitro generations. Spontaneous virion release was found after HEL-12 cells had been propagated for 58-80 cell generations. Virions were barely detectable by the 90th in vitro cell generation. Virion antigen expression was detected with the two antisera during the period of spontaneous virion production. Antigen levels were maximal just prior to the period of spontaneous virion release and declined in parallel with the decrease in particle production.

The ability of HEL-12 cells to produce virion in response to 2-DG treatment followed a different pattern. Cells were not responsive to type C virions induction by 2-DG during the early cell generations. 2-DG mediated virion release from HEL-12 cells occurred during a brief period prior to spontaneous virion release. These data were reproduced on four separate occasion when HEL-12 cells were plated from primary freezer stocks and serially propagated. The following sequence of events for the expression of type C virions in HEL-12 cells is postulated: (a) Primary or early cell cultures do not express virion antigens and do not produce particles. (b) Virion antigen expression occurs spontaneously after 4-6 weeks in culture. (c) Cells become susceptible to transient particle production following treatment with 2-DG during this time. (d) HEL-12 cells spontaneously release virions for a short period of time, during which period the cells are refractory to virion induction with 2-DG.

**Comparative Studies Of Type C, Type B And M-PMV Oncornaviruses** – *L. Dmochowski, J.M. Bowen, B. Myers, E.S. Priori, M.F. Miller, G. Seman, J.C. Chan, M.L. Dodson and M. Scanlon, M.D. Anderson*

Oncornaviruses comprise three morphologically different types: type C viruses associated with leukemia, lymphoma and sarcoma of animals of various species; type B viruses (MMTV) associated with mammary cancer of mice of inbred, outbred strains and wild mice; and Mason-Pfizer monkey virus (M-PMV) of a monkey mammary cancer. Type B and type C particles have been demonstrated in human neoplasia, such as breast cancer, leukemia, solid and soft tissue tumors. Particles resembling type B and type C and M-PMV particles have been found in a variety of human tumor cell lines. Comparison of morphological and antigenic properties of the three types of virus particles was undertaken to arrive at an understanding of the nature of present and future virus isolates from human leukemia and solid tumors.

Type C particles are distinguishable from type B particles present in animal or human material by morphological and immunological means, even if both types of particles are present in cells of the same tumors. Type C and type B particles, irrespective of origin, show within each type an essential similarity by morphological and immunological tests, in spite of extensive variation in their internal structure and biological behavior.

Fixed immunofluorescence (FIF), ferritin labeled antibody (FLA), peroxidase labeled antibody (PLA), immunodiffusion (ID) and radioimmunoprecipitation (RIP) tests using heterologous antisera to whole MMTV particles, sera of MMTV hyperimmunized and of mammary tumor-bearing mice have not revealed any differences between type B particles, irrespective of origin, and have demonstrated lack of cross-reactivity between type B and type C particles.

Morphological studies of M-PMV particles in simian mammary tumor cells, cocultures with monkey embryo cells, or infected human cells have shown similarity in size and appearance of these particles and their developmental forms in spite of variation in internal structure. The M-PMV particles show similarity in size and appearance and developmental forms to those of particles isolated from HEp-2 human tumor cell line but differ morphologically from type B and type C particles. FIF and ID tests have demonstrated that M-PMV and HEp-2 particles are related but differ antigenically from MMTV particles. Similar results in ID tests have been reported. These findings may be helpful in characterization of virus isolates from human leukemia and related tumors.

**The Epidemiology And Virology Of C Type Virus-Associated Cancer And Paralysis In Wild Mice** – *Murray Gardner, Vaclav Klement, Suraiya Rasheed, Brian Henderson, Malcolm Pike & Robert Huebner, Univ. of Southern California*

Among several different populations of wild mice *(Mus musculus)* trapped in Southern California, a direct correlation was found between the prevalance and titer of spleen complement fixing gs (p30) antigen in newly trapped healthy mice and a predilection to lymphoma and a neurogenic hind leg paralytic disease upon aging in the laboratory. An increased incidence of breast carcinomas, hepatomas, and pulmonary adenomas associated with type C virus also occurred in the lymphoma-paralysis prone LC colony as compared with the tumor-resistant colonies. However, our findings leave unanswered the possible role of indigenous type C virus on non-lymphomatous tumorigenesis in LC and other wild mice. Virus strains isolated from the cancer-paralysis prone LC mice are N-tropic and have an unusually wide host range in vitro ("amphitropic"). Infectious virus is demonstrable in multiple tissues and sera of these mice soon after birth and throughout life. Differences in the pathogenesis of lymphoma and paralysis are attested to by differences in sex distribution, cumulative incidence curves and level of serum p30 antigen by radioimmunoassay at trapping. Specific immunologic nonresponsiveness to the indigenous virus is suggested by the complete lack of free-antibody or of glomerular immune complex deposition as studied by several techniques in LC mice, including those inoculated with indigenous virus vaccines. Control of the increased level of type C virus expression and reduction in lymphoma and paralysis incidence in the progeny was accomplished at the genetic level by cross breeding LC wild mice with C57 B1/10Sn inbred mice, homozygous for the Fv-$1^b$ allele.

## CONTRACT AWARDS

**Title:** Operation and maintenance of rodent production center
**Contractor:** Harland Industries, Cumberland, Ind., $43,105.

**Title:** Operation and maintenance of the drug distribution system
**Contractor:** Value Engineering Co., $193,592.

## SOLE SOURCE NEGOTIATIONS

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

**Title:** The national consultative programs for hospitals
**Contractor:** American College of Surgeons.

**Title:** Support services to maintain studies of the role of viruses in experimental oncogenesis and human cancer
**Contractor:** Hazleton Laboratories.

**Title:** Procurement of embryonic cell lines with with variable growth rates
**Contractor:** Litton Bionetics.

## RFPs AVAILABLE

***Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.***

### RFP NCI-CP-VO-61025-54

**Title:** *Monitoring of biohazards containment facilities*

**Deadline:** *Not yet determined*

NCI is seeking a contractor to perform the following tasks: (1) Perform site visits to research facilities involved in the handling of hazardous chemicals including carcinogens for the purposes of evaluating compliance with recommended safety guidelines and for providing advice to enhance the safety of work practices. (2) Provide a monitoring and analytical capability for the purpose of detecting chemical carcinogens in the research environment. (3) Provide safety consultation to NCI on matters pertaining to the safe handling of chemical carcinogens in the laboratory environment.

Accomplishment of these tasks will require expertise in industrial hygiene, environmental health, analytical chemistry, organic chemistry, etc., mechanical engineering, and technical writing. The capability of performing continual literature review for recent developments in risk assessment, research techniques, and environmental control will be required.

Contract Specialist: J. Thomas Lewin
Cause & Prevention
301-496-1781

### RFP NCI-CM-67069

**Title:** *Operation of an animal virological diagnostic laboratory*

**Deadline:** *Nov. 26*

This project will be concerned with the virological monitoring of all rodent colonies under contract to the Div. of Cancer Treatment, NCI, and animals and tumors using various testing and research programs. Emphasis will be placed on the examination of serum, plasma, and tumor specimens for the presence of various viruses. It is anticipated that approximately 95,000 individual tests will be performed each year. A three year contract is anticipated.

Contract Specialist: T.R. Hardy
Cancer Treatment
301-427-7463

### RFP NO1–CO-55331-08

**Title:** *Preparation of carcinogen safety monographs*

**Deadline:** *Not yet determined*

NCI is soliciting proposals for the preparation of approximately 18 carcinogen safety monographs in an effort to protect workers in laboratories and other facilities by the use of suitable safeguards and to protect the general environment by preventing the escape of these materials.

The offeror should obtain, organize and review for comprehensiveness and reliability the pertinent background information and all available safety information on each designated chemical carcinogen. This information shall be reviewed by NCI and upon approval, ultimately arranged to form a carcinogen safety monograph for each particular chemical carcinogen.

Contract Specialist: Anita Schwartz
Control & Rehabilitation
301-427-7984

### RFP NO1–CO-65278-08

**Title:** *Development of a short training course on principals and techniques for the safe handling of chemical carcinogens*

**Deadline:** *Not yet determined*

NCI is soliciting proposals for a comprehensive training course on the safe handling of chemical carcinogens for laboratory workers and others who may have responsibilities in this area. The course may consist of lectures, demonstrations or participation in laboratory exercises, or any combination of these elements and should be between two and five days in length. A course manual should be developed for distribution and should contain abstracts, data tables, references and other supporting material for each of the lectures and topics covered by the course.

The course may be presented at NIH or at any other facility suitable to the contractor and convenient to NCI. It is anticipated that the training course will be repeated a minimum of five times at the same or different locations in order to meet the requirements of NCI.

Contract Specialist: Anita Schwartz
Control & Rehabilitation
301-427-7984

**The Cancer Newsletter**—*Editor* JERRY D. BOYD

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