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SOME OF COMMUNITY CONTRACTORS WON'T SURVIVE, SOME "SUPERB", SOME MAY GET MORE TIME, MONEY

The Community-Based Cancer Control Program, the ambitious effort by NCI to demonstrate that cooperation and coordination at the local level can pay off in reducing morbidity and mortality, apparently will survive its second major test.

The first test came last year when Benno Schmidt, chairman of the President's Cancer Panel, announced his opposition to the program just as the nine planning contracts were being awarded. Schmidt felt that if the program succeeds, it would stimulate demands from Congress for similar NCI-funded efforts in every community, drain away too much

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In Brief

SHUBIK, RHOADS, DIXON AFFILIATIONS WITH INDUSTRY LISTED BY HOUSE SUBCOMMITTEE

WHEN CONGRESSMAN David Obey (D.-Wisc.) participated in the House HEW Appropriations Subcommittee hearing on NCI's budget, he asked Director Frank Rauscher for a list of firms for which members of the National Cancer Advisory Board have worked as consultants. Obey specifically asked about Philippe Shubik of Eppley Institute; Obey's questioning of Rauscher appeared to be aimed at discrediting NCI's efforts in environmental carcinogenesis, and Shubik has been chairman of NCAB's subcommittee in that field. The hearing record is now available, and here are the firms for which Shubik has consulted—Royal Crown Cola, Abbott Laboratories, Miles Laboratories, Procter & Gamble, Colgate-Palmolive Co., Extract Manufacturers Assn. and Calorie Control Council. He has also served on General Foods' scientific advisory board. NCAB Chairman Jonathan Rhoads is a director of Penwall Corp., and Board Member Frank Dixon has been a consultant for Eli Lilly. Regulations require that advisory group members absent themselves from the room when matters come up relating to any organization with which they are affiliated. Rhoads told *The Cancer Letter* he has been a director of Penwall for many years and that no discussion or action involving any of the conglomerate's subsidiaries, which include pharmaceutical and chemical manufacturers, has ever come up when he was present. . . . **EDWARD BURGER**, who as senior policy analyst for the National Science Foundation has been an ex-oficio member of the National Cancer Advisory Board, has resigned from NSF to accept a position with the Cosmetic, Toiletry & Fragrance Assn. . . . **HAROLD RUSCH**, director of the Univ. of Wisconsin Comprehensive Cancer Center, has been one of those rumored as a potential NCI director if Rauscher leaves. Rusch has only three years left before he retires at Wisconsin, however, and doesn't want to leave before then. "That job (at NCI) should go to a younger man anyway," he told *The Cancer Letter*.

FIRST REVIEW OF COMMUNITY-BASED PLANNERS SCHEDULED FOR OCTOBER

(Continued from page 1)

research money and involve NCI in health care delivery. Schmidt also was sympathetic to the unsuccessful applicants who had involved other people in their communities in putting together proposals only to suffer the embarrassment of being turned down by NCI.

The program had the support of Director Frank Rauscher, and the National Cancer Advisory Board voted to proceed with it, persuading Schmidt to go along.

The second big test now will be to move the planning contractors into the implementation phase, "when we have to look beyond the honeymoon letters," said Ruby Isom, chief of the Community Resources Development Branch in the Div. of Cancer Control & Rehabilitation.

In addition to the nine planning contracts, two are in the process of being awarded for implementation without going through the planning phase—to the Univ. of New Mexico and the Michigan Cancer Foundation in Detroit. But it is in determining the fate of the nine with planning contracts where most of the action will be during the next few months.

Applications from the nine for implementation awards are due Aug. 1, but Isom told the Cancer Control & Rehabilitation Advisory Committee that those that need additional time probably will get it. First review by the Community Activities Review Committee is scheduled for October.

Isom said the nine probably will fall into one of three categories—those that show little or no promise of being able to achieve the program's goals and which will be dropped from the program; those who have made "superb efforts" and will be awarded implementation contracts immediately after review; and those who will need some additional planning, perhaps with some additional money.

"One year is not very long, and $100,000 (the planning awards) may not be enough," Isom said. "We've already got a lot for our money. Although matching was not required, many have put their own money into it."

DCCR has sent consultants to work with contractors on some of the problems they have encountered. "This contract is supposed to work, and it's our job to make it work," Isom said.

Gregory Lewis, acting associate director for community activities (Laurence Callan, who held that position when the program was initiated, left NCI to accept a position with the Univ. of New Mexico) said, "It is my impression that those who have come the farthest have a close working and planning association with their local American Cancer Society chapters."

The program evolved out of recommendations presented to NCAB in early 1974. The concept is based on the hypothesis that a comprehensive cancer control system at the community level will reduce the fragmentation and unnecessary duplication of cancer services and that this coordinated and comprehensive approach will, in turn, lead to greater impact upon cancer problems. It was recommended that demonstrations be carried out to indicate what can be accomplished through comprehensive community-wide cancer control activities.

The program contractors must have a defined plan for continuous surveillance evaluation and for reporting status and progress. Because they are designed as demonstrations, it is critical to their success that activities and results be well documented and subjected to detailed evaluation. In addition to determining whether the impact on cancer morbidity and mortality is significant, the demonstration must also produce lessons concerning the organization and maintenance of the cooperative arrangements which are the heart of the CBCCP concept.

In their implementation proposals, contractors are expected to specify the three to five cancer sites on which they intend to concentrate, and the projects by which they will achieve a greater degree of coordination in their communities. An essential ingredient of the community-based programs is the involvement of a broad range of interested groups. NCI hopes the proposals will demonstrate a high degree of community participation in the planning phase.

Another key feature of the proposals will be the data systems that the communities are establishing to aid in tracking, coordinating and evaluating their program's activities.

The nine institutions with planning contracts, principal investigators and key staff members, and targeted cancer sites are:

- Long Island Cancer Council, John Dibeler, Joe Welfield; colo-rectal, uterine, breast, prostate.
- Connecticut State Health Dept., Harold Schell, Diane McMillin; colo-rectal, breast, lung.
- Research Corp. of the Univ. of Hawaii, Lawrence Piette, Richard Lee, Fred Gilbert, Ruth Denney, colo-rectal, breast, cervical/uterine corpus, lung.
- Univ. of Pittsburhg, Bernard Fisher, L. Kuller, Ronald Tess; targeted sites to be determined.
- Los Angeles Community Cancer Control, Helene Brown; lung, breast, cervix.
- Univ. of Wisconsin System, Harold Rusch, William Donegan, Peter Sheldon; colo-rectal, breast, uterine/cervical, lung.
- Rhode Island Dept. of Health, Fiorindo Simeone, Louise Leone, Steve Sirota; lung, breast, colorectal, uterus-cervix.
- Fred Hutchinson Cancer Research Center, John Hartmann, Rick Zandstra, Bob Liffering; sites not yet selected.
- Genesee Region Community Cancer Control

Program, W. Bradford Patterson, Ellen Hawkes; breast, colo-rectal, lung.

RAUSCHER RESPONDS TO SAFFIOTTI'S CHARGES IN LETTER TO SEN. KENNEDY

Umberto Saffiotti ran "much of the Carcinogenesis Program as an academic department, often to the neglect of activities at the national level," NCI Director Frank Rauscher said in a letter to Sen. Edward Kennedy in response to a request from the Massachusetts Democrat for Rauscher's side of the story that led to Saffiotti's resignation as director of the program.

That neglect, Rauscher wrote, resulted in conflicts among Saffiotti's staff, "and many responsible scientists threatened to leave unless relocated."

Among Saffiotti's complaints was the contention that members of his staff had been moved elsewhere over his objections.

His most serious charge was that he had been denied adequate staff in the face of the big buildup in the Carcinogenesis Program, particularly in the bioassay portion that has increased the workload to the point that analysis and publication of test results have been delayed for months (***The Cancer Letter***, April 30, May 7).

Rauscher told Kennedy, "Our continuing advice to Dr. Saffiotti has been to reduce intramural research efforts and to utilize new positions authorized by Congress or available by attrition in the development of scientific management staff that could run the program utilizing outside expert advisors from all sources. We also urged him to formulate administratively self-sufficient projects capable of producing results with a minimum of supervision from NCI and with sufficient quality control prescriptions to ensure reliability. We also urged him to delegate decision making authority to his immediate staff in an effort to get the job done and allow them a feeling of personal contribution, thus fostering agility of action throughout the program."

Rauscher said that Saffiotti's resignation "is the culmination of a divergence of opinion concerning the philosophy of program management which became of great significance upon the passage of the National Cancer Act of 1971. The Act emphasizes the importance of formulating and initiating programs on a national scale, an initiative well founded in the well established efforts of the cancer chemotherapy and viral oncology programs.

"Dr. Saffiotti, on the other hand, belongs to the academic tradition, and he found it difficult to cope with the new demands of the National Cancer Program, and particularly with the need to provide a truly national forum where all interested voices could be heard, where decisions could be made after a broad base of opinion had been rendered, and where the function of the government would be not that of a contending advocate but rather that of policy making in the national interest.

"This is particularly true in the field of carcinogenesis, where decisions on the carcinogenicity of chemicals are often judgmental. Indeed, experience of the past has taught that data on carcinogenicity do not provide readily interpretable information in terms of human hazard. It is, therefore, essential that we rely upon the most outstanding experts in this national and internationally to assure the soundness of our conclusions.

"Dr. Saffiotti, however, felt and still feels that he had an independent role in decision making," Rauscher's letter continued. "This stemmed from his position and personal experience and made him reluctant to accept counsel from the contending parties. In order to justify his position, he viewed himself as being at the top of a pyramid of an intramural research program reflecting all expertise necessary in the carcinogenesis field. There are several constraints to this approach. Important among them are: first, the voices of different national interests who insisted that they be heard and that they be given the opportunity to provide their input in the decision making process; second, the policies of OMB toward new full-time positions at NCI; and third, the dramatically expanding budgets that the National Cancer Program obtained during the last few years."

Rauscher told Kennedy that "some dogmatic positions taken by Dr. Saffiotti caused considerable consternation among regulatory agencies, and program deficiencies came to the attention of the National Cancer Advisory Board. The director of the Div. of Cancer Cause & Prevention was forced to assume a central role in the coordination with other government agencies to fill the inadequacies of the Carcinogenesis Program in this area, and NCAB instituted an Environmental Carcinogenesis Subcommittee to oversee the entire operation. The subcommittee sought to clarify a major area of neglect, namely the definition of carcinogens, and recommended that the entire bioassay program be regrouped under the advice of a National Clearinghouse on Environmental Carcinogenesis, which would provide a truly national input in the selection of compounds to be tested, the design of experimental protocols, the interpretation of data, and the assessment of risk.

"Therefore, it is not surprising that Dr. Saffiotti felt unable to continue under circumstances so contrary to his personal philosophy of scientific management, and we appreciate the honesty of his decision to step down as associate director of the division. He will continue as chief of the Experimental Pathology Branch, where he will have every opportunity to make significant contributions as a scientist."

Rauscher then proceeded to answer specific questions asked by Kennedy regarding Saffiotti's various charges. Rauscher pointed out a number of factors

which he indicated made the staff shortage not quite so crucial as Saffiotti had contended. These included retaining a prime contractor to help manage the bioassay program; the staff has grown since 1968, now with five doctoral level professionals full time, and another seven part time where the majority of their time is with the program; 12 additional senior staff level individuals full time and another 10 tangentially involved providing support.

In reference to Saffiotti's complaint that there has been inadequate opportunity for participation by staff scientists in the development of NCI policy, my question is: What policy has been developed without such participation? Looking back over the three years alluded to in Dr. Saffiotti's memorandum, the following policy actions were taken:

"1. A new branch of environmental epidemiology was established under Dr. Joseph Fraumeni in Dr. Schneiderman's Field Studies & Statistics area of the Div. of Cancer Cause & Prevention. The individuals of this branch were responsible for the development of the national cancer atlas, or cancer maps as they are commonly referred to. The development of these maps has provided a basis for conducting epidemiologic studies with a high probability of identifying important causes of cancer in humans. We view this activity as being of high potential in terms of providing meaningful opportunities for the prevention of cancer.

"While this organizational change was outside of his area, the development was discussed with him and Dr. Schneiderman, and Dr. Saffiotti was always supportive of providing additional emphasis to this activity.

"2. The second major policy decision in the environmental carcinogenesis area concerned the request that NCAB establish a Subcommittee on Environmental Carcinogenesis to advise the institute on programs in this area and to get an advisory view as to their assessment of the opportunities for prevention. This subcommittee has been one of the most hardworking advisory groups we have had. They have advised on programs, program priorities, and policy. Verbatim transcripts of several of their meetings are available should you like to have them.

"Dr. Saffiotti and Dr. Schneiderman, and on occasion members of Dr. Saffiotti's staff, have participated thoroughly in the deliberations of the subcommittee, as the record will show. Indeed, Dr. Saffiotti served as a staff consultant to the institute's highest level advisory group on environmental carcinogenesis to ensure necessary interaction between program operations and advice rendered to NCAB and to me. The record will also show that I attended several of their meetings and have followed with keen interest their deliberations and recommendations and have discussed the progress of their proceedings on many occasions with the division director, his immediate staff, and with Dr. Saffiotti. After the subcommittee chairman's presentation of Nov. 18, 1975, I met on Jan. 30, 1976, with Dr. Saffiotti, his division director, and members of my immediate staff and discussed in depth the recommendations of the subcommittee.

"3. The most recent policy decision made in environmental carcinogenesis has been to establish a Clearinghouse on Environmental Carcinogens. Briefly, the Clearinghouse, which will soon be functional, will have four components called working groups which will meet in announced public meetings to conduct the following functions:

"a) A final selection of chemicals for bioassay.

"b) Design of appropriate experiments for assessing carcinogenic hazard.

"c) The review and evaluation of carcinogenicity data.

"d) The assessment of carcinogenic risk.

"The need for public meetings of such an advisory body has been apparent to me for some time now. I have been particularly concerned with the delicate and sensitive nature of chemical selection and that it not be arbitrary or capricious but based on defensible and well defined criteria. Early public release of information on carcinogenicity data in a public forum is, I believe, essential.

"We have learned that the data on carcinogenicity are often neither 'black' nor 'white' but all too frequently 'gray'. Our experiences with cyclamate and the public meetings held by us on the subject of its carcinogenicity and the experiences of the new FDA Toxicology Advisory Committee and its review of FD&C Red No. 2 have amply demonstrated the need for public discussion of the 'gray' chemicals. When scientists cannot make a clear decision on matters of this sort, then at least their deliberations, including the uncertainties identified in those deliberations, must be a matter of public record. Granted, the process is new and unproven and will require patience, forebearance, and courage on all our parts. But I believe the objectives are worthy of the risks.

"Dr. Saffiotti did not agree, and that is his prerogative. It is inaccurate to suggest that the matter was not discussed fully at my level and at the division level with Dr. Saffiotti. I can assure you that that was the case and that, when the review and evaluation activity was conceived as a separate committee, Dr. Saffiotti recommended that Dr. James Sontag of his staff be executive secretary. He also proposed several individuals for membership, which were accepted as well. I am pleased to say that while Dr. Saffiotti was not supportive of the effort he nevertheless continued in the discussions and made useful recommendations.

"We view the Clearinghouse as a newly developed national resource to be used by those federal regulatory agencies that have over the years requested assistance from us for those functions for which the Clearinghouse was established."

Saffiotti had also complained about some com-

ponents of his program, with resulting "fragmentation" of program direction.

"The Smoking & Health Program was the first activity removed from Dr. Saffiotti's area," Rauscher wrote. "That action was taken in 1973 and was based on his philosophy that NCI should not attempt to develop a less hazardous cigarette since it would ultimately profit special interests in the private sector. While he was never faulted for his philosophy, a policy decision was made—a pragmatic one— resulting in the development of cigarettes of far lower tar and nicotine levels than those previously available. We believe that this development will significantly contribute to the reduction of smoking-associated cancers in our population.

"Another component removed from the Carcinogenesis Program was a small group of three people headed by Dr. Herman Kraybill, a man with 30 years of research experience and over 100 publications in carcinogenesis and toxicology. Dr. Kraybill, who has twice been employed by NCI, was hired for the second time in 1973 as the scientific coordinator for environmental carcinogenesis. Dr. Kraybill, with support and encouragement from Dr. Saffiotti and the division director and my staff, established the Interagency Collaborative Group on Environmental Carcinogenesis. This is an information information group involving more than 20 agencies of the federal government. It has been the key to keeping other federal agencies, particularly the regulatory agencies, informed of program plans and developments on environmental carcinogens. There were several reasons for elevating Dr. Kraybill's activities as scientific coordinator to the division level. The most fundamental was to provide the activity with adequate visibility and to engender greater objectivity by removing it from program advocacy.

"I have worked very closely with Dr. Saffiotti, as his immediate supervisor when I was scientific director of etiology, and as director of NCI. I am keenly aware of his management practices and philosophy and I, along with my staff, have tried to assist him in his administrative actions. At his initiative, most of the Biology Branch, some 20 individuals, was transferred this year from the Div. of Cancer Cause & Prevention to the Div. of Cancer Biology & Diagnosis. This transfer was agreed to by the chief of that branch, Dr. Herbert Rapp, as being the best solution to a long-time problem. Dr. Rapp contended that his branch, which dealt primarily with immunology of carcinogenesis, was under-supported. In any case, the loss of positions, as shown on page 12 of Dr. Saffiotti's memorandum, was due to his initiative to transfer these positions to another division.

"In other instances, the loss of personnel, particularly from bioassay, was initiated by the affected individuals who claimed they were underutilized and that proper use was not being made of their time, talents, or abilities. These individuals had management responsibilities for critical aspects of the overall program, i.e., management of the bioassay segment, direction of the animal resources in carcinogenesis, and management of the in vitro program. Each of the concerned individuals indicated that unless other tasks could be found for them within the division they would definitely leave the program area. In the case of the manager of the in vitro program, who has a doctorate and considerable experience in the field, a highly successful effort was begun to evaluate the utility of in vitro tests as prescreens for carcinogenicity. The program has an advisory committee for planning and evaluation composed of experts of unexcelled capabilities with in vitro systems. The manager of the bioassay program segment, who had served as the executive secretary of the temporary committee to review and evaluate carcinogenicity data on cyclamate, was proposed by Dr. Saffiotti as executive secretary to the Committee to Review and Evaluate Carcinogenicity Data, one of the components to the Clearinghouse. This individual, while expressing gratitude for what he had leanred in the course of serving as program manager, indicated his intent to leave the program area and the division unless he could be relocated. In support of Dr. Saffiotti's comments, this individual was too valuable to lose while a critical job appropriate to his skills existed. We are pleased he accepted the position as executive secretary of the Clearinghouse and has agreed to train a new individual for his former position.

"The veterinarian in charge of the animal resources was adamant that he could perform his previous functions and still carry out his new duties under Dr. Kraybill, scientific coordinator for environmental cancer.

"In my view, the decisions resulting in the removal of individuals and components from Dr. Saffiotti's program area have resulted or will result in greater effectiveness and efficiency. It is my belief that the individual policy decision made and the administrative actions taken based on that policy are fully defensible in terms of program needs. The recent administrative actions are intended to deal with the totality of problems that have affected morale and slowed progress," Rauscher concluded.

RAUSCHER DECISION DELAYED TO JUNE 30 WHILE WAITING FOR ACTION BY CONGRESS

Frank Rauscher has dealyed to June 30 his deadline for determining if he will remain as NCI director. If Congress has approved a pay increase by then, or even if it has shown some solid indication that such a bill will be acted upon, he would remain for a minimum of six more months to a year, "and indefinitely if the increase is enough," he told ***The Cancer Letter.***

By press time this week, the only bill introduced was one by Rep. Paul Rogers, chairman of the House

Health Subcommittee, authorizing the HEW secretary to award up to 25 annual bonuses of a maximum of $15,000 each.

That wouldn't be enough to keep Rauscher around indefinitely, but it might keep him for a year.

A bill has been drafted which would raise the salaries of the NCI director, NIH director and director of the Heart & Lung Institute to $65,000, but Rogers for some reason has been reluctant to introduce it. The Civil Service Commission, the Office of Management & Budget (which means the White House), and the chairman of the House Post Office & Civil Service Committee all have said they would not oppose it.

SOLE SOURCE NEGOTIATIONS

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

Title: Coordinating committee for the radiologic physics centers
Contractor: American Assn. of Physicists in Medicine, Chevy Chase, Md.

Title: Studies on the role of hormonal factors in the induction of mammary tumors in MBMV infected animals
Contractor: Mason Research Institute, Worcester, Mass.

Title: Curatorial preservation and development of reference-grade tumor viruses
Contractor: American Type Culture Collection, Rockville, Md.

CONTRACT AWARDS

Title: Joint U.S.—U.S.S.R. symposiums on membrane biology and chemistry and biochemistry of proteins
Contractor: National Academy of Sciences, $92,000.

Title: Health education program for the Tyler asbestos workers and their families
Contractor: Texas Chest Foundation/East Texas Chest Hospital, $231,049.

Title: Latin American Cancer Research Information Project
Contractor: Pan American Health Organization, $267,836.

Title: Breast cancer detection demonstration project
Contractor: Samuel Merritt Hospital, Oakland, $304,147.

Title: Prototype clinical chemotherapy program in cancer control
Contractor: Children's Hospital, Cincinnati, $55,983.

Title: Studies of natural occurrence of RNA tumor viruses
Contractor: The Jackson Laboratory, $470,000.

Title: Evaluation of BCG immunotherapy of patients without detectable disease after removal of tumor containing lymph nodes
Contractor: Univ. of California (UCLA), $87,000.

Title: Immune status and effects of immunostimulants in patients receiving localized radiation therapy
Contractor: Univ. of California (San Francisco), $84,139.

Title: Modified tumor cell membranes as immunotherapeutic agents
Contractor: Stanford Research Institute, $62,710.

Title: Incorporation of an additional alteration/renovation project as necessary for the performance of the cancer research program at Frederick Cancer Research Center
Contractor: Litton Bionetics, $611,550.

Title: Mechanisms by which tumors avoid destruction
Contractor: Weizmann Institute of Science, Rehovot, Israel, $120,000

Title: Studies of alteration in translation of genetic messages induced by viruses and carcinogenesis
Contractor: Weizmann Institute of Science, Rehovot, Israel, $144,900.

Title: Human blood cells isolation and characterization
Contractor: Sidney Farber Cancer Center, $77,057.

Title: Specificity of antigen-binding receptors on T-cells
Contractor: Jefferson Medical College of Thomas Jefferson Univ., Philadelphia, $54,000.

Title: Immunodiagnosis of carcinoma of the gastrointestinal tract
Contractor: Scripps Clinic & Research Foundation, $107,669.

Title: Immune-related cells in tumor masses
Contractor: Pennsulvania State Univ., $39,767.

Title: Study of immunobiologic responses of the cat to feline oncornaviruses
Contractor: Ohio State Univ., $220,823.

Title: Search for DNA virus sequences in genetic material
Contractor: St. Louis Univ., $652,842.

Title: Search for RNA virus-specific genetic material
Contractor: St. Louis Univ., $261,559.

Title: Oncogenic studies of RNA tumor viruses in experimental systems and tumor cells
Contractor: UCLA, $125,000.

Title: Implementation of cervical cancer screening program
Contractor: Wyoming State Dept. of Health, $166,659.

Title: Detection of antibodies against human tumor cells
Contractor: Mt. Sinai School of Medicine, $90,465.

Title: Improvement of assays for cell-mediated immunity
Contractor: Johns Hopkins Univ., $70,126.

Title: Improvement of Assays for cell-mediated immunity
Contractor: Sidney Farber Cancer Center, $19,968.

ABSTRACTS OF OUTSTANDING PAPERS PRESENTED AT ANNUAL AACR MEETING

The program committee for the 67th annual meeting of the American Assn. for Cancer Research selected 44 papers as among the outstanding ones presented at the meeting. The following abstracts are from that list, chosen from sessions on biology and genetics, cell kinetics, chemical carcinogenesis, viral immunology, immunology, biochemistry and experimental chemotherapy. Others appeared in the previous three issues of ***The Cancer Letter*** and the rest will be published next week.

COMPARATIVE ANALYSIS OF ^{35}S-LABELED PROTEINS PRODUCED IN THE WHEAT GERM TRANSLATIONAL SYSTEM BY LIVER AND NOVIKOFF HEPATOMA mRNA BY AUTORADIOGRAPHY AFTER 2-D GEL ELECTROPHORESIS – B.C. Wu, M. Rao, K. Kumar and H. Busch, Baylor

Comparisons were made of the proteins synthesized on liver and Novikoff hepatoma mRNA in vitro by the wheat germ cell-free system with ^{35}S-methionine as a tracer. 2-D polyacrylamide gel electrophoresis on cylinders of 10% polyacrylamide, 0.9 M acetic acid, 4.5 M urea followed by 12% polyacrylamide, 0.1% SDS slabs separated approximately 40-50 highly labeled spots. Correspondence of spots labeled in vivo and in vitro with ^{35}S-methionine was shown for several highly labeled proteins. In the 2-D gel pattern of the tumor products, some of the most highly labeled proteins comigrated with proteins of the 40S and 60S ribosomal subunits but in the normal liver most of the ^{35}S distributed into 5 major protein spots. On the basis of the percent total cpm in individual spots, several spots corresponding to the 40S ribosomal subunit proteins were labeled 3-11 times more in the tumor than in the liver, indicating that the content of poly A+ mRNA for ribosomal proteins is 3-11 times greater in Novikoff hepatoma cells than in liver cells.

In 10-hour regenerating liver there is also an increased concentration of ribosomal protein mRNA. However, both normal and regenerating liver mRNA translate common proteins that are absent from the products of tumor mRNA.

CONTROL OF DNA HELIX OPENINGS DURING IN VITRO NEOPLASTIC CELL MATURATION – John Frenster, Sharon Landrum, Marilyn Masek, and Lennard Wilson, Stanford Univ.

Localized DNA helix openings are needed for the initiation of both the selective gene transcription and the asynchronous gene replication characteristic of proliferating mammalian cells (Nature 208, 894 (1965). Both carcinogenic chemicals (Nature 257, 151 (1975) and oncogenic viral DNAs (Virology 65, 524 (1975) prefer to bind to such single-stranded portions of the host genome (Biophys. J. 15, 137a (1975). Applying a quantitative electron microscopic probe technique (Nature 248, 334 (1974) for detecting DNA helix openings within individual cells to the lymph nodes taken from untreated patients with Hodgkin's Disease at initial staging of their disease (Natl. Cancer Inst. Monogr. 36, 239 (1973), it was found that neoplastic cells early in the maturation sequence (mono- and binuclear Reed Sternberg cells) display a significantly ($p<0.01$) greater number and size of DNA helix openings than do neoplastic cells later in the maturation sequence (multi-nuclear Reed Sternberg cells), correlating with the reduced proliferative activity of these more mature cells.

DNA helix openings are confined to the euchromatin portion of the cell nucleus, correlating with the localization with euchromatin of derepressor RNA and other DNA ligands (Nature 206, 680 (1965) capable of inducing the formation of DNA helix openings and initiating gene transcription (Nature 208, 1093 (1965).

PROGNOSTIC VALUE OF ANTIBODIES TO MEMBRANE ANTIGENS OF MELANOMA CELLS – K. Irie, R.F. Irie, D.L. Morton, UCLA

This study was designed to determine the correlation between humoral response to membrane antigens of tumor cells and prognosis for stage II melanoma patients. IgG and IgM antibodies were measured by Indirect Membrane Immunofluorescence using a cultured allogeneic melanoma cell line (M10) as target. Of 45 postoperative patients tested, 15 were treated by vaccination with allogeneic melanoma cells, 15 were BCG treated, and 15 had no additional treatment. Nontumor associated reactions were minimized by growing target melanoma cells in gamma globulin-depleted human sera to eliminate natural antibodies reaction to HM antigen, a product of animal sera used in medium and by pre-absorbing patients' sera with cultured lymphoid cells derived from the donor of the target melanoma cells to remove isoantibodies such as anti-HLA. Of 23 samples that displayed increase of either IgG or IgM antibodies, 19 (82%) remained free of disease at 1 year whereas of 22 samples that had no antibody increase, only 6 (27%) remained free of disease. Of 11 with IgM increase, 11 (100%) remained free of disease at 1 year.

These results suggest that humoral response to tumor antigen may be an important indicator of prognosis in cancer patients.

GENETIC RESISTANCE TO MARROW TRANSPLANTATION AS A LEUKEMIA DEFENSE MECHANISM – John Trentin, Michael Gallagher and Eva Lotzova, Baylor

Genetic resistance to marrow transplantation is a phenomenon seen in certain F_1 hybrid and inbred strains of mice, which even after lethal irradiation are able to reject large numbers of parental, allogeneic, or xenogeneic bone marrow cells (Biomedicine 18, 86, 1973) Genetic resistance seems to be mediated by radioresistant cells having some of the properties of macrophages (Biomedicine 22, in press, 1975). The function of this resistance mechanism, in the normal biology of the mouse, is unknown.

(C57xAKR)F_1 hybrid mice show genetic resistance to C57 parental bone marrow cells, but not to AKR parental bone marrow cells. (C3HxAKR)F_1 hybrids show no genetic resistance to bone marrow transplantation from either parental strain.

However, transplantation of AKR lymphoma cells into lethally irradiated "resistant" (C57xAKR)F_1 and "non-resistant" (C3HxAKR) F_1 hybrids produced lymphomatous spleen colonies in "non-resistant" hybrids but not in "resistant" hybrids. Thus "resistant" (C57xAKR)F_1 hybrids can recognize and reject AKR lymphoma cells, but not normal AKR bone marrow cells.

A normal biological role of lymphoma surveillance is postulated for genetic resistance to marrow transplantation, directed at antigens which, like TL, are expressed on normal hemopoietic cells of some strains, but only on leukemic cells of other strains.

T CELL RESPONSE IN H-2 CONGENIC MICE TO FRIEND VIRUS-INDUCED TUMOR CELL LINES – Kenneth Blank, Herbert Freedman and Frank Lilly, Albert Einstein College of Medicine

Mice immunized with cells from a syngeneic Friend virus (FV)-induced cultured tumor cell line produced T killer cells which did not kill FV-induced tumor cells derived from mice differing genetically only at the H-2 region.

Congenic BALB.B ($H\text{-}2^b$) and BALB.K ($H\text{-}2^k$) mice and (BALB.Bx BALB.K)F_1 mice were immunized with histocompatible tumor cells from cell lines (HFL/b from BALB.B and HFL/k from BALB.K) induced in vivo by FV. Tumor cells from these lines express the FMR cell surface antigen and the gp70 virus envelope antigens. In an in vitro lymphocyte mediated cytotoxicity (LMC) assay, peritoneal exudate cells (PEC) from BALB.K and (BALB.B x BALB.K) F_1 mice immunized with HFL/k killed both HFL/k and HFL/bk [induced in (BALB.B x BALB.K)F_1 mice] but not HFL/b whereas PEC from BALB.B and (BALB.B and (BALB.B x BALB.K)F_1 mice immunized with HFL/b killed both HFL/b and HFL/bk but not HFL/k. Pretreatment of the PEC with anti-thy 1 and C' abolished killing in the LMC assay.

Thus, the tumor cells used for immunization and as target cells must share a common H-2 haplotype for T cell killing to occur. It

appears that T lymphocytes do not respond to virus-induced antigens per se since HFL/b, HFL/k and HFL/bk all express the same viral antigens but perhaps to some virus-induced alteration in the H-2 molecule.

HUMORAL IMMUNE FACTORS IN RESISTANCE TO SOLID TUMOR GROWTH – Jan Vaage and Sudha Agarwal, Pondville Hospital, Walpole, Mass.

This study was done to investigate the collaborative roles between humoral immune factors and normal lymphoid cells to suppress the in vivo growth of syngeneic fibrosarcoma cells. The tests used several passive transfers of antiserum with or without the additional transfer of normal lymphnode cells to irradiated recipients. Protection by transferred immune serum was effective if the radiation-suppressed recipients were also given normal lymphnode cells, and was most clearly expressed when the mice were challenged intravenously.

The results indicate that humoral immune resistance factors are effective in controlling the in vivo growth of a syngeneic, solid tumor, and suggest that antitumor antibodies may be particularly important in preventing vascular dissemination of tumor growth.

CYCLIC NUCLEOTIDES AND INTRACELLULAR MEMBRANES IN NORMAL AND NEOPLASTIC LIVER – Henry Pitot, Rameshwar Sharma, and Charles McLaughlin, Univ. of Wisconsin

Studies from this laboratory have demonstrated that the smooth and rough endoplasmic reticulum of normal and neoplastic rat liver possess one and two specific binding sites for cyclic AMP respectively. The constants for cyclic AMP binding to the intracellular membranes of the Morris hepatomas 5123C and 7777 exhibit two binding sites, the binding constant of one comparable to that of cyclic AMP for normal liver membranes whereas the value of the second intrinsic association constant differs by up to 40-fold from that of liver. Reticular membranes of these hepatomas also exhibit a binding site for cyclic GMP which is absent from the intravellular membranes of liver. The intracellular membranes of liver and the Morris 5123C hepatoma also possess endogenous cyclic nucleotide independent protein kinase activity which phosphorylates five groups of proteins in liver but only three of the 5 protein bands in the hepatoma.

These findings demonstrate distinct differences in the cyclic nucleotide binding proteins of liver and 2 hepatomas as well as an inability of the cyclic nucleotide independent protein kinase of hepatoma intracellular membranes to phosphorylate protein species that are found in membranes of both liver and the 5123C hepatoma.

HYPERSIALYLATION: A MECHANISM FOR ACCUMULATION OF ACID GLYCOPROTEINS IN MALIGNANCY – Samuel Waxman, Carol Schreiber and Lawrence Helson, Mount Sinai, and Memorial Sloan-Kettering

A serum B_{12} binding protein with increased sialic acid content ($HB_{12}BP$) causing elevations (500 times normal) of serum B_{12} and unsaturated B_{12} binding capacity ($UB_{12}BC$) has been found in hepatoma. We now report another patient with hepatoma with initial near normal $UB_{12}BC$ which increased 400 fold as the disease progressed and then fell 50% with response to chemotherapy. A perfusate of the liver had 5 times more B_{12} binding protein than the serum and was immunologically the same as serum $HB_{12}BP$ isolated from the previous cases. The perfusate and the serum $HB_{12}BP$ had two isoelectric components (pI 2.8 and 3.2). A cell line derived from hepatoma in another patient with normal $UB_{12}BC$ produced B_{12} binding protein which contained two isoelectric components (a minor pI 2.9 and a major 3.9). Cell lines derived from normal liver and the Chang hepatoma produced B_{12} binding proteins similar to that in normal serum (2/3 Transcobalamin II). The hepatoma sera and perfusate had an increase in sialyltransferase.

These data suggest that some hepatomas produce increased hypersialylated $B_{12}BP$ (pI 2.8) which is cleared slowly and accumulates in the serum as $HB_{12}BP$. This may happen to other unsaturated but not saturated sialoglycoproteins in malignancies where elevated sialyltransferase has been reported.

DIACRIDINES: BIFUNCTIONAL INTERCALATORS AS INHIBITORS OF NUCLEIC ACID SYNTHESIS – R.M. Fico, Y.H. Shaw, and E.S. Canellakis, Yale Univ.

A large series of diacridines connected through the 9-amino position by a chain of varying length and composition has been synthesized for use as chemotherapeutic agents. The basic rationale has been that such molecules should act as more effective inhibitors than the parent compound because DNA could only be free if both acridine rings were to deintercalate simultaneously. In conformance with these expectations the T_m of DNA in 0.1 SSC is raised by 45° by octyldiamine-9,9' diacridine (C8) but only by 17° by 9-amino acridine (9-AA). In 0.3 SSC 9-AA does not affect the T_m of DNA while C8 still gives a 12° increase.

The diacridines are very effective inhibitors of a)45 S RNA synthesis b) the processing of 45 S RNA c) the methylation of t-RNA and d) the growth of P-388 cells in mice. The diacridines are also effective inhibitors of the in vitro synthesis of RNA by DNA dependent RNA polymerases of Azotobacter Vinellandii and T7 Escherichia coli. In addition, C8 is concentrated at least 20 times more effectively by a variety of cells than 9-AA and is preferentially accumulated in the nucleus.

THE PHARMACOKINETICS AND RADIATION HAZARD OF TRITIATED THYMIDINE IN MAN – Stephen Straus and Marc Straus, NCI and Boston Univ.

Doses of tritiated thymidine (^{3}HTdR) of 5-60 mCi are generally required for adequate in vivo cell kinetic (CK) analyses of tumor in man. One deterrent to these studies is lack of adequate radiation dosimetry data. As part of tumor CK studies, plasma and extreta were sampled serially for up to 79 days after IV injection of ^{3}HTdR (0.2 mCi/kg) to 9 consenting cancer patients. Within minutes a decline in initial plasma (P) tritium activity (3H) was associated with the appearance of 3H in urine (U), saliva and expired air. In accord with the turnover of body water (BW), mean P 3H decayed after day 1 with a half-life of 10.8 days. U 3H was >100 times P 3H within 1 hr but approached and paralleled P 3H after day 2. During day 1 34% of injected 3H appeared in U. In 12 days there were 54% U and 11% insensible losses. Total excretion was 87.5% with 12.5% presumably remaining in cell DNA. Balance studies revealed that 7% of the dose may have been initially incorporated into DNA but later metabolized and excreted. The radiation dose to BW was 0.7 rads. Autoradiography and CK analysis of tumor biopsies indicated a maximum dose to cell nuclei of 20.5 rads. These levels are not known to be associated with measurable biological effects. Determination of 3H in personnel and room air indicated the absence of a hazardous environment.

These data support the use of this dose of ^{3}HTdR in this experimental setting.

HEPATIC MICROSOMAL GLUCURONIDATION OF N-HYDROXY ARYLAMINES – F.F. Kadlubar, J.A. Miller and E.C. Miller, Univ. of Wisconsin

In the presence of UDPGA and hepatic microsomes from rat, dog, or human [^{3}H] N-hydroxy-2-naphthylamine (N-HO-2-NA) was rapidly glucoronidated (20-30 nmoles/min/mg protein). Treatment of the product with β-glucuronidase released 98% as the parent N-hydroxy amine. Conversion to 2-aminonaphthol did not occur during conjugation or after enzymatic hydrolysis. [^{3}H] N-Hydroxy-1-naphthylamine (N-HO-1-AN and [^{3}H] N-hydroxy-4-aminobiphenyl (N-HO-ABP) were similarly metabolized (N-HO-1-AN>N-HO-2-AN>N-HO-ABP) and and treatment with β-glucuronidase released 80-90% as ether-soluble derivatives. Each glucuronide was relatively unreactive at pH 7. At pH 5 reactive derivatives were formed that bound covalently to DNA, and binding was increased in the presence of β-glucuronidase. At pH 5, N-HO-1-AN, N-HO-2-AN, and N-HO-ABP were themselves highly reactive and formed adducts with nucleic acids (0.1-1.0 molecules bound/100 nucleotides).

These data support the concept (see Radomski et al, Cancer Res. 33, 1284) that arylamine bladder carcinogens are N-oxidized and conjugated in the liver, transported to the bladder, and released as N-hydroxy amines by urinary pH (4.5-7.0) or by urinary β-glucuronidase or both. The conversion of N-hydroxy arylamines to highly reactive derivatives at urinary pH must be considered in arylamine carcinogenesis in the bladder epithelium.

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