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NCAB TO STUDY RECOMMENDATIONS ON COOPERATIVE GROUPS, COORDINATION OF NCI TREATMENT PROGRAMS

The National Cancer Advisory Board Monday accepted Giulio D'Angio's report on the Potomac Conference but withheld action on the recommendations of the conference on the future of the Cooperative Clinical Cancer Research Program.

Board members expressed no opposition to the recommendations, but agreed with Benno Schmidt's comment that "some of these are very deep and we don't want to accept them casually." The Board approved

(Continued to page 2)

In Brief

BIOASSAY PRIME CONTRACT RENEWED FOR FOUR YEARS, $34.2 MILLION; CANELLOS QUITS AS CLINICAL DIRECTOR

TRACOR-JITCO'S prime contract with NCI for managing the carcinogenesis bioassay program has been renewed for four years, at a total of $34.2 million. At an annual average of a little more than $8.5 million, that is a substantial increase over the $6.6 million handled by Tracor-JITCO during the first term of the prime contract, which covered 15 months. The renewal contract will be signed in a ceremony June 27 at the company's Rockville, Md. headquarters. . . . **PERSONNEL CHANGES:** George Canellos, NCI clinical director, will leave July 1 to accept a position at the Sidney Farber Comprehensive Cancer Center. Sidney Cutler, associate chief of the Biometry Branch and chief of the SEER program, is retiring. W. Emmett Barkley has been appointed director of the NCI Office of Research Safety. . . . **HEW'S CIVIL RIGHTS** office has warned 29 colleges and universities that their federal contracts, including some with NCI, could be held up or terminated if they don't develop acceptable affirmative action programs. NCI executives say HEW has not yet told them anything about it. . . . **FIRST MEETING** of the temporary Committee for the Review of Data on Carcinogenicity of Cyclamate will be July 10-11 at NCI, Bldg 31 Conference Room 10. The committee is charged with determining what further studies, if any, are needed to permit FDA to determine if cyclamate should be permitted back on the market. Persons wishing to submit relevant data may contact James Sontag, executive secretary of the committee, at NCI, Landow Bldg, Room A-306, Bethesda 20014, or phone him at 301-496-5471. The meeting is open both days, 9-5. . . . **NCI EXECUTIVES** awarded meritorious service medals by NIH this month included Richard Tjalma, Vincent DeVita, Diane Fink, Robert Gallo, Guy Newell, Samuel Price, Richard Sherbert and Maxine Singer. . . . **PUBLICATIONS** recently released by NCI include: "Cancer Rates & Risks, 2nd Edition," (HEW Publication NIH 75-691); "Recent Trends in Survival of Cancer Patients," (HEW Publication 75-767); and "National Cancer Program 1975 Fact Book," (HEW Publication NIH 75-512. Write to Office of Cancer Communications, NCI.

RHOADS SUGGESTS SMALL ADVISORY GROUP TO HELP RAUSCHER ON REORGANIZATION

(Continued from page 1)

Schmidt's motion to table the recommendations for future consideration.

In his report, D'Angio presented the recommendations hammered out at the Potomac Conference (*The Cancer Letter,* May 30 and June 6), but some were revised to accommodate a broader consensus of conference participants than originally stated, and others were consolidated. The revised recommendations were:

1. Independent investigator-initiated research, evaluated by peer review and supported by grants, should be continued.

2. The NCI director should conduct a thorough review of the organization and activities of all divisions and branches of NCI concerned with clinical investigation. The purpose of the review would be to identify areas of duplication, competition and overlap, as well as those requiring strengthening and increasing support. Public meetings, such as the Potomac Conference, should be convened when necessary to obtain pertinent information.

3. A mechanism should be developed by the NCI director to ensure continuing review, surveillance, and coordination of treatment-related activities under way within the four divisions concerned. A coordinating council is suggested, with representation from each of the four divisions, and chaired by a senior staff member responsible to the director. In addition, a committee should be established that would be advisory to the directors of both the Div. of Cancer Research Resources & Centers (which administers the CCCRP) and the Div. of Cancer Treatment. This committee, made up of distinguished scientists from the academic community, would be designed to ensure a continuing dialogue and coordination of effort between the divisions most concerned with clinical research. In time, the mission of the committee should be expanded to encompass those other divisions within NCI that also are involved in clinical investigations.

4. The Clinical Investigation Branch of DCRR&C should develop mechanisms and provide adequate financial support to foster the interdisciplinary approach to cancer. "Heretofore clinical investigations were largely evaluations of the efficacy of drugs and combinations of drugs in patients with advanced disease," D'Angio said. "The CCCRP has matured beyond this point. It has now developed techniques and methods whereby clinical strategies for the cure of patients with earlier disease can be tested. Only by the active participation of medical oncologists, surgeons, radiation therapists, pediatricians, pathologists, immunobiologists and allied clinicians and scientists can suitable patients be entered in studies, be treated effectively, and be profited thereby."

5. It is mandatory that adequate staff be provided to DRR&C for prompt, efficient, constructive protocol review; staff representation at all cooperative group meetings; coordination of research activities with the divisions and among divisions; and frequent analyses and reports of fiscal and scientific progress.

6. Adequate funding of appropriate training and education programs should be provided to increase the number of experienced investigators available in areas of identifiable need—cancer surgeons, radiation therapists, pathologists, immunobiologists, and clinical oncologists are needed.

7. Group chairmen and biostatisticians should be involved more actively in giving advice and helping guide the policies and procedures governing clinical investigations.

NCAB Chairman Jonathan Rhoads said he saw the recommendations as involving three main issues:

- The internal organization of NCI and how all divisions involved in clinical research relate to the CCCRP. It is Director Frank Rauscher's responsibility to make any reorganization decisions. Rhoads suggested that a "small advisory group" to include the President's Cancer Panel and a few NCAB members could be established to "consider this with him."
- The phasing out of some of the cooperative groups and enhancement of others. The Cancer Clinical Investigation Review Committee will be considering those actions, Rhoads said, and the committee may need some help.
- Increased funding for CCCRP. The figure recommended by the Potomac Conference was an additional $5 million above the $22-23 million the program received from NCI in fiscal 1975.

Rauscher noted that this would pose another new demand on NCI funds, along with pressures for more money for carcinogenesis, centers and other programs at a time when it seems the pace of NCI appropriations increases is slowing down. "We may have to make some decisions on what to cut," Rauscher said.

Schmidt and other Board members were impressed by figures D'Angio presented which show that NCI funds only a small part of the work of the cooperative groups. Schmidt asked why some groups were funded by NCI and some not.

"Some groups are on probation, and some are participating without requesting funding," D'Angio said.

"But that number is greater than the number of funded groups," Schmidt said.

"Twice as great," D'Angio answered.

Board member Denman Hammond said the amount of money going into the program "far exceeds the amount NCI contributes, by a factor of five or 10."

D'Angio noted that 460 institutions, including 74 medical schools, participate in CCCRP. In 1974, 2,400 physicians participated along with 16,000 patients. The 2,400 physicians treated an additional 80,000 patients and consulted on another 40,000.

"The influence of CCCRP methods and procedures on medical education and training is clear," D'Angio said, "because those engaged in clinical research are active teachers and clinicians. They are in the strongest possible position to influence the teaching of modern, scientific, coordinated cancer care by precept and example, as well as through didactic lectures."

He listed as some accomplishments of the program:

- Progressively increasing survival of children with acute lymphocytic leukemia as a consequence of the cooperative clinical studies of remission induction, consolidation and maintenance.
- The value of combination chemotherapy in the induction of remissions in patients with disseminated Hodgkin's disease.
- The potential superiority of combination chemotherapy over single agents in the management of metastatic breast cancer.
- Improvement in survival of patients with multiple myeloma.
- Comparative testing of the relative curative potential of various radiation techniques in the management of Hodgkin's disease and other malignant lymphomas.
- A randomized comparative study designed to define the proper indication for radical and less radical surgery in the primary management of breast cancer.
- National protocols for the study of pediatric solid tumors including Wilms' tumor, rhabdomyosarcoma, and Ewing's sarcoma.

NCI, USSR SIGN AGREEMENT FOR NEW COLLABORATIVE CANCER CONTROL STUDIES

NCI has signed a new agreement with the Soviet Union for collaborative studies in five areas of cancer control—early detection, rehabilitation, evaluation of the efficacy of cancer therapy, the role of cancer centers, and methodology of teaching oncology and manpower development.

Diane Fink, director of the Div. of Cancer Control & Rehabilitation, and George Rosemond. president of the American Cancer Society, reported the results of their recent USSR trip to the Cancer Control & Rehabilitation Advisory Committee, when the agreement was negotiated.

The agreement calls for:

* A collaborative project on early detection of breast cancer.
* A multidisciplinary effort in a collaborative study of objectives and methods of rehabilitation of breast cancer patients, and development of joint protocols in rehabilitation of colon/rectum and head and neck cancer patients.
* Development of compatible coding of breast cancer data to facilitate information exchange.
* Exchange data on respective roles of cancer centers, including clinical and fundamental research.
* An exchange of education materials including textbooks, handbooks and other training materials for both professional and public education; joint publication of monographs on training; and an exchange of personnel for extended periods of study.

Rosemond presented the Soviets with an offer by ACS to cooperate with the exchange, particularly on the public and professional education phase. No final action was taken on that offer. "They don't understand voluntary organizations at all," Rosemond said.

Fink and Rosemond agreed that, "at least in the institutions they showed us," Rosemond said, the Soviets have first-rate equipment and facilities and "the people know what they are doing."

The committee accepted reports from its subcommittees on reimbursement (***The Cancer Letter,*** June 13), and prevention.

Louis Fink, chairman of the Subcommittee on Prevention, presented its recommendations, all of which at this time dealt with smoking. They were:

- Every attempt be made to eliminate direct as well as indirect advertising from all media (Fink defined indirect advertising as primarily cigarette smoking by television performers).
- Subsidies to tobacco growers be opposed.
- NCI obtain information on what other federal agencies are doing or can do about anti-smoking activities.
- Materials from last week's Third World Conference on smoking be reviewed and recommendations be developed from them for implementation in the U.S.
- NCI should go on record as supporting the toxic substances bill.
- Consideration should be given to supporting substantially increased special tax on cigarettes to deter smoking, and that a portion of this money be used to support diversification of tobacco farmers and cigarette manufacturers into more economically attractive activities.
- A merit review group be appointed to meet with with National Clearinghouse on Smoking & Health in order to obtain information on results of the two years of NCI-supported Clearinghouse programs and to make specific recommendations on future activities.

UNIV. OF ALABAMA PRESIDENT TO BE NEW HEW SECRETARY, POST REPORTS

David Mathews, president of the Univ. of Alabama at Tuscaloosa, will succeed Caspar Weinberger as HEW secretary, the *Washington Post* reported last week. Mathews, 39, is a Democrat, considered to be a liberal, and reportedly is not on the best of terms with Alabama Gov. George Wallace.

"He's a real, fine person, extremely intelligent and articulate, just a good man," said Howard Skipper, member of the National Cancer Advisory Board and president of the Southern Research Institute in Birmingham.

WRONG DATE LAST WEEK

Note to librarians: The date shown on page 1 of last week's issue, Vol. 1 No. 24, of ***The Cancer Letter*** was shown as June 1 instead of June 13. The correct date was listed on inside pages.

SOLE SOURCE NEGOTIATIONS

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

Title: Immunodeficiency-cancer registry
Contractor: Univ. of Minnesota.

Title: Studies on the role of hormonal factors on the induction of breast tumors
Contractor: Mason Research Institute

Title: Inter- and intraspecies identfication of cancer cells in vitro
Contractor: Child Research Center of Michigan

Title: Collection of large quantities of human milk
Contractor: Michigan Cancer Foundation

CONTRACT AWARDS

Title: Resynthesis of bulk chemicals and drugs
Contractor: Ash Stevens Inc., Detroit, $1,142,801.

Title: Resynthesis of bulk chemicals and drugs
Contractor: Starks Associates Inc., Buffalo, $875,633.

Title: HL-A Typing and matching for platelet and leukocyte transfusions
Contractor: UCLA, $378,512.

Title: Synthesis of bleomycin and structural modifications
Contractor: MIT, $65,051.

Title: Chemotherapy of ovarian carcinoma
Contractor: M.D. Anderson, $200,000.

Title: Computerized problem-oriented medical information system
Contractor: Univ. of Vermont, $33,208.

Title: Continued study of growth alteration of mammary neoplastic cells obtained by manipulation of cellular environment
Contractor: Univ. of Texas (Galveston), $98,200.

Title: Continuation of research into the content of DNA
Contractor: Stanford Univ., $85,000.

Title: Studies on the prevention of metastasis in mammary cancer.
Contractor: New York State Dept. of Health, $105,000.

Title: Study basic biological events in the pathogenesis of mammary cancer
Contractor: New York State Dept. of Health, $73,000.

Title: Continuation of research into the hormonal requirements of normal and abnormal human mammary tissue in organ culture
Contractor: Univ. of California (San Francisco), $79,900.

Title: Immunological studies of human breast cancer
Contractor: Albert Einstein College of Medicine, $92,700.

Title: Continuation of model system for screening agents against spontaneous murine mammary cancer
Contractor: Catholic Medical Center of Brooklyn & Queens, $331,391.

Title: Funding of alterations and renovations for expansion of rodent colony
Contractor: Catholic Medical Center of Brooklyn & Queens, $636,410.

Title: Prediction of hormone dependency in human breast cancer
Contractor: Univ. of Chicago, $96,200.

Title: Testing of antibiotic beers and purified preparation
Contractor: State of Michigan, $54,166.

Title: Study of the possible biological and chemical regulation of the microflora of leukemic laboratory animals
Contractor: Univ. of Notre Dame, $29,647.

Title: Immunological assays for DNA and RNA viruses
Contractor: Litton Bionetics, $265,425.

Title: Investigate Natural Occurrence of RNA tumor viruses
Contractor: The Jackson Laboratory, Bar Harbor, Me., $489,567.

Title: Immunological studies on the relationship of embryonic antigens to virus induced tumor antigens
Contractor: Univ. of Tennessee, $239,680.

Title: Stimulation of immunity to virus associated and tumor associated antigens in animals
Contractor: Mt. Sinai School of Medicine, $44,864.

Title: Studies of host restriction of Friend leukemia virus
Contractor: Albert Einstein College of Medicine, $30,020.

Title: Cellular immunity studies to simplex associated antigens
Contractor: Johns Hopkins Univ., $234,714.

Title: Study of sarcomas and their possible viral etiology
Contractor: St. Joseph's Hospital, Tampa, Fla., $60,000.

Title: Support of a cancer surveillance system
Contractor: Fred Hutchinson Cancer Research Center, Seattle, $424,970.

MORE ABSTRACTS FROM SYMPOSIUM ON IMMUNOLOGIC CONTROL OF TUMORS

Abstracts from presentations made at the NCI-Fogarty International Center symposium on "immunologic Control of Virus-Associated Tumors in Man: Prospects and Problems" were published here last week. Following are more selections from the symposium.

HUMAN ANTIBODIES BINDING TO THE MOUSE MAMMARY TUMOR VIRUS: A NON-SPECIFIC REACTION – *Kent W. Newgard and Robert D. Cardiff, Dept. of Pathology, School of Medicine, Univ. of California (Davis), and Phyllis B. Blair, Dept. of Bacteriology and Immunology, and Cancer Research Laboratory, Univ. of California (Berkeley)*

The mouse mammary tumor virus (MTV) shares a number of biophysical, biochemical and morphological characteristics with virus-like particles found in human milk and human breast cancer. Recently, a number of reports have appeared which suggest that an immunological relationship between MTV and the putative human particle also exists. Charney and Moore observed that sera from breast cancer patients apparently neutralize MTV. Mueller and Grossmann have observed antigens in human sera which react with antisera against MTV. Hoshino and Dmochowski, using human immunoglobulin tagged with horseradish peroxidase, demonstrated that adsorbed human sera reacted with the envelope of B particles. Mueller and his colleagues, using immunoferritin, demonstrated a reaction between adsorbed human sera and intracytoplasmic A particles. One can infer from these reports that an immunological relationship between MTV and the putative human breast cancer agent exists. It is important, therefore, to verify previous observations and to examine the nature of the reactions involved.

Recently, we developed a rapid, accurate method of studying antibody-antigen reactions in the MTV system using radioimmune precipitation. In this technique, antibodies are reacted with the surface antigens of intact iodinated virions and the resulting antibody-antigen complexes are then precipitated with antiglobulin. The specificity of the precipitation reaction can be analyzed using competition by unlabeled inhibitors.

Preliminary experiments indicated that not only sera from rabbits immunized against MTV but also sera from rabbits immunized with MTV-free mouse tissues can precipitate MTV. We now report that human antisera can also precipitate ^{125}I-MTV. The specificity of each of these three reactions was examined with competitive inhibitors, and each was found to differ from the other two.

TUMOR-SPECIFIC AND VIRAL-ASSOCIATED ANTIGENS OF HUMAN BREAST CANCERS: BIOLOGICAL CONSIDERATIONS – *Maurice M. Black, Reinhard E. Zachrau, Bella Shore, and Henry P. Leis Jr., New York Medical College–Flower and Fifth Avenue Hospitals*

In vivo and in vitro studies bearing on tumor-specific and viral-associated antigenicity of human breast carcinomas were reviewed with particular attention to the following clinical considerations: 1. breast carcinomas arise in a nonrandom fashion, 2. in situ carcinomas precede invasive breast carcinomas, 3. the heterogeneous behavior of invasive breast cancers.

In vivo, lymphoreticuloendothelial responses and skin window tests as well as in vitro leukocyte migration procedures indicate that tumor-specific antigenicity develops in association with mammary carcinogenesis. Such antigenicity is maximal in in situ carcinomas without associated invasive breast cancer and is minimal in invasive breast cancers associated with metastases. Immunogenic breast cancers tend to have antigenic characteristics which are similar to one another and to some component(s) of murine mammary tumor virus.

The nonrandom distribution of tumor-specific antigenicity and specific hypersensitivity is paralleled by a nonrandom occurrence of MuMTV-homologous RNA in human breast tissues. Advances in our understanding and control of human mammary carcinogenesis and biological behavior are dependent on the sophistication of the clinicopathologic characterization of individual patients and their breast tissues as well as the sophistication of the analytical procedures employed.

The use of the singular designation, breast cancer, in contrast to the plural form, breast cancers, is so universal that nonclinical investigators, epidemiologists, biochemists, immunologists, virologists, etc., come to believe that their precise techniques are being applied to precisely defined homogeneous test materials. Even clinical investigators commonly conduct their studies or apply therapy as if they were dealing with homogeneous populations.

If all breast cancers were similar in development and biological behavior it would be reasonable to expect uniformly positive or negative results with diverse investigative techniques, viz. epidemiological, virological, biochemical, immunological and therapeutic. If on the other hand the development and biological behavior of breast cancers were influenced by constellations of exogenous and endogenous factors it would not be surprising if different investigators, using unselected targets, obtained different answers to the same question. The failure to take cognizance of the latter possibility is responsible for many a pointless polemic. On the other hand an awareness of the nonrandom development of breast cancer, the distinction of the developmental from the

progressive phase and an appreciation that the biological behavior of invasive breast cancers reflects complex interactions between tumor and host may allow the investigator to give meaning to his data.

Equally important, such awareness allows the investigator to be perceptive of experiments of nature which provide uniquely valuable insights into the role of particular components of cancer development and behavior. A better understanding of human mammary carcinogenesis and biological behavior is no less dependent on the sophistication of the clinicopathologic characterization of individual patients and their breast tissues than it is on the sophistication of the analytical procedures employed.

When the available data are viewed in the light of the above considerations it appears that immunologic phenomena do indeed play a significant role in the biological behavior of breast carcinoma in individual patients. The critical variables include tumor-associated antigenicity and specific cellular hypersensitivity responses of the host. Both characteristics are maximally expressed during the preinvasive phase and minimally expressed in patients with disseminated breast cancer. However, antigenicity and hypersensitivity may vary independently. Such variability presages specific limitations to the development of effective immunotherapy of breast cancer. It is unlikely that breast cancers lacking antigenicity would be affected by attempts to increase the immunological responsiveness of the host. Nor is it likely that nonspecific immunostimulation would increase specific responsiveness against tumor-associated antigens. The point to be emphasized is the need to relate putative immunotherapeutic procedures to the characteristics of individual breast cancer patients. The same caveat is applicable to the use of adjuvant immunodepressive chemotherapy and radiation therapy.

On the other hand, the antigenic similarity between ISC from different patients suggests that immunoprophylaxis is potentially attainable. The antigenic similarity among in situ carcinomas and immunogenic invasive breast cancer tissues is also of interest in regard to viral participation in mammary carcinogenesis. This possibility is further suggested by the finding that some components of immunogenic breast cancer tissues seem to be antigenically and physicochemically similar to some components of MuMTV.

Here again we would emphasize that the use of analytical procedures, be they immunological or molecular hybridizations, should be related to precisely defined test material. Cooperative efforts between multiple disciplines appear to be a basic requirement for advancing knowledge and achieving control of breast cancer. While such efforts may not guarantee success, the lack of a cooperative approach is likely to guarantee failure.

EBV BEHAVIOUR IN DIFFERENT POPULATIONS – IMPLICATION FOR CONTROL OF EBV ASSOCIATED TUMORS – *Guy de-The', Unit of Biological Carcinogenesis, International Agency for Research on Cancer, Lyon, France*

There is a basic dilemma in understanding the role of the herpes virus EB in the development of both Burkitt's lymphoma and nasopharyngeal carcinoma; this virus is present all over the world yet these two tumors are quite rare and, furthermore, have distinct epidemiological characteristics. The question thus raised is whether some epidemiological characteristics of the EBV infection could shed light on the pathogenesis of BL and/or NPC. This task is not an easy one since the epidemiological characteristics of BL and NPC are basically different; BL epidemiological behaviour suggests the intervention of strong environmental factors relatively close in time to the clinical expression of the disease, whereas NPC epidemiological behaviour stresses the importance of genetic factors in the risk of tumor development.

In any case, the dilemma we have with EBV calls to mind the dilemma polio workers faced before vaccine was introduced regarding the relationship between polio virus infection, which was as ubiquitous as the EBV infection, and paralytic poliomyelitis. This example, although referring to an acute disease whereas slow viral infections may be more appropriate here as a model, is given to stress the unique role of sero-epidemiology in the establishment of the pathogenesis and in the control of virally induced diseases.

We have been conducting a comprehensive sero-epidemiological survey in representative samples of four different populations being at different risk for EBV associated diseases; namely Hong Kong and Singaporian Chinese at very high risk for NPC, Singaporian Indo-Pakistanis at very low risk for both NPC and BL, Africans from the West Nile District of Uganda at high risk for BL, and finally Caucasians from Nancy in France at low risk for both EBV associated tumors but at risk for infectious mononucleosis.

The geographical distribution of infectious mononucleosis in different populations can be explained by the distribution of age at which primary infection with EBV occurs. When EBV infection takes place early in life, as for example in Uganda and the Far East, no infectious mononucleosis is seen. Could then the high rate of EBV infection at a very early age in Uganda be connected to the risk for BL? Viral infections during the neonatal period, in infants whose reticulo-endothelial system is immature, may result in heavy and prolonged viral infections. That EBV infection in Uganda takes place shortly after birth is betrayed by the very high GMT against both VCA and CF/S in the age group of one to three years in the general population. The pathogenesis of the relationship between neonatal infection and risk for BL

is not known but it may involve an EBV-specific impairment of cell mediated immunity. Indeed, if we take the example of oncogenic RNA virus in birds, it is well established that the age and mode of infection are critical factors for the tumor type and tumor risk. If this were the case for BL, one could propose an intervention which would delay this infection until a later age and see if it had any effect on BL risk. This intervention could be achieved through simple measures of hygiene and may not involve a vaccine.

The second possibility for control of EBV infection concerns a vaccine. It may be too early to discuss the respective advantages of different types of vaccine, but now is the time to discuss the respective advantages and disadvantages of an EBV vaccine from the theoretical points of view. Several facts would favour such a discussion at this time: Marek's disease is actually controllable, to an acceptable extent, with a live virus vaccine. Laufs et al (1975) have successfully used a killed virus vaccine on lymphomas induced by oncogenic primate herpesviruses. When one considers the oncogenic potential of EBV for its in vitro transforming ability and its in vivo oncogenic properties in primates, one certainly wishes for a viral vaccine; not so much because it may be helpful in controlling the disease, but because it could be the ultimate stage in proving or disproving the role of EB herpesvirus in the development of human tumors. However, as discussed by Higginson et al in the past, the use of a vaccine against a potential oncogenic virus will pose enormous problems from the epidemiological and public health points of view.

Intervention against co-factors may thus prove to be more rewarding in the immediate future for the scientist, epidemiologist and the public health worker than the development of a vaccine. The intervention of an environmental factor shortly before (6-18 months) the development of BL fits in with most of the epidemiological characteristics of the disease and holo-hyperendemic malaria has been claimed as a very likely co-factor in the development of BL. No definite study has established this point but IARC is contemplating a partial malaria suppression scheme in collaboration with the Tanzanian health authorities in an area where the relative frequency of BL has been followed for 10 years (North Mara District of Tanzania). However, this study would take a few years to yield the results and would pose a number of technical and ethical problems as yet unresolved. Another unexpected but possible intervention has emerged from data which suggests that BCG may have an effect on the incidence of BL.

A fourth possibility for the control of these virally associated diseases is to detect the individuals at highest risk for the tumor, permitting early diagnosis and efficient treatment. If the viral markers used as criteria for selection proved to be the right ones to identify the cohort at highest risk, this could consequently reinforce the association between the viral infection and the tumor. This possibility might exist for NPC, where both the immunogenetic HL-A profile, as described by Simons et al (1974), and the characteristic high EBV antibody profile could represent marks for groups at high risk. If males from such groups aged 35-45 could be followed up regularly, it might be possible to achieve earlier detection of the disease and also to determine the serological pattern preceding the development of the tumor, which might in turn help to determine the pathogenesis of the relationship between EBV and NPC.

In conclusion, it appears that, at the present time, intervention against co-factors may be the most rewarding action to propose. In the long run, and if the link between infectious mononucleosis and subsequent risk for lymphoma should strengthen, a vaccine might become the best possible tool for the viral oncologist, the physician and the public health worker.

THE IMMUNE RESPONSE TO LEUKEMIA VIRUS AND TUMOR ASSOCIATED ANTIGENS IN CATS

— M. Essex, A. Sliski, W.D. Hardy Jr., and S.M. Cotter, Dept. of Microbiology, Harvard Univ.; and Sloan-Kettering Institute for Cancer Research

Cats represent an unusually valuable model for studying the role of the immune response to leukemia and other neoplastic diseases. This is because the laboratory species and experimental etiologic agents are essentially unaltered from those involved in the development of spontaneous neoplasia. Unlike the situation in man however, the responsible etiologic agent is known and well characterized. These studies concentrate on the immune response to the tumor cell itself.

It is convenient to divide the relevant antigen systems into three categories: (1) the tumor cell surface, (2) the virion envelope, and (3) the virion core. The immune responses can also be conveniently divided into three categories based on mechanisms: (1) humoral immunity, (2) cell-mediated immunity, and (3) agent related immunosuppression.

The feline leukemia viruses (FeLV) are thus far serologically indistinguishable from feline sarcoma viruses (FeSV) and/or their helpers. The feline oncornavirus associated cell membrane antigen (FOCMA) is also common for all known isolates of FeLV and FeSV, but non-crossreacting with analagous antigens associated with other oncornavirus groups, including the endogenous feline group (RD 114). ROCMA was proposed as an operational term, based on the demonstration of humoral antibodies that are correlated with tumor progression in cats. It is now known that several virus core and envelope antigens are present at the surface of permissively infected cells. Which of these, if any, is the target of the immune reactivity that is associated with tumor progression in the autochthonous host remains unanswered.

Cats that survive laboratory inoculations of FeSV

and FeLV and resist tumor development or undergo tumor regression have high antibody titers to FOCMA. Cats that develop spontaneous leukemia have a deficient FOCMA antibody response, while household associates that resist leukemia development following natural exposure to FeLV have high antibody titers. This appears to be a clear example of immune surveillance in an outbred species under natural conditions. The virus neutralizing antibody response does not parallel the FOCMA response and therefore it does not parallel tumor progression.

At yet we know very little about the cell-mediated response by either T or B cells to FOCMA, so it is theoretically possible that either or both of these may parallel the antibody response.

FeLV has been shown to be immunosuppressive under laboratory conditions. It is likely that this action of FeLV is also important under natural conditions, because healthy cats with naturally acquired FeLV-viremia show both a pronounced lymphopenia and a greatly increased risk for development of numerous other infectious diseases.

FETAL ANTIGENS AND RNA TUMOR VIRUSES

– Joseph H. Coggin Jr., Univ. of Tennessee

The great bulk of data suggests that many human and rodent tumors have detectable embryonic antigens either at the cell membrane or synthesized in the cytoplasm and elaborated from the cell surface into the body fluids. Included in the list of rodent tumors with fetal antigens are both virally and chemically induced sarcomas and carcinomas of the rat, mouse, hamster or guinea pig and leukemias and lymphomas of several of these species. Solid tumors from all major organ systems are included. Human neoplasms of both the solid and blood-born types are now recognized to demonstrate embryonic or fetal autoantigens.

Controversy exists over the character of the embryonic antigens present on human and rodent cancers, their immunogenic traits in vivo and the quality of the host response to fetal autoantigens on the tumors. Fetal autoantigens may be responsible for the cross-reactivity exhibited in in vitro tests between histologically related cancers. Nevertheless, their widespread occurrence, particularly on human neoplasms, affords a new, general approach to the detection of tumors not previously available.

The spectrum of rodent tumors which carry fetal antigens that are induced by RNA viruses or by chemicals which may activate an endogenous virus will be reviewed and parallel systems in humans will be examined.

Embryonic or fetal antigens do not appear to be virion associated and the data supporting this conclusion will be reviewed. Possible mechanisms by which oncorna- or oncodnaviruses may activate the reexpression of fetal antigens will be considered. A summary of application possibilities for using fetal antigens for the detection of early transformation caused by oncogenic viruses or for cancer therapy monitoring will be presented.

ANTIBODY TO HERPES SIMPLEX VIRUS TYPE 2 INDUCED NONSTRUCTURAL PROTEINS IN WOMEN WITH CERVICAL CANCER AND IN CONTROL GROUPS

– T. Anzai, G.R. Dreesman, R.J. Courtney, E. Adam, W.E. Rawls, and M. Benyesh-Melnick, Dept. of Virology & Epidemiology, Baylor College of Medicine

The present study was undertaken to detect the presence of antibodies to early "nonstructural" antigens of HSV-2 in sera of patients with cervical cancer and of control groups. Attempts were made to identify the virus-specific nonstructural antigens reactive with sera from patients with cervical cancer. For this purpose, an indirect radioimmune precipitation (RIP) test was developed in combination with polyacrylamide gel electrophoretic (PAGE) analysis of immune precipitates (RIP-PAGE test). Sera from patients with cervical cancer, from patients with breast cancer and from control women, with predetermined levels of neutralizing antibodies to HSV-2, were coded and subjected to the RIP-PAGE test.

The results obtained suggest that (1) sera from patients with cervical cancer possess a higher reactivity to early nonstructural proteins synthesized by HSV-2 as compared to the two control groups, and (2) the reactivity is independent of the level of neutralizing antibodies in the sera examined.

On the other hand, PAGE analysis of the immune precipitates revealed a significantly higher reactivity to protein VP134 among sera from patients with cervical cancer than among sera from control women or patients with breast cancer. Previous studies have shown that women with cervical cancer are infected with HSV-2 earlier in life and have higher neutralizing antibody titers to HSV-2 than control women, and that a preceeding HSV-1 infection may modify the response to an infection with HSV-2. However, the higher reactivity to VP134 in the patients with cervical cancer was not related to the level of neutralizing antibody to HSV-2. Furthermore, the breast cancer cases and most of the normal control women enrolled were selected because they had high HSV-2 neutralizing antibody titers; yet they failed to show a similar high antibody activity to protein VP134 as did the cervical cancer patients.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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