THE CANCER LETTER
RESEARCH EDUCATION CONTROL

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SURVIVAL OF CONTROL PROGRAMS AFTER NCI MONEY RUNS OUT DEVELOPING INTO A WORRISOME ISSUE

NCI is attempting to come to grips with the problems its ambitious Cancer Control Program will encounter when the planning, the implementation, and the demonstrations have been completed, the contracts have expired, and the local agencies are left with programs in place but no more NCI money to support them.

A Subcommittee on Reimbursement of the Cancer Control & Rehabilitation Advisory Committee has determined that one way to approach this problem is to draw up a new contract program and issue an RFP inviting third party payers and other health care reimbursing agencies to submit proposals on how cancer control programs can be continued using all available financial resources.

The subcommittee this week heard presentations on three federal programs which pay substantial portions of the costs of cancer care for

(Continued to page 2)

In Brief

HOUSE APPROPRIATIONS COMMITTEE GIVES NCI $725 MILLION, SMALLEST INCREASE SINCE 1970

HOUSE APPROPRIATIONS Committee has approved $703.5 million for NCI for the 1976 fiscal year, *The Cancer Letter* has learned. That figure does not include money for training programs, authority for which will expire June 30. That authority undoubtedly will be renewed, but Chairman Dan Flood of the HEW Appropriations Subcommittee had to exclude the money for it until new legislation is passed. If the training programs get at least the $22-23 million they received in FY 1975, the total would be about $725 million—which would mean the smallest increase over the previous year for NCI since 1970. NCI originally asked the full amount authorized by the National Cancer Act, $898.5 million. . . . "ADVANCES in Cancer Treatment," a fact sheet published by NCI over the signatures of DCT Director Vincent DeVita and NCI Director Frank Rauscher, is available from the Office of Cancer Communications, NCI, Bethesda, Md. It describes in general terms progress being made in the various modes of treatment; goes into a little more detail on new treatment being developed for breast and bone cancer; describes combination therapies under study; and lists advances in basic research which appear to be leading toward improved treatment methods. The fact sheet might prove useful in answering critics who claim the cancer program isn't getting anywhere. . . . **GIULIO D'ANGIO**, chairman of the Cancer Clinical Investigation Review Committee, on the impossibility of developing all the recommendations needed for improving the clinical cooperative groups at the so-called Potomac Conference: "We'll need a series of meetings, named after all the rivers in the country". . . . **RALPH CLAYTON**, El Paso, one of the organizers of the Assn. of Community Cancer Centers, has resigned from the ACCC board of directors. Gerald Kallas, Milwaukee, was appointed to the vacancy.

RFP MAY BE ISSUED TO HELP LINE UP ONGOING FUNDING FOR CONTROL PROGRAMS

(Continued from page 1)

eligible patients—Medicare, Medicaid, and the Veterans Administration.

Milton Kelman of the Social Security Administration described how Medicare pays for treatment of cancer patients who are eligible for that coverage. Kelman noted that while Medicare originally was set up to cover persons over 65, it has been expanded to pay benefits to permanently disabled adults who are covered by Social Security. It also pays most costs incurred by those suffering from end stage renal disease, the bulk of which is for kidney dialysis and kidney transplants.

Kelman said that persons disabled by cancer, if they survive the six month waiting period and meet other rules of the disability program, could receive the disability payments.

Mary Jo Gibson, now with the NCI Cancer Control staff but formerly with the Medicaid program in HEW, discussed the instances in which Medicaid pays cancer treatment costs. Payments are not uniform throughout the U.S., since Medicaid is a state-federal matching fund program and states are permitted to impose their own limitations. In general, Medicaid pays treatment, hospitalization and drug costs for the medically indigent, including such persons who are cancer patients. Skilled nursing home and home health services also can be covered.

Lyndon Lee, a member of the subcommittee who is assistant chief medical director for professional services of the Veterans Administration, said that VA makes no distinction for cancer in determining eligibility of patients for the agency's $3.6 billion a year medical and surgery program.

VA must treat patients for service-connected illnesses, which cancer generally is not; and it will accept veterans "who used to have to sign what amounted to a pauper's oath" but now only are required to certify that they would have difficulty paying their medical bills, Lee said. "And what cancer patient can't truthfully say that?"

Subcommittee Chairman Grace Monaco asked if veterans whose health insurance does not cover certain services can go to VA for those services. "They can and frequently do," Lee said.

William Johnson of the Blue Cross Assn. and Robert Lupien of the Blue Shield Assn. explained various types of coverage offered by their organizations, noting those that apply to cancer patients and those with certain exclusions which withhold payments for some cancer therapy and rehabilitation.

Virtually all Blue Cross contracts include in-patient medications and drugs, including chemotherapy treatment of cancer, Johnson said.

In addition, many Blue Cross plans offer riders which provide additional coverage for services used extensively in the treatment of cancer for hospitalized and/or ambulatory patients—x-ray therapy, radium therapy, radium and isotopes. Also, all of the plans have additional major medical or extended benefits riders which cover x-ray and radium therapy when charges go beyond those covered under the basic program, Johnson said.

In addition to major medical there are 13 plans which have what is known as a dread disease endorsement covering specific named illnesses. The dread disease endorsement acts in the same manner as major medical benefits but it is specifically designated to cover certain named dread diseases, including cancer.

Another concern, John said, is the question of diagnosis of cancer. There is an additional rider which can be added to the basic national contract which provides for full service benefits to the member admitted to a hospital primarily for diagnostic studies rather than treatment of a specific condition. The riders can be extended to cover the ambulatory patient who requires services but not as a bed-patient in the hospital.

Blue Shield plans specialize in the reimbursement of physicians and other professional providers, whereas Blue Cross reimburses institutions, Lupien noted.

"Because health coverage must compete with other needs, subscribers establish their own priorities as to which prepayment coverages they wish to purchase from the scope that is offered," Lupien said. "So any question concerning Blue Shield coverages for cancer detection, prevention and treatment must differentiate between those offered and those actually purchased by the public.

"Blue Shield plans do not isolate cancer related coverage from coverages for any other illness. We are concerned that subscribers get treatment for illness irrespective of the cause. As respects specific cancer related treatment, we have been advised that the most prevalent treatment methods are combinations of surgery, radiation therapy and chemotherapy. All of our plans underwrite surgery and radiation therapy for group and non-group members. Although we understand that the value of chemotherapy is still debated in some areas, plans cover this service for group subscribers excluding oral administration. Most plans also cover chemotherapy for non-group subscribers (about 11% of all members) who buy coverages directly without the advantage of the pooling of group resources.

"Blue Shield plans try to be alert and responsive to advances made by medical sciences," Lupien said. "As new techniques for the detection and treatment of cancer are proven, we extend our coverages. For example, immunotherapy, mammograms, nuclear blood analyses, while cell separation runs, and thermogram benefits are offered by plans in those areas where the procedures are performed and accepted. One plan is is providing payment for breast prosthese in a test program."

Lupien admitted that while major expenses for

cancer treatment are covered for most subscribers, "coverages for preventive and diagnostic services seem to be less than adequate. The reasons have to do with the cost of such services. Programs containing such benefits as annual physical examinations and "screening" diagnostic tests have restricted availability only because the marketplace has indicated a refusal to pay the price. But their costs are never catastrophic.

"Even our largest employer groups which have purchased programs for their employees more comprehensive than those of most of our other members, seldom have adequate diagnostic and preventive services coverage. I must emphasize that this is true of general coverages of this kind applicable to all illnesses–and not those solely related to cancer."

"One of Blue Shield's largest groups, the auto workers, will have coverage for routine pap smears for the first time as of Oct. 1, 1975. "Historically Auto has been a leader in new benefit acceptance, and we view this as an encouraging development," Lupien said.

INVESTIGATORS PRESENT LATEST DATA ON IMMUNOLOGIC CONTROL OF TUMORS

NCI and NIH's Fogarty International Center sponsored a three-day symposium this spring on "Immunologic Control of Virus-Associated Tumors in Man: Prospects and Problems." Much of the data presented there was based on studies still under way and has not yet been published.

Selected abstracts from those presentations, preceded by an introduction by Paul Levine of NCI which outlined the scope of the symposium, follow:

Rapidly accumulating evidence for the role of viruses in etiology of human cancer makes the topic of antiviral agents, such as vaccines, of great interest to tumor immunologists. Without the knowledge of how a virus demonstrates its oncogenic potential, however, a discussion of controlling virus-induced human tumors must draw on observations taken from apparently relevant animal models.

Three groups of viruses known to cause tumors in animals have been suspected of causing similar types of cancer in man – the DNA herpes-viruses, the "C-type" RNA viruses and the "B-type" RNA mammary tumor viruses. Other DNA viruses, particularly the papova viruses are also demanding attention as potential oncogenic agents. Because of the relatively little information we have on the biology of the candidate tumor viruses, in vitro as well as in vivo, the risks inherent in vaccinating normal individuals with live virus are currently considerable.

Killed virus, a possibility in spite of the problems of defining adequate bioassay systems, is a possibility but shares with subviral fractions the problem of providing only short term immunity. Yet, as immuno-epidemiologic studies demonstrated "periods of high risk," whichare common in animal tumor systems and logically are present in tumors of childhood, the utility of such vaccines should not be completed ignored.

The use of antiviral vaccines at the present time would seem to be far more appropriate as part of an immunotherapy regimen in patients already afflicted with the disease. The accumulating evidence that persisting susceptibility, perhaps genetically related, maintains certain individuals at high risk to cancer indicates that "relapse" in a number of cases may indeed be re-induction of the disease. Three examples of human tumors where viral reinduction has been postulated include Burkitt's lymphoma (BL), acute lymphocytic leukemia (ALL), and breast cancer.

In Burkitt's lymphoma, Zeigler has described two types of relapse, early and late, and has provided clinical evidence suggesting that late relapse is actually disease reinduction. His studies demonstrate that "relapse" usually presents in sites other than the first tumor site and is very responsive to retreatment with the drugs used at disease onset, whereas the early relapse is resistant to the drugs used initially and local disease recurrence is the rule. Presuming the late relapses (particularly those following unmaintained remissions of six months) have the same etiology as the primary disease, control of the candidate etiologic virus must be a matter of concern.

An even more dramatic example is acute leukemia, where apparent control of the disease through bone marrow transplantation has been thwarted by the transformation of the donor cells. One logical explanation given for the phenomenon is that the anti-tumor effect of the donor lymphocytes was successful but the putative human leukemia virus then infected the donor cells because there was no operating mechanism for controlling the virus. A similar case can be made for breast cancer, where apparent cure of the disease is followed years later by a second primary in the other breast.

Thus in those diseases where a viral etiology is likely, immunological control of the tumor may require control of the etiologic agent as well. There are numerous difficulties in planning a combined antiviral-antitumor approach to the immunotherapy of virus-associated tumors, the greatest being the difficulties in characterizing the associated virus. Antigenic modulation, "private" virus-related antigens, and separation of "xenotropic" and "ecotropic" isolates, are only a few. Delaying the evaluation of the viral aspects may be a mistake in immunotherapy studies, however, since the persistence of the virus that initially caused the tumor may prevent the success of otherwise successful approaches. Some groups are empirically approaching this problem by adding antiviral agents to their chemotherapy armamentarium in leukemia patients.

In this meeting, we have chosen to concentrate on four tumors where we have information about specific candidate viruses. In two of these tumors, cervical

cancer and Burkitt's lymphoma, the candidate viruses have been isolated and are being well characterized. There appears to be sufficient data linking EBV and Burkitt's lymphoma to move to the ethical considerations of how best to utilize the information in definitive clinical studies on etiology, prevention and cure. The role of HSV-II in cervical cancer is less clear but, as will be discussed later, HSV-II is certainly a human virus with oncogenic properties and it is not premature to focus on more definitive clinical studies with this virus as well.

Two other human tumors, breast cancer and acute leukemia, were chosen because of the clinical and experimental evidence for a viral etiology with the hope that tumor-specific and virus-related approaches can be utilized even without a definite eiologic agent in hand.

Because of the multiple problems associated with each virus-tumor system, each one presenting with unique epidemiologic as well as virologic questions, the approaches that are relevant to one tumor may not pertain to another. Two of the diseases to be discussed in depth during this symposium provide examples of this diversity: Burkitt's lymphoma, where the candidate DNA virus is ubiquitous but infection is clearly influenced by environmental factors, and acute leukemia, where experimental evidence suggests that the oncogenic agent is most frequently transmitted vertically and derepression rather than external infection is important.

BURKITT'S LYMPHOMA

A. Problems in prevention

The Epstein-Barr virus (EBV), the DNA virus most closely associated with BL, should be considered in any discussion of possible human tumor viruses for the following reasons:

(a) It is a bona fide human virus that has been demonstrated to be pathogenetic for humans, producing a lymphoproliferative disease at times resembling a malignancy,

(b) It is oncogenic for subhuman primates,

(c) In two tumor systems where the virus has been etiologically implicated by seroepidemiologic studies, NPC and BL, the viral genome has been shown to be harboured within the neoplastic cells.

While linked to a number of lymphoproliferative tumors, at the present time the evidence for EBV being a human oncogenic agent rests most strongly on its association with BL. For the purposes of this program, which is oriented primarily toward control measures rather than problems in etiology, the discussion will review the difficulties in controlling EBV associated BL even though the nature of EBV's relationship to BL remains open.

The major impetus to a preventive vaccine for BL (or other EBV-associated tumors) has come from the success of a practical vaccine for Marek's disease, a herpesvirus induced lymphoma of chickens. This live vaccine is highly effective but the precise mechanism of action is still unknown. The impact of this vaccine on the poultry industry has been dramatic, and in looking for a human tumor where the principle of preventive vaccination could be effective, BL initially has some promising features. The identification of a high risk group (children in holoendemic malaria areas) makes a limited field trial practical, and epidemiological evidence suggesting a short latent period (time and space clustering) enhances the likelihood of a vaccine being effective. The protective effect of a vaccine is more easily demonstrated in a pediatric tumor where the young age peak would permit demonstration of effectiveness within three to five years.

In spite of these attractive features, however, the prospect of a preventive vaccine appears remote given our current level of knowledge. First, BL is a rare tumor even in the high incidence areas. Since there are no methods currently available to monitor virulence, the risk of vaccination greatly outweighs the potential benefit. Second, the same type of laboratory data (hybridization and fluorescence studies detecting EBV genome in the BL tumor cells) cited as strengthening the data etiologically linking EBV to BL also suggests that some cases may have different etiologies, thereby diminishing the possible effect of an EBV vaccine on BL.

The possibility that there is more than one strain of EBV has been suggested for some time, but only recently have studies begun to concentrate on the differing properties of various EBV isolates.

The pursuit of such studies, still in their infancy, will be critical to determining whether different patterns of EBV induced diseases (IM, abacterial tonsillitis, asymptomatic URIs and possibly cancer) are the result of infection with different virus strains or the result of differing host response to the same agent. Certainly it will be important to analyze cross-reactivity between strains before a vaccine is to be considered.

Vaccines have effectively diminished the incidence of common childhood viral illnesses because of their impact on preventing primary infection with a pathogenic virus. The possibility that EBV induced BL as a primary agent even in a seronegative African child will be a precondition for a preventive vaccine to be utilized in BL. This question is now being investigated in a prospective study in the West Nile regions of Uganda, where 30,000 children are being bled and followed for the development of Burkitt's lymphoma. It has been hypothesized that the time-space clustering seen in African BL results from episodes of EBV infection in unprotected children who are also suffering from the burden of malaria. If BL is found to occur only in individuals whose pre-disease sera are negative (and the current pattern of 100% seropositivity in post-BL serum is maintained), the prospective studies responsible for proving EBV to be a cause of IM will have been duplicated in a tumor system and will provide a great impetus to the idea of vaccin-

ation with EBV, at least in a high risk (EBV seronegative) patient.

It is also possible that very high EBV titers will be found in the pre-disease serum, which could be subject to at least two interpretations, both of them tending to eliminate the possibility of vaccination. The first possibility is that repeated infection with EBV (possibly associated with repeated assaults of malaria) is necessary for BL to occur. A second possibility is that the high EBV titers are only a marker for susceptibility to BL which may be independent of a specific etiologic role for EBV. This possibility is suggested by our family studies which have shown that normal individuals in families where there are multiple first degree relatives with cancer, have significantly higher antibody titers to both the EBV viral capsid antigen (VCA) and early antigen (EA), even in families where the tumor type is very unlikely to be EBV induced (sarcomas, pheochromocytomas, and thyroid carcinomas, for example). The observation by Zeigler et al that late relapses of BL, which he indicates may be reinduction of disease rather than true relapses, are often preceded by high antibody titers to EA also indicate that vaccination against EBV as a protective measure is not likely to be useful. A third possible explanation for high titers in pre-disease serum, that of a long latent period, is unlikely in view of the explosive nature of the tumor and the presence of time-space clustering.

B. Therapy

Several aspects of BL make it a prime target for immunotherapy: it is highly antigenic; it appears to produce tumor-associated immunity in the host which at times is more important than the conventional therapy; and chemotherapy effectively produces a minimal tumor burden. From the viral point of view, there are additional favorable aspects: the virus associated with the tumor is readily identified by specific techniques; there are useful viral assays of apparent prognostic value, and the concerns of inoculating a normal individual with an oncogenic virus are obviated since the patient has already been infected. . . the purpose of the therapy being to give him a more useful immune response.

Initial attempts at specific immunotherapy of BL have not been encouraging. The observation of tumor regression after the receipt of immune serum was followed by a controlled study which demonstrated no effect, thus suggesting that the initial report was comparable to the apparent spontaneous remissions documented by others. Because of the close relationship of EBV titers to the course of disease, emphasis on serological monitoring of patients has been emphasized to date. The apparent failure of antibody (except perhaps membrane associated antibody) to protect against tumor growth emphasizes the need for further development of CMI assays. Other approaches, including the use of viral inhibitors and transfer factor with anti-EBV as well as anti-tumor activity, have yet to be evaluated.

ACUTE LEUKEMIA

A. Studies in prevention

The epidemiology of acute leukemia in the animal system indicates that the spontaneous form of the disease is generally the result of virus transmitted via the gametes from parent to offspring. The presence of the viral genome in the newborn had initially been considered to lead to immunologic tolerance and led to a general pessimism concerning immunologic control of the diesease but it is now apparent that tolerance is not complete. There is epidemiologic evidence that at least some cases of animal and human leukemia are induced by environmental factors. More important, recent clinical studies have clearly demonstrated that patients and close contacts are not tolerant to leukemia associated antigens.

Attention to the possibility of a vaccine for prevention was generated by early studies of Fink et al, demonstrating cross-reactivity between human leukemic cells and a laboratory strain of an RNA leukemia virus. A number of subsequent studies, biochemical as well as immunological, have continued to suggest that this cross-reactivity is real, but the specific antigens involved in the cross reaction have never been identified and there is some evidence that these antigens may not be specific for RNA viruses. Attempts to develop a specific viral vaccine for human leukemia have not been generated because of the absence of this data on immunologic specificity as well as serious concerns about the risks of a vaccine as compared to potentiel benefits. A series of recent reports, however, have raised the possibility of BCG as a non-specific preventive vaccine and in this symposium we will look at the possibilities for non-specific as well as specific preventive measures for leukemia.

B. Therapy

Immunologic management of acute leukemia will also be discussed later but it is worth commenting on several studies related to the viral aspects of the problem. Because of the apparent cross-reactivity between Rauscher leukemia virus and human leukemic cells, Hersh and his colleagues attempted to define the parameters of immune response to RLV in humans as the basis for possible therapeutic studies in the future. By demonstrating that a good immune response could be mounted against prototype oncogenic RNA virus, Hersh's studies laid the groundwork for the use of a viral vaccine in conjunction with chemoimmunotherapy. Additional studies on the immune response and a definition of which ones are important to a favorable outcome must still be carried out, but the approach of intercalating antivral immune stimulants with other forms of therapy still seems to have a sound basis.

Use of allogeneic cells with enzymatic modification or in conjunction with BCG has provided exciting leads in clinical studies on acute leukemia, but the relationship to viruses is now just beginning. An animal model for anti-viral, anti-tumor management of

acute lymphocytic leukemia is being investigated by Bekesi and his colleagues and the combined approach of anti-viral drugs, conventional chemotherapy, and neuraminidase treated leukemia cells appears to be more effective in the Gross-AKR system than any other regimen applied thus far. The translation of their animal studies to human leukemia, apparently successful in the initial phases, is being followed with great interest.

In summary, the success of preventive vaccines in apparently relevant virus-induced animal tumor models has provided a hope for similar human tumor vaccines greatly outweigh the potential benefits at the present time.

The use of anti-viral immunologic and chemotherapeutic agents is quite appropriate, however, in attempting better control of the disease in patients already suffering from tumors suspected of having a viral etiology. The initiation of such studies may not only improve the cure rate of the cancer patients but will undoubtedly add to our knowledge concerning the important immune responses needed to control these viruses.

Furthermore, knowledge of the epidemiology of each virus and the distinctive features inherent to each virus-tumor system is critical and it may be possible to develop an individual approach in the prevention as well as control of one tumor-virus system that will provide us with useful data in others.

PRACTICAL CONSIDERATIONS IN THE DEVELOPMENT OF A HUMAN ONCORNAVIRUS VACCINE – ***S.A. Mayyasi, D. Larson, M. Ahmed, The John L. Smith Memorial for Cancer Research, Pfizer Inc.***

Several studies have been reported in which laboratory animals being immunized with formalin inactivated or live attenuated oncornavirus vaccine are protected against neoplasia induced by the virus. With the assumption that some types of neoplasia are transmitted horizontally by an oncogenic virus as the case appears to be with feline leukemia and the disease is disseminated in the host by cell division, then the use of vaccines might be of value in protection against those malignancies. However, if the viral genome is transmitted vertically or by prior infection, then the value of vaccine immunization suppressing genetic expression and control of tumor development is more difficult to predict with optimism.

In the development of viral vaccines, we can consider three main types: 1) live attenuated; 2) inactivated whole virus and 3) purified subviral components that have been rendered free of viral nucleic acids.

Vaccines representing types 1 and 2 have been described for animal leukemias. We published our results on successful attentuation of Rauscher virus and the excellent protection it provided to the mice against challenge with leukemogenic virus or tumor cells transformed by the virus. However, in a later study, we noted inconsistencies with some virus preparation which exhibited significant leukemogenic activity, even after many passages in tissue culture.

In addition, we noted that the leukemogenic activity of the virus is dependent upon the type of the host cell used to propagate the virus. Many very difficult problems are associated with the successful and safe use of live oncogenic virus vaccines in human populations.

The prospect of developing such a live vaccine for human cancer in our opinion is a very remote possibility, but long term thinking should be given to consideration of that approach particularly as more information is developed about latent viruses that do not trigger neoplasia, but which may engender immunity.

Although the nature of virus involvement in human cancer is still a mystery, we can, at this point, venture an opinion and prediction. An increasing array of evidence has accumulated in the past two years to suggest some correlation between presence of virus genome and the expression of the disease. The isolation of SSV-1-like virus from a patient with myelogenous leukemia points toward that direction, and it creates a sense of urgency to develop preventive approaches to control the disease.

The current reports from several laboratories encourage us to consider the possibility of using specific structural components rather than a whole virion for developing a vaccine. In particular, the immunologic properties of purified structural proteins or glycoproteins, free of viral nucleic acid, are of greatest interest. The two major structural components that have been recently studied are the glycoprotein of the virus envelop (gp 69/71), and the core protein (p30). They have been found to carry multiple antigenic determinants, including those rendering type, group, or interspecies specificities. Group specific and type specific determinants of gp 60/71 are apparently located on virus envelop and thus are readily accessible to neutralization by specific immune serum.

In the mouse model, antiserum to purified gp 69/71 of the RLV has been shown to neutralize infectivity, and perhaps the tumorigenic potential as well of several naturally occurring murine oncogenic determinants seems to be a most realistic approach in developing a vaccine for a human cancer virus.

BCG VACCINATION: A CRITICAL REVIEW OF THE HUMAN EXPERIENCE – ***Robert Hoover, NCI***

The role of BCG vaccination in the possible prevention of human leukemia and other malignancies is highly controversial. There have been three followup studies that have shown no effect of BCG on the frequency of malignancy. Proponents of a protective effecti for the vaccine have indicated their belief that in order to be effective, the vaccination must be done neonatally, a procedure not evaluated by the above mentioned studies. In support of this position, the two studies showing apparent protection against child-

hood leukemia have involved children vaccinated neonatally.

On the other hand, both of these studies have involved serious methodologic flaws which could have allowed biases to operate in a manner to spuriously imply protection. Indeed, when the study showing the greatest degree of protection was reanalyzed in a manner permitting correction of only a few of these flaws, the apparent protection was markedly reduced from the initial estimate. More recently, population-based studies that have evaluated areas where neonatal BCG vaccination is widely practiced have failed to note any appreciable decline in leukemia mortality attributable to the vaccination. An additional complication is that one of the follow-up studies has actually raised a suspicion of increased lymphoma risk in a BCG vaccinated group when this group entered its early adult years.

While the question of whether BCG vaccination protects against human leukemia cannot be answered with certainty, several conclusions seem warranted at this time:

1) There is no evidence that such vaccination outside of the neonatal period is effective.

2) If there is an effect of neonatal vaccination, it must convey only a very small amount of "protection."

3) Follow-up studies adequate to assess long-term effects of such vaccination, including risk of lymphoma, have not been conducted, and recent reports indicate that such evaluation is warranted.

If these points are accepted then prudence would dictate that 1) there is certainly no justification for a massive BCG vaccination program as a leukemia prophylaxis; and 2) every population group vaccinated in an anti-tuberculosis program that can be studied, should be studied (particularly those vaccinated neonatally).

The question of a prospective clinical trial of neonatal BCG vaccination as a leukemia prophylaxis is a difficult one, since all the information needed to make such a decision is not known. However, several practical aspects of such a course should be pointed out. If the protection conveyed by BCG vaccination is even as high as 30% in children under age 15 (a generous estimate given all of the data to date), this would involve an average sparing of one child per year for every 100,000 vaccinated. In other words, a cohort of 100,000 vaccinated and 100,000 non-vaccinated children would have to be completely followed up for 15 years in order to just attain statistical significance at the 5% level (based on 30 observed leukemia deaths versus 45 expected by that time).

THE PREVENTION OF MAREK'S DISEASE – A REVIEW – ***H. Graham Purchase, U.S. Agricultural Research Service***

Marek's disease (MD) is a highly infectious neoplastic condition of chickens caused by a herpesvirus. The virus is cell associated in tumors and in all organs except in the feather follicle where enveloped infectious virions egress from the body. From this source, infection is spread horizontally by the airborne route to the environment and to other chickens. Vertical transmission from dam to offspring does not occur or at best is very rare.

The nonpathogenic herpesvirus of turkeys (HTV) is ubiquitous in turkeys and is probably spread horizontally by the airborne route. When chickens are inoculated with this virus, they do not subsequently develop MD even after infection with virulent Marek's disease virus (MDV). The MDV, not the HVT will spread horizontally from dually infected birds. The HVT vaccine is safe and highly effective in preventing MD under field conditions, and most chickens throughout the world are vaccinated with this vaccine.

When a candidate vaccine virus for the prevention of herpesvirus-induced malignancy in humans is developed, the purity of the vaccine preparations will be easily determined by modern techniques. However, measurements of safety and effectiveness are a significant problem. If, analogous to the MD model, the vaccine will have to be administered shortly after birth, and the incubation period to development of neoplasms is long, pathogenicity tests in nonhuman primates and other animals may be of limited value. However, biochemical demonstration that the segment of the nucleic acid responsible for oncogenesis is absent from the vaccine virus may be the major indication that the vaccine is nononcogenic and therefore safe.

RFPs AVAILABLE

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

RFP NO1-CP-55710-68

Title: *Development, management and support services to the Diet, Nutrition & Cancer Program (DNCP)*

Deadline: *Aug. 4, 1975*

NCI is interested in initiating a two year contract with an organization qualified to provide technical and managerial support to the Diet, Nutrition & Cancer Program.

In the first year, the contractor will function in a

purely supportive role, carrying out specific tasks. The contractor will be responsible for assisting in the management and administration of DNCP and will prepare and monitor budgets, perform program analysis and evaluation, and provide support and logistics services.

As the contractor performs and obtains a grasp of the scientific contents of the program, its goals and objectives, the role will be enlarged to include direct management of selected tasks of the DNCP under the surveillance of the project officer, and may eventually lead to a prime contractor role for which the contractor will be eligible to compete.

The successful offeror must have office space within a 25 mile radius of the NIH campus in Bethesda, Md. no later than the date of contract award.

NCI offers its estimate that the two year contract should cost between $325,000 and $475,000. The issue date of this RFP is June 16, 1975. A pre-proposal conference will be held in Bethesda July 2.

Contract Specialist: S.W. Ranta
Cause & Prevention
301-496-6361

RFP NCI-CB-63987-41

Title: *Biological studies of solubilized tumor antigens*

Deadline: *July 31, 1975*

Identify, characterize in experimental models and solubilize and purify those tumor-specific antigens of the transplantation type (TSTA) that are undoubtedly concerned with the induction, the control and elimination of cancer cells in man. Thus, knowledge concerning TSTA is directly related to immunodiagnosis and immunotherapy of cancer in man.

Because of the need to rapidly exchange biological materials between NIH and the contractor, the contract site must be within a 45 minute drive of the NIH campus, Bethesda, Md.). Any organization possessing the capability of performing this service may request a copy of RFP as of 16 June 1975.

Contracting Officer: Harold Simpson
Biology & Diagnosis
301-496-5565

CONTRACT AWARDS

Title: In vivo and in vitro studies of immune response to virus-associated antigens
Contractor: George Washington Univ., $78,835.

Title: Immunological studies on relationship of embryonic antigen to virus induced tumor antigens
Contractor: Univ. of Alabama, $65,298.

Title: Conduct studies on the role virion associated DNA polymeryase
Contractor: Univ. of California (San Francisco), $228,960.

Title: Immunological studies on relationship of embryonic antigens to virus induced tumors
Contractor: Duke Univ. Medical Center, $104,880.

Title: Processing of clinical patient research data
Contractor: Control Data Corp., $49,831.

Title: Operation and utilization of a population based cancer registry
Contractor: Univ. of New Mexico, $247,308.

Title: Support for special analysis and characterization of a newly isolated virus
Contractor: Pfizer, Inc., $88,610.

Title: Development of propagation procedures, purification and characterization of viruses
Contractor: Electro-Nucleonics Laboratories, Inc., $359,247.

Title: The study of effects of carcinogens on the in vitro synthesis of complement components
Contractor: Children's Hospital Medical Center, Boston, $73,778.

Title: Study of factors influencing experimental respiratory carcinogenesis by alpha radiation and chemical carcinogens
Contractor: Harvard College, $314, 479.

SOLE SOURCE NEGOTIATIONS

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

Title: Population-based cancer registry for Surveillance, Epidemiology and End Results
Contractor: Commonwealth of Puerto Rico.

Title: San Francisco Bay Area Resource for Cancer Epidemiology
Contractor: California Dept. of Public Health.

Title: Characterization of the nucleic acids of the avian myeloblastosis virus
Contractor: Massachusetts General Hospital.

Title: Continuation of animal holding and breeding for detection of tumor virus information
Contractor: Flow Laboratories.

Title: Maintenance of a low-temperature repository and establish cell lines from human tumors
Contractor: Flow Laboratories.

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