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COOPERATIVE GROUPS FIGHT BACK: MEMBERS SEEK MOVE TO MULTIDISCIPLINARY APPROACH, MORE FUNDS

Using the axiom that the best defense is a strong offense, defenders of the Clinical Cooperative Trials Program pressed arguments at the Potomac Conference for new cooperative groups, more money, increased NCI staff to support the program, and the first crack at NCI generated treatment projects.

Selected chairmen of cooperative groups met with members of the Cancer Clinical Investigations Review Committee, NCI staff and other

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In Brief

YARBRO TO LEAVE AS NCI CENTERS CHIEF TO HEAD MISSOURI CANCER PROGRAM; REPLACED BY CANTRIL

JOHN YARBRO will leave as chief of NCI's centers program June 30 to become chairman of the Dept. of Oncology at the Univ. of Missouri where he'll head up the university's efforts to develop a new cancer center. **SIMEON CANTRIL**, deputy director of the West Coast Cancer Foundation, will replace Yarbro in the Div. of Research Resources & Centers. Cantril, an M.D. from Harvard, is a radiotherapist, helped Jerome Vaeth establish the West Coast organization, and was secretary-treasurer of the Assn. of Community Cancer Centers. . . . **CONFLICT** in meetings of professional societies was pointed out by Vincent DeVita, director of NCI's Div. of Cancer Treatment. DeVita attended both the AACR/ASCO meeting in San Diego and the American College of Radiology meeting in Puerto Rico which were held the same week, but most members of the respective organizations attended only one. "Obviously some members could have benefitted from both meetings," DeVita said. "It's a pity we don't have a federation of cancer organizations to coordinate these things" . . . . **FRONT AND CENTER** problem" being addressed by the Biomedical Research Panel is technology transfer, primarily the question of who should have that responsibility, Benno Schmidt told the President's Cancer Panel. Schmidt is a member of both Panels. He said the Biomedical Panel, which is looking into all federally supported biomedical research, has heard testimony from scientists who doubt that NIH is the appropriate agency to apply the results of its own research. "They worry that it may be the path from the transfer of funds from research to control," Schmidt said. HEW's Alcohol, Drug Abuse & Mental Health Administration is an example of an agency that has permitted funds to be diverted from basic research to control. Schmidt said he has not heard any criticism so far of NCI's cancer control program, probably because its budget is less than 10% of the total NCI budget and is not considered a disproportionate amount. "I would hate to see the theory prevail that technology transfer should be somewhere else if in fact that means it wouldn't be done," Schmidt said.

CLINICAL RESEARCH OVERLAPS, LACK OF COORDINATION CITED AT CONFERENCE

(Continued from page 1)

group members at the three-day conference last week. They offered a variety of suggestions in answer to their critics, including a proposal that the program's emphasis be switched from single modality to multidisciplinary therapy.

Stephen Carter, deputy director of the Div. of Cancer Treatment, offered his view of the problems the CCTP is facing, and they effectively summarized the views of most NCI senior staff members.

Overlapping research projects are the "major problem we have to come to grips with," Carter said. It results in undesirable duplication, competition for resources and lack of coordination, he contended.

"No one in this room will deny that these problems exist," Carter said. "The question is, how do we overcome them?"

Carter pointed out that there are five uncoordinated programs in broncogenic carcinoma funded by NCI units—the lung cancer working party and VA study groups in DCT; seven cooperative groups and the various work being done in the centers, funded by the Div. of Research Resources & Centers; and an immunotherapy program in the Div. of Biology & Diagnosis.

Carter said that in advanced epidermoid carcinoma of the lung, there are 17 different regimens in clinical trials. "I would guess that if we asked the chairmen of these different groups working on the advanced epidermoid carcinoma of the lung to come up with 17 different regimens, they would not come up with these," he said. "We have to ask ourselves how to come to grips with this. What is the best way to use this mechanism (the cooperative groups) to advance treatment research?"

The criticisms expressed by Carter and those mentioned by NCI Director Frank Rauscher in an exchange of letters with CCIRC Chairman Giulio D'Angio (*The Cancer Letter*, May 9) were mild compared with some offered privately by NCI executives and others. One who has observed the cooperative groups for many years and from several vantage points made these comments to *The Cancer Letter*:

"Much of their work is poor. The major problem is inadequate review by CCIRC. There are only a few good groups. They have a tendency to draw up protocols to fit their weakest members. Strong leadership can and has overcome this problem with the good groups, but too many let the inadequate members dictate what the group can do.

"Coordination is non-existing. The cooperative groups need to be in DCT, where Vince DeVita (DCT director) could stop overlaps, or assure that duplications are controlled, and where they could coordinate the groups with the contract programs to fill in the gaps.

"Merely reporting to each other what they are doing and attempting to cooperate has not been successful in the past. Treatment research should be moved into DCT, and let DeVita and Carter clean out the bad groups."

That may be more of a responsibility than either DeVita or Carter want. Neither were that extreme in their remarks, the thrust of which indicated they would settle for some strong and effective means to ensure coordination.

DeVita agreed with CCTP defenders, that NCI puts a relatively small amount of money into clinical research. Much of DCT's budget goes for drug development. "Actually, basic research is very well funded, and when a shortage of funds exists, clinical research is cut first because it is called targeted research," DeVita said. "The cooperative groups are underfunded in certain respects."

The cooperative groups were started because of an absence of any other mechanism, DeVita pointed out. "Now we have others—those in the centers, in the cancer control program, in DCT contracts."

Thomas King, DRR&C director who is the most senior NCI executive responsible for administration of CCTP, said that "we recognize the validity of some of the criticism. We should not shy away from it. But we should also recognize the valuable contributions to training and to treatment advances made by the cooperative groups."

King said that there has been "a lot of loose talk" and one result has been "divisiveness and confusion heard from the outside. The situation is not irretrievable, but something has to be done—in the interest of cancer patients, science and the cancer program, or our greatest supporters may become opponents."

William Levin, Univ. of Texas (Galveston), presented a ringing defense of CCTP. "In my view, it should be used as a model by other disciplines," he said. "Examples include the great uncertainty that still exist about oral hypoglycemic agents, 15 years after they were introduced, and the anti-coagulants used for myocardial infarction for 30 years and for which there still is no sound data. If properly designed comparative studies of these drugs had been made, some of the consequences might have been avoided."

Levin pointed to dramatic results achieved by some groups—childhood leukemia, Hodgkin's disease, and others—and admitted there have been "many disappointments, many with less dramatic results than others.

"One of the dividends has been the hundreds of young investigators who have participated and are now emerging" as highly skilled clinicians.

Levin offered his recommendations for the program:

- Maintain and strengthen peer review, which is essential to the quality of CCTP.
- Continue to use the grant mechanism rather

than contracts "to avoid control by federal scientists."

• Leave the administration of the program in the NCI branch responsible for the management of extramural research. "It is absolutely essential that this branch be adequately staffed."

• NCI should develop a mechanism for cataloguing all research activities. The staff for doing this should be administratively located in the NCI director's office. The catalog should be continually updated and distributed to investigators.

• The total effort should be planned and coordinated by the groups working with NCI staff.

James Holland, Mt. Sinai, was the most aggressive CCTP defender, insisting the groups included "the cream" of cancer clinical investigators, that they are "a tremendous resource" whose potential is relatively untapped, and that rather than be cut back, the program should be expanded with a substantial increase in funds from NCI.

Holland pointed out some comparative cost figures which showed that NCI contract clinical trials reached about 5,000 patients in one year at a cost of $2,000 per case. CCTP in 1974 reached 16,000 patients at a cost of $750 per case, he said.

It was Holland who made the major pitch for expanding the program into a multidisciplinary one.

"The large multidisciplinary group should constitute and reflect the leading edge of clinical cancer research," Holland said. "At the minimum, this entails conjoint participation of medical oncologists, surgical oncologists, radiation oncologists, and biostatisticians. . . .

"Major emphasis should be placed on multidisciplinary groups with broad responsibilities in cancer investigation of multiple diseases. The characteristics of a successful group seem to be the inclusion of at least one or two strong institutions with leadership potential in evolving new protocols, and in early pilot studies of imaginative scope.

"Additional smaller groups for specific body regions, for specific disciplinary techniques, and for specific rare diseases are reasonable. For common diseases, proliferation of competing monomalady groups with disproportionate funding and isolation from the cooperative clinical trials groups should be discouraged until pursuit of such research within the clinical trials groups had been demonstrably unsuccessful, a condition which this observer believes does not exist. Scientific competition should, however, be encouraged.

"In groups, as in other activities, where you are is less important than who you are, and geography should play little role in selecting group members. The tide of current cancer research bring surgery, radiotherapy, chemotherapy and immunotherapy to close juxtaposition. Restructuring and refunding the cooperative clinical trials groups to allow for this constellation of strength is imperative. The groups should have easy communication in both directions with the Div. of Cancer Treatment, to allow for formulation of policies and goals of therapy, and a broad national strategy."

Holland acknowledged that some groups should be dropped. "NCI might, with critique, wise assessment and peer review, dissolve those groups with a desultory record of performance. . . .

"Simultaneously, those groups found to be successfully functioning should be aided and encouraged with appropriate resources to . . . fulfill a concerted research mission in cancer therapy.

"A critical look at single disease groups might allow their pruning to the extent that continued existence would depend on characteristics such as rarity of disease, as well as on demonstrated competence, and impact of successful treatment of the disease on the principles of cancer therapy.

"I believe something of the order of 10 multidisciplinary cooperative groups could be justified in the United States but then membership need not all be American. They should provide a major new resource. These 10 groups and their members could help focus the existing professional manpower, and could take over the functions of some of the currently active groups which might be discontinued. Optimal size for a group might constitute something of the order of 15 to 30 institutions, together with ample operational and biostatistical support.

"The group chairman should have a special grant to facilitate new research.

"Lastly, if there were a network of these groups, it is highly likely that their member institutions could serve as the most effective units for translation of cancer research to clinical implementation in their own areas, under the programs of the Div. of Cancer Control."

Barth Hoogstraten, Univ. of Kansas (Kansas City), commented that "Duplication of effort is not a cooperative group problem. Rather, it is an NCI and a national problem. . . . When you talk about competition for resources, duplication, and lack of coordination, you should look at the entire cancer program. . . .

"It's about time you (NCI) stop asking us what we can do for you; ask what you can do for the cooperative groups."

Commenting on Holland's proposals, Hoogstraten said, "The essence of his presentation was that new groups should be created, some existing ones eliminated for which a need no longer exists. . . Let's look at the cooperative groups closer and eliminate the weakies."

Hoogstraten suggested that funding of the CCTP should be done across NCI division lines. "I'm told this is impossible, that there are personality conflicts. I say, to hell with personalities. If the personalities can't work together, get rid of them.

"I look upon Rauscher, DeVita and King as men of high integrity, dedicated, who make less money than we do and knowingly so which proves their dedication. They can change directions for the good of the program. We need decisive action. We need to review the entire cancer program, and not just the cooperative groups."

A further report on the Potomac Conference, including an analysis by NCI executives and CCTP members of suggestions presented there, will appear next week, along with reports and comments which were not included in the above article.

COMPREHENSIVE CENTERS COULD LOSE THAT DESIGNATION BY NOT PRODUCING

Twenty-five cancer centers have informed NCI of their intention to seek comprehensive status, and another 15 or 20 may add their names to the list in the near future.

Meanwhile, the 17 existing comprehensive cancer centers as well as any others named in the future should be aware that they could lose their highly-prized official "comprehensive" designation if NCI and its advisers determine at renewal time that they haven't measured up.

The National Cancer Advisory Board's Subcommittee on Centers is tackling some of the problems encountered by review committees, NCAB and Director Frank Rauscher in the selection of centers for "identification" as comprehensive. The subcommittee also has started to put together some criteria for evaluating the impact of comprehensive centers on the cancer program in general and the quality of cancer treatment, education and prevention programs in their respective areas.

Could failure to meet these yet-to-be-determined standards or at least failure to show any progress toward meeting them result in a center being stripped of its comprehensive title? "It most certainly could," an NCI staff member told ***The Cancer Letter.***

Denman Hammond, director of the USC-Los Angeles County Comprehensive Cancer Center and an NCAB member, is chairman of the subcommittee.

The subcommittee and NCI staff were charged by NCAB to develop impact evaluation criteria, and they started by taking a look at the 10 "characteristics" originally established to help guide in the selection of comprehensive centers. Those guidelines decreed that a comprehensive center must:

* Have a stated purpose that includes carrying out of basic and clinical research, training and demonstration of advanced diagnostic and treatment methods relative to cancer.

* Have high quality interdisciplinary capability in the performance of diagnosis and treatment of malignant diseases.

* Have an environment of excellence in basic science which will assure the highest quality in basic research.

* Have or develop an organized cancer detection program.

* Maintain a statistical base for evaluation of the results of its program activities, including records with standardized disease classification to enable exchange of information between institutions.

* Provide leadership in developing community programs involving active participation by members of the medical profession practicing within the area served by the center.

* Have a strong research base (fundamental and applied) and related training programs, with an organizational structure which will provide for the coordination of these activities with other facets of the center program.

* Participate in the National Cancer Program by integrating its efforts with the activities of other centers in an integrated nationwide system for the prevention, diagnosis and treatment of cancer. For this purpose, the center must have sufficient autonomy to facilitate this function.

* Have an administrative structure that will assure maximum efficiency of operation and sound financial practices. The administration should include responsibility for program planning, monitoring and execution as well as preparation of the budget and control of expenditures. Administration and management would include staff appointment and space allocation, the intent being that such a center will have the authority to establish the necessary administrative and management procedures for carrying out its total responsibility as defined in the criteria.

* Have sufficient beds for cancer patients to give the program cohesion, identification and favorable facilities for the clinical research program to be carried out. In general, it is expected that existing inpatient facilities will be committed for this purpose.

John Yarbro, director of the centers program, said at a subcommittee meeting last week that "My attitude has changed toward those 10 characteristics" since earlier agreeing that they should be revised. "We didn't leave anything out. They really do represent the essential elements of a comprehensive center."

"The problem is that they are unsuitable for impact evaluation," Hammond replied. "They are suitable for determining whether or not a center was a comprehensive center."

Jonathan Rhoads, NCAB chairman, suggested several items evaluators could look for:

- A bibliography of publications by center staff, including cross references over a five-year period of key journals. "See whose work is being referred to."
- Feedback from the community on utilization of the center, statistics on number of patients, admissions, patient days, the trend. "That would let you know the extent to which a center is participating in the community's problem."
- Education programs conducted by the center.

post graduate and continuing, who is enrolled, how many.

• Scrapbook of newspaper clips. "Unfortunately, Congress will be more aware of a center's activities through the clipping services because congressmen have those services anyway. Centers are stimulated to spend money on public relations, some of it good education and some improper advertising."

NCAB member Mary Lasker suggested that the death rate from cancer in the area served by a comprehensive center would be the best way to determine whether or not a center was doing its job. Rhoads and Yarbro agreed that would be the ultimate test, but pointed out the lack of up to date statistical data. The latest death rate figures now generally available are for 1969.

Lasker said she had obtained recently some cancer death data from the National Center for Health Statistics for 1973. "If the National Cancer Institute were to request the figures for 1974, I'm sure they could get them," she said.

Hammond insisted on a point he made to NCAB last March, that the Board should consider creating new recognized categories of centers in addition to comprehensive and specialized. He feels that too many centers not qualified for either classification are driven to seeking comprehensive recognition because "there is nowhere else to go." New categories might be multidisciplinary cancer centers, coordinated cancer centers, community cancer centers, and consortiums of multiple institutions.

Such centers do exist, although there is no official NCI recognition of them as such.

Yarbro argued that all centers not yet labeled comprehensive could be considered specialized.

As for multidisciplinary centers, Yarbro said "the most common reason why a multidisciplinary center decides not to go comprehensive is that it can't or won't face up to selecting a leader and permitting him to run it. Naming a leader and putting him in charge is the most critical decision of all."

Hammond said he felt the major difference between comprehensive and multidisciplinary centers is that the former are committed to community outreach cancer control efforts, "meaningful participation in the community."

NCAB member Gerald Murphy said the subcommittee should consider "the real world. There is a fourth committee involved, called the Office of Management & Budget." His point was that OMB not only wants to limit the number of comprehensive centers to no more than 20 but also is holding back federal grants for new construction (*see following story*).

Hammond said the subcommittee should "look at the needs of the program and not at the keeper of the copper or whether or not the copper will be available."

"We should do what is important for the program, then get the money for it," Lasker said.

"I don't think we have to hold the line on the number of centers," Rhoads said. Since comprehensive centers receive little if any additional federal funds over and above what they are already getting through grants and contracts, identifying new ones does not increase the financial burden, Rhoads commented. "I think the addition of 25 more comprehensive centers is possible."

GOOD NEWS FOR UCLA, NYU – MONEY, COMPREHENSIVE STATUS COMING UP

UCLA and New York Univ. received some welcome news this week. The Office of Management & Budget finally agreed to release money to both institutions for construction of new cancer centers it had been withholding (illegally in the opinion of some).

And the National Cancer Advisory Board's Subcommittee on Centers gave tentative approval to the designation of UCLA and NYU centers as comprehensive cancer centers. That step depends on certain requirements being met by both institutions, but NCI staff and subcommittee members are confident that will be done.

NCI Director Frank Rauscher makes the final decision on comprehensive status, but he probably will follow NCAB's recommendations in these cases. The announcement probably won't be made at the June NCAB meeting, but is likely to come later in the summer.

OMB had been holding back funds approved by NCAB for NYU, UCLA and Salk Institute because all were for new construction. The White House has opposed federal financing of health facilities except for alterations, renovations and the filling of "shell space" in existing buildings.

NCI appealed that decision, and Benno Schmidt, chairman of the President's Cancer Panel, carried the argument directly to the President. NCI had the support of HEW Secretary Caspar Weinberger and Asst. Secretary for Health Theodore Cooper, and OMB backed down.

OMB Deputy Director Paul O'Neill made the point in his letter to NCI agreeing to release the money that this was not to be considered a precedent, and that future requests for new construction funds would be turned down.

O'Neill went on to say that HEW would order NCI not to accept any applications for new construction grants in fiscal 1976.

That order has not yet come down to NCI, and when it does, it probably will be ignored.

Jonathan Rhoads, NCAB chairman, said "The Board's responsibility is defined by law and not by that letter."

Asked by ***The Cancer Letter*** if that comment meant the Board would advise NCI to continue to accept applications for new construction, review them and determine which ones should be recom-

mended for funding, Rhoads answered, "Yes. The public has the right under the law to submit those applications, and we have the right to review them."

UCLA will receive $5.1 million, Salk $1.8 million, and NYU $704,000 from a total award of $3.35 million. Of that amount for NYU, a little more than $2 million was for alteration and renovation and was not in dispute. The amount for new construction was $1.3 million, but the NCI construction budget of $30 million was reached with the award of $704,000. The remainder will be available from 1976 fiscal year funds.

The cancer centers at Cleveland, Columbus and Hawaii, previously named as leading contenders for the next round of comprehensive identification (*The Cancer Letter*, May 9), apparently are not quite far enough along in their development to achieve that recognition this year.

NCI ADVISORY GROUP MEETINGS FOR JUNE

Cancer Control Working Group on Reimbursement—June 9, 9 a.m.—5 p.m., Bldg 31, Conference Room 4, all open.
Cancer Control Working Group on Prevention Activities—June 9, 9 a.m.—5 p.m., Landow Bldg C418, all open.
Cancer Control & Rehabilitation Advisory Committee—June 10, 9 a.m., Bldg 31 Conference Room 4, open 9 a.m.—1 p.m.
Breast Cancer Epidemiology Committee—June 13, 9 a.m., Bldg 31 Conference Room 9, all open.
Subcommittee on Centers—June 15, 8 p.m., Bldg 31 Conference Room 7, open 8—8:30 p.m.
National Cancer Advisory Board—June 16—18, 9 a.m. each day, Bldg 31 Conference Room 6. Open 9 a.m.—5 p.m. June 16; open 7:30 p.m.—8 p.m. June 16 (Bethesda Holiday Inn); open 2:30 p.m.—5 p.m. June 17; open 9 a.m.—adjournment June 18.
Cancer Control Supportive Services Review Committee—June 16, 8:30 a.m., Bldg 31 Conference Room 8, open 8:30—9 a.m.
Committee on Cancer Immunodiagnosis—June 16-17, Landow Bldg C418, open June 16 7 p.m.-7:30 p.m.; open June 17 8:30 a.m. adjournment.
Cancer Control Intervention Programs Review Committee—June 17, 8:30 a.m., Blair Bldg Conference Room 8, all open.
President's Cancer Panel—June 18, 2:30 p.m., Bldg 31 Conference Room 6, open 2:30—3:30 p.m. (Rescheduled from May 29.)
Committee on Cancer Immunobiology—June 26, 2 p.m., Bldg 10 Conference Room 4B14, open 2—2:30 p.m.

ABSTRACTS OF OUTSTANDING PAPERS FROM AACR MEETING

The program committee for the 66th annual meeting of the American Assn. for Cancer Research singled out 29 papers as among the outstanding ones presented at the meeting. The following abstracts are from that list; the others were published in the last two issues of The Cancer Letter.

DEVELOPMENT OF TERATOMAS FROM THE ECTODERM OF MOUSE EGG CYLINDERS — *Sanjivani Diwan and Leroy C. Stevens, The Jackson Laboratory*

Testicular teratocarcinomas are congenital tumors composed of various somatic tissues and foci of undifferentiated embryonal carcinoma cells. The undifferentiated cells of teratomas are the stem cells from which all the tissues originate. Teratomas originate from multipotential germ cells. Recently, Damjanov et al. (J.N.C.I. *46*:471, 1971) have shown that the undifferentiated cells of teratomas are histochemically and ultrastructurally similar to the ectomesodermal cells of 7-day mouse egg cylinders. In the present investigation, 6-day F_1 embryos of hybrids between strains 129/Sv-SICP and A/He mice consisting of primary ectoderm and endoderm were treated with 2.5% pancreatin for 5 minutes at 4°C. After washing with bovine serum albumen in Tyrode's solution and later with pure saline, the germ layers were separated with needles and grafted individually into the testes of isogenic males. The grafts were recovered after 30 days and examined histologically. Teratocarcinomas developed from grafts of ectoderm. In addition to undifferentiated embryonal carcinoma cells and embryoid bodies, the teratomas were composed of various tissues originating from the three definitive germ layers. The endodermal grafts did not develop at all. They were completely resorbed.

VIRUS-SPECIFIC INFORMATION IN THE DNA OF HUMAN CELLS INFECTED WITH NON-TRANSFORMING TYPE-C VIRUSES — *M. Nicolson, F. Hariri, M. Krempin, and R. McAllister, Univ. of Southern California School of Medicine; Children's Hospital of Los Angeles*

Cultured human cells productively infected with non-transforming mammalian type-C virus may contain in their cellular DNA sequences which specify complete information for progeny virus formation. This question was approached by examining the infectivity of isolated cellular DNA in cells permissive for the parental virus. Cellular DNA's from human rhabdomyosarcoma cells (RD) infected with the feline viruses RD-114 or FeLV, or with gibbon ape lymphosarcoma virus were inoculated into human or canine cell cultures. Within eight weeks, nearly all inoculated cultures gave rise to progeny virus identical in biochemical and antigenic properties to the parent virus. Alkaline denaturation did not alter the DNA infectivity, whereas digestion with deoxyribonuclease caused complete inactivation. The infectivity appeared to be associated with the chromosomal DNA. The minimum amount of DNA required to induce infection was approximately 50 ngm, giving a calculated efficiency of one infectious unit per 1.5×10^5 viral gene copies. RD-114 cellular DNA did not infect feline embryo fibroblasts.

BCG IMMUNOTHERAPY (IT) IN REMISSION MAINTENANCE OF ADULT ACUTE LEUKEMIA: A 3 YEAR STUDY — *J.U. Gutterman, E.M. Hersh, K.B. McCredie, V. Rodriguez, G.P. Bodey, and E.J. Freireich, M.D. Anderson*

To prolong complete remission (CR), IT with fresh liquid Pasteur BCG, 6×10^8 viable units given by

scarification, was evaluated in 3 consecutive studies. In Study I, BCG was given alone after late consolidation chemotherapy (CC) to 17 patients in CR 12-24 months. In Study 2, BCG+Oncovin+Arabinosyl Cytosine-Prednisone (OAP) maintenance was given to 23 patients after induction of CR by OAP. In Study 3, OAP+BCG was compared to OAP+BCG+unirradiated autologous tumor cells (TC) maintenance after induction of CR by Adriamycin+OAP+BCG in 37 patients.

In Study 1, 12/14 myeloblastic (AML) and 1/3 lymphoblastic (ALL) patients remain in CR, a median of 15+ months after CC. This was significantly longer than 12 months for 40 patients on chemotherapy alone, $p < .05$. In Study 2, 13/17 AML patients remain in CR after a median of 72+ weeks on OAP+BCG compared to 60 weeks for 21 AML patients on OAP alone, $p < .05$. In contrast, 6/6 ALL patients on OAP+BCG relapsed, not benefiting from IT. In Study 3, 8/9 OAP+BCG patients remain in CR at a median of 50+ weeks compared to 24/37 on OAP+BCG+TC at 40+ weeks. TC may be abrogating the effect of BCG. BCG IT was associated with increased delayed hypersensitivity to recall antigens. Chemoimmunotherapy with BCG applied early or late in CR may result in long term control of AML.

DETECTION OF INAPPARENT PRENEOPLASTIC-TRANSFORMED CELLS BY IN VIVO CULTIVATION OF DISSOCIATED MOUSE MAMMARY GLANDS — *Marilyn J. Miyamoto, Kenneth B. Deome and Rebecca C. Osborn, Cancer Research Laboratory and Dept. of Zoology, Univ. of California (Berkeley)*

The purpose of this study is the development of methods to detect subpopulations of preneoplastic-transformed cells within the mouse mammary gland. Mammary tissue from BALB/cfC3H (MTV+) virgin and parous female mice (3-15 mo. old) is dissociated to the single cell level by sequential enzyme incubations. 10^5 cells are injected into the gland-free fat pads of 3-wk.-old isologous virgin mice. In these fat pads normal cells produce mprhologically normal ductal outgrowths, whereas preneoplastic-transformed cells produce lobulo-alveolar (LA) outgrowths. The occurrence of tumors in primary and retransplanted outgrowths demonstrates their preneoplastic significance. Thus of 11 LA outgrowths tested, all reached the 50% tumor endpoint within 16 wk. of transplantation. In contrast, of 5 ductal outgrowths tested, none produced tumors within 6 mo. These data demonstrate that inapparent populations of preneoplastic-transformed cells can be detected in mammary glands of BALB/cfC3H virgin females as young as 3 mo. of age. Preneoplastic cell populations identifiable as hyperplastic alveolar nodules are not present at this early age, thus transformed cells with preneoplastic significance are not confined to hyperplastic alveolar nodules and are present in mammary glands well before nodules appear.

NON-RANDOM METHYLATION OF RAT LIVER CHROMATIN DNA BY DIMETHYLNITROSAMINE (DMN) IN VIVO — *R. Ramanathan, D.S.R. Sarma, S. Rajalakshmi and E. Farber, Fels Research Institute, Temple Univ. School of Medicine*

Very little is known about the intragenomal distribution of sites of interaction of chemical carcinogens. The present study was designed to investigate whether the alkylation of chromatin DNA by DMN and the subsequent in vivo removal of alkylated bases are random. Chromatin was fractionated by differential digestibility by nuclease. ^{3}H-DMN (0.5 mg/200 µCi/100 g bwt.) was injected into male rats 4 hrs. before killing. Digestion of the liver chromatin with pancreatic DNase I or micrococcal nuclease released 70-74% of the total methyl label in DNA as cold PCA soluble radioactivity compared to 54% of the total nucleotides released as cold PCA soluble absorbance at 260 nm. In contrast purified DNA methylated in vovo by DMN showed equal rates of release of radioactivity and of nucleotides. The nuclease digestion of hepatic chromatin from rats injected with ^{3}H-DMN and killed 3 days and 7 days thereafter yielded 62% and 57% respectively, of the methyl label under conditions in which 54% of the nucleotides were released. These results indicate i) an increased alkylation of regions of chromatin DNA that are readily accessible to DNase I and, ii) a preferential in vivo removal of the alkylated bases from these regions of chromatin DNA.

POTENTIATION OF ANALOGS OF ADENOSINE BY AN INHIBITOR OF ADENOSINE DEAMINASE — *William Plunkett and Seymour S. Cohen, Univ. of Colorado Medical Center*

Deamination of 9-β-*D*-arabinofuranosyladenine (araA), 3'-deoxyadenosine (cordyceptin) and 9-β-*D*-xylofuranosyladenine by adenosine deaminase (AD) results in the loss of their toxicity to mammalian cells. A potent inhibitor of AD, *erythro*-9-(2-hydroxy-3-3nonyl)adenine (ADI), inhibits deamination of these compounds by AD from calf intestine, L cells, and Ehrlich ascites carcinoma, and greatly increases the activity of these nucleoside analogs. Simultaneous administration of cytostatic concentrations of araA (0.10 mM) and nontoxic concentration of ADI (0.01 mM to L cells in suspension culture killed greater than 99.9% of the cells in 36 hr. AraA (50 mg/kg) plus ADI (3.1 mg/kg extended the mean survival of mice bearing Erhlich ascites carcinoma compared to araA (50 mg/kg) alone. A cytostatic concentration of cordycepin (0.10 mM) administered with ADI (0.01 mM), killed greater than 99.9% of cultured L cells in only 8 hr. During the latter incubation, both RNA and DNA synthesis were markedly inhibited and incorporation of uridine and thymidine was almost arrested after 30 min and 2 hr, respectively. These studies suggest that administration of a nontoxic inhibitor of adenosine deaminase with chemotherapeutically interesting adenine nucleosides may be useful in increasing the therapeutic efficacy of the latter.

CELLULAR LOCI OF ACTION OF BCG AND ITS COMPONENTS – *M.S. Mitchell, M.B. Mokyr and I. Kahane, Yale Univ. School of Medicine*

Experiments were performed in vitro to determine which lymphoid cells are activated by BCG and which components of BCG are responsible. C3H mouse spleen cells, splenic nonadherent cells (lymphocytes), splenic adherent cells (macrophages), or thymus cells were incubated with various amounts of BCG. DNA synthesis was the index of activation of lymphocytes. Production of lymphocyte-activating factor (LAF) by macrophages was also assayed. BCG strongly stimulated spleen cells, splenic lymphocytes and thymus cells, and caused a 20-fold increase in LAF. Reduction of macrophages from 10% to 1% increased the stimulatory effect of BCG on splenic lymphocytes. The response of thymic lymphocytes to BCG was abolished by complete removal of macrophages and was restored by adding them back (to 0.5%). Likewise, more LAF was elicited by BCG from macrophages when lymphocytes were also present. BCG thus potentiated the interaction between the 2 types of cell, with highly activated populations of each resulting. Cell wall-protein (CW-P) and methanol extract residue (MER) fractions were at least equivalent to BCG with spleen cells and splenic lymphocytes, but only MER stimulated thymus cells. Lipid fraction alone was largely ineffective. MER and CW-P increased LAF but less than did BCG. These tests may prove helpful in screening and probing the sites of action of immunological adjuvants.

ON THE ABSENCE OF SPECIFIC mRNA SPECIES IN HEPATOMA CELLS – *P. Feigelson, L.R. Murthy, A. Sippel and H.P. Morris, Institute of Cancer Research, Columbia Univ.*

Basal and hormonally induced levels of tryptophan oxygenase (T.O.) were present in host livers, but absent in hepatomas 7793, 5123C, 5123D. It was therefore of interest to explore whether the loss in the ability of hepatomas to synthesize certain hepatic proteins like T.O. and their inability to respond to hormonal control represents a transcriptional or translational deficiency. mRNA from the livers of hosts bearing any of the three tumor strains, but not from their corresponding hepatomas, direct, in a cell-free translational system, the synthesis of radioactive subunits of T.O. as identified by immunoprecipitation and SDS-polyacrylamide gel electrophoresis of the solubilized immunoprecipitate. The mRNA from host livers, but not their hepatomas, showed enhanced rates of synthesis of T.O. after hydrocortisone administration. Thus, all three Morris Hepatomas are devoid of detectable levels of functional mRNA for T.O. under basal and inducing conditions. 5123D hepatomas lack and livers of their male hosts c[illegible] the mRNA for *a*2u globulin, an urinary protein esized under androgenic control in the liver. In hepatomas, the genes for T.O. and *a*2u globulin have either been cytogenetically deleted or more probably are in a transcriptionally silent state preventing the synthesis of the corresponding mRNA and consequently that of the protein.

CONTRACT AWARDS

Title: Installation and implementation of a chemical information processing system
Contractor: Univ. of Pennsylvania, $132,761.

Title: Additional construction in support of the chemotherapy fermentation laboratory at the Frederick Cancer Research Center
Contractor: Litton Bionetics, $1,269,186.

Title: Optimizing electrophoretic separation of proteins with new hydrogels
Contractor: Polysciences Inc., Warrington, Pa., $79,517.

SOLE SOURCE NEGOTIATIONS

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

Title: Japan-Hawaii cancer study
Contractor: Kuakini Hospital & Home

Title: Organic synthesis of cold and tritiated polycyclic hydrocarbon derivatives
Contractor: Omni Research Inc., San German, P.I.

Title: Immunological assays for DNA and RNA viruses
Contractor: Litton Bionetics.

Title: Continue pharmacology study of anti-leukemic and other anti-cancer drugs
Contractor: Southern Research Institute.

Title: Study in the distribution, disposition, and metabolism of antineoplastic agents
Contractor: Instituto Di Ricerche Farmacologiche "Mario Negri," Milan, Italy.

Title: Processing of clinical patient research data
Contractor: Control Data Corp.

Title: Intrathecal toxicity of antineoplastic agents
Contractor: Hazleton Laboratories

Title: Studies of new anticancer agents
Contractor: Children's Hospital of Los Angeles

Title: Continue support for a cancer surveillance system
Contractor: Fred Hutchinson Cancer Research Center

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