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NCI, FDA ARE FEUDING AGAIN, THIS TIME OVER CHARGE THAT DCT MOVED TOO SLOWLY ON TOXICITY NOTIFICATION

After more than three years of relative tranquility between the two agencies, NCI and the Food & Drug Administration are at each other's throat's again, this time over charges by two FDA officials that NCI was negligent in reporting that methyl CCNU can produce significant renal toxicity.

The charges were made last week at a hearing by the House Science & Technology Committee Subcommittee on Investigations. Stuart Nightingale, FDA acting associate commissioner for health affairs, and Alan Lisook, chief of the Clinical Investigations Branch of the Bureau of Drugs, told the subcommittee that as much as 10 months had elapsed from the time NCI received information on the drug's renal toxicity until investigators using it were notified.

No response from NCI was made at the hearing. The following day, when an account of the hearing appeared in the *Washington Post*, NCI executives were furious.

"The *Post* story was absolutely inaccurate," one told ***The Cancer Letter.*** "We did exactly what we were supposed to do."

Lisook told the subcommittee that FDA had received an "angry letter" in September 1978 from the mother of a child with a brain tumor

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In Brief

RFPs FOR RECOMPETING FREDERICK CONTRACT STILL BEING DRAFTED; PANEL MEETS APRIL 13

NCI RESEARCH Contracts Branch and other staff members involved with developing the RFPs for recompeting the Frederick Cancer Research Center contract are still drafting the new workscopes. The contract, held by Litton Bionetics Inc. since NCI established the center in 1972, will be recompeted in two major portions—one for research, the other for resources production, central services and management. Separate RFPs are being written, but organizations may compete for both contracts if they wish. In addition, two or three RFPs for small business set-aside contracts are being written for services in the production-management side of the operation. NCI's goal has been to have the RFPs on the street no later than one year before the present contract ends, in September 1982. . . . **PRESIDENT'S CANCER** Panel will meet April 13, 9 a.m., in the NIH Bldg 31 Rm 4. Joshua Lederberg remains as chairman, although his term has expired. The White House is aware that the position is open, but has made no decision yet on whether to reappoint Lederberg or name someone else. . . . **BIOMETRY & EPIDEMIOLOGY** Contract Review Committee meeting scheduled for April 16 has been canceled—no contract proposals to review.

NCI REFUTES CHARGE IT WAS TOO SLOW ON MeCCNU TOXICITY NOTIFICATION

(Continued from page 1)

who had been receiving MeCCNU. The child suffered kidney failure, and the mother was unhappy because she had not been told that that could be one of the side effects. The *Post* story said:

"In this instance, the FDA officials said that the time lag between the NCI's learning of the kidney problems caused by the drug and its report was at least 10 months, possibly longer."

Now for the facts.

In animal toxicology tests with MeCCNU, some evidence of renal toxicity was observed, and investigators watched closely for it when the drug was taken through phase 1 trials. No renal toxicity was observed in phase 1 or phase 2 trials, nor during the first six years of its rather widespread use in a variety of clinical trials.

In June, 1978, Thomas Strike, NCI project officer for the Brain Tumor Study Group, received a communication from the investigator treating the 14-year-old boy informing him that a kidney problem had developed. The boy had received MeCCNU from 1973 to 1975. Strike immediately sent a letter to all BTSG members asking if they had observed any similar toxicity. None had.

NCI's Div. of Cancer Treatment staff continued to study the one case relating MeCCNU to kidney failure, but it was difficult to pin down. The boy had been treated previously with BCNU and had numerous problems which complicated the study.

In November 1978, Richard Fisher, investigator with DCT's Medicine Branch, observed renal failure in one of his patients at the NIH Clinical Center. The patient had received MeCCNU. He discussed the problem with Michael Jensen-Akuna, who was the drug monitor for MeCCNU in DCT's Investigational Drugs Branch. Jensen-Akuna had just become aware of a study by William Harmon, of Boston Children's Hospital and the Sidney Farber Cancer Center, which indicated that some patients receiving MeCCNU were having kidney problems. Jensen-Akuna had discussed this by phone with Harmon, who told him he would forward a written report on the study.

By this time, NCI staff was concerned about the possible problem but had no hard evidence on which to take action. That evidence became available only on Jan. 10, 1979, when a draft of the report Harmon later published in the *New England Journal* was received at NCI. Harmon had reviewed 17 patients who had received MeCCNU; five had renal problems, and one had died from that problem.

NCI moved quickly from that point. Following the step by step procedures called for in its "Master Plan" developed for monitoring anticancer drug clinical trials—a plan which FDA helped draw up and agreed with—NCI filed an adverse drug reaction report with FDA, on Feb. 21, 1979; sent a letter on Feb. 23 to 1,078 investigators known to be using MeCCNU advising them of the possible renal effects and requesting notification of similar problems; and amended the guidelines for Group C use of MeCCNU (by physicians receiving the drug free from NCI for use following approved protocols with patients not enrolled in clinical studies).

"The key point," an NCI executive said, "is that the Master Plan gave NCI responsibility for investigating adverse reaction reports. We followed every step of the plan to the letter."

The *Post* article included at least one error of fact which tended to make NCI look bad. The article stated:

"The Washington Post has learned that the FDA testimony was based on a series of documents that the FDA found in the files of the cancer institute. They include one letter to the institute dated Nov. 13, 1978, four months before NCI notified anyone of the danger, in which Dr. Harvey Cohen of the Children's Hospital of Boston described at least 14 cases of kidney damage that occurred in cases where the drug had been used."

Cohen denied this week that he had ever written to NCI about the situation. NCI insists that no written documentation on the case was received in November, and that Harmon's report in January was the first in which multiple cases of nephrotoxicity were reported.

Lisook told the subcommittee that in July 1979, FDA went to NCI to investigate why a faster response had not been made. "We were quite surprised to find that they couldn't identify who the clinical investigator was, they couldn't identify what the protocol was, and they could only speculate why (physicians administering the drug) were not notified."

NCI executives were extremely skeptical, to say the least. "That is a completely phony statement," said one. "It doesn't ring true. We know who we send the drug to. We know what protocols we have approved for use of MeCCNU. And why should we 'speculate' about notification? We sent our notification as soon as we had the evidence. Who did he talk with? I think it is very convenient that he didn't name anyone."

Lisook refused to tell ***The Cancer Letter*** who the individual or individuals were who seemingly did not know anything about the situation. He excused the supposed ignorance on the grounds that the questions related to investigators and protocols using the drug from 1973 to 1976 (the questions being asked in July 1979), and that the Master Plan did not go into effect until 1977. Before then, NCI's monitoring and reporting on investigational drug use was much less defined and more lax.

Irate NCI executives charged that Lisook and Nightingale could make the comments they did to

the subcommittee only if they were complete ignorant of the Master Plan. But Lisook said he was "very much aware" of the memorandum of agreement in which FDA and NCI agreed to the plan, ending for the most part a two year battle over FDA's capricious interruption and rejection of IND protocols.

Lisook insisted that NCI should have moved immediately when the information was received by phone in November 1978. The NCI reaction (unofficially): "FDA does not have the competence to make that determination. We were dealing with late effects among persons who had been treated with a variety of other drugs and with other problems. There is no easy way to determine if the renal effects were due to that particular drug." It was pointed out that there still are only 26 known cases of nephrotoxicity from MeCCNU.

NCI executives were especially infuriated by the fact that after FDA's "investigation" in July, 1979, they were promised that a report would be written and submitted to them. "A year and a half later we still haven't received that report. Then they surface with this collection of misstatements at a congressional hearing. That's dirty pool."

HEPATITIS B VACCINE READY, COULD LEAD TO PREVENTING LIVER CANCER: BLUMBERG

The imminent prospect of widespread use of a vaccine against the hepatitis B virus, which will probably prevent primary hepatocellular carcinoma that appears to be a consequence of HBV infection, was reported at the annual American Cancer Society Science Writers Seminar by 1976 Nobel Prize winner Baruch Blumberg.

Among other reports made at the meeting were those on identification of high risk members of melanoma prone families; human hybridomas in studying human disease; immunization against chemical carcinogens; selenium, chemoprevention and breast cancer; and carcinogenesis and cancer prevention. Summaries of those reports follow:

Hepatitis B-Like Viruses and the Prevention of Primary Liver Cancer—Baruch Blumberg, associate director for clinical research, Institute for Cancer Research, Philadelphia.

The regions of the world with high frequencies of HBV carriers coincide with the high incidence areas for primary cancer of the liver. In all regions where it has been studied (including the United States) the frequency of infection with HBV virus is significantly higher in PHC patients than in appropriate controls. The diseases which often precede and accompany PHC (cirrhosis, other forms of chronic liver disease) are also due to infection with hepatitis B virus. The virus (both its antigens and its specific DNA) can be identified in the liver cells of patients with PHC, but is not found in controls.

In several cases the viral DNA has been found integrated into the DNA of liver tumor cells of patients with PHC. Beasley and his colleagues have undertaken a prospective study of 3,000 carriers in Taiwan, an area of high PHC incidence. The controls were approximately 20,000 males who were not carriers. After about five years of followup, they ascertained 50 cases of PHC. All but one of these occurred in a carrier. This is a very rigorous test of the hypothesis and indicates that HBV infection precedes the development of clinical cancer.

Prospective studies have also been done in patients with chronic liver disease, some of which was apparently due to HBV and some not. A significantly higher frequency of PHC developed in the liver disease cases associated with HBV.

There is a family clustering of HBV carriers, PHC and chronic liver disease. There is direct and indirect evidence that mothers often infect their children early in life and that there may be a very long incubation period (30 or more years) for the development of PHC. Taken all together these findings provide substantial support for the hypotheses stated above, namely that persistent infection with HBV is required for the development of primary cancer of the liver.

HBV has several unusual characteristics which distinguish it from other viruses. There is a very high frequency of asymptomatic carriers in some populations, and very large amounts of viral antigens may be present in their blood. The DNA, which is about 3100 base pairs in length, is both double and single stranded, and a specific DNA polymerase is present in the core of the virus—both of which are unique characteristics. There are three particle forms of HBV. The whole virion, which includes a surface antigen (HBsAG), a core with its own antigen (HBcAg) which contains the DNA and the specific DNA polymerase. There are also two particles which consist only of HBsAg, a small particle of about 22 nm and an elongated particle of about the same diameter but of varying length.

These and other characteristics marked HBV as significantly different from other viruses, and in 1971 we proposed that HBV was representative of a class of viruses which are designated as icrons (an acronym on the name of the Institute for Cancer Research). This "class" became particularly interesting when it was recognized that infection with HBV was necessary for the development of PHC, and it followed that other icrons might also be related to cancer and chronic diseases.

Our attention was first directed to woodchucks (marmota monax) by our colleague Dr. Robert Snyder of the Philadelphia Zoological Gardens who reported high frequencies of PHC in this species. Our initial investigation, using the immunodiffusion technique to detect HBsAg, was unsuccessful. However,

our colleague Dr. Jesse Summers of the Institute for Cancer Research, screening for particles with endogenous DNA polymerase, discovered a virus which he termed woodchuck hepatitis virus (WHV) which had many of the characteristics of, but was not identical with, HBV. He and his coworkers demonstrated its relation to primary cancer of the liver in woodchucks. He found that the DNA of the WHV was integrated with the liver cancer cells in the same region in all of the cells examined. This implied that infection had occurred prior to or at the time of, but not after, the event which precipitated cancer.

Another virus of the icron group has been found in Beechey ground squirrel (spermophilus beecheyi) in California, but its disease associations, if any, are not known.

While traveling in People's Republic of China in 1977, I was told that certain domestic ducks in areas of high liver cancer endemicity also had high frequencies of primary liver cancer. We collaborated with Dr. T.-T Sun of Beijing and J. Summers of our Institute and found a virus very similar to HBV in the blood of ducks from one of these regions. Mason and Summers found a similar virus in U.S. domesticated ducks. The ancestors of Pekin ducks had been imported from China to the U.S. in the 19th century.

This finding of other animal species with an icron-cancer relation similar to HBV and PHC in humans adds additional strength to the hypothesis that HBV infection is required for the development of PHC and encourages the design for prevention programs. In 1970 Dr. Millman and I introduced a novel method for preparing a vaccine from the surface antigen particles in the peripheral blood of the HBV carriers. This vaccine has now been produced, and in a recent field trial, Szmuness and his colleagues showed that it is safe and highly effective. This vaccine, when it becomes widely available (probably in about a year) in conjunction with other public health measures, may lead to the prevention of one of the most common and deadly cancers in the world.

Identifying High-Risk Members of Melanoma-Prone Families: The Dysplastic Nevus Syndrome—Mark Greene, senior clinical epidemiologist, NCI, Environmental Epidemiology Branch.

The Family Studies Unit of NCI's Environmental Epidemiology Branch conducts interdisciplinary studies of cancer-prone families to identify mechanisms of cancer susceptibility and to explore host-environmental interactions in cancer pathogenesis. The general approach in this program entails identification of families at increased risk of specific malignancies, documentation of the tumors that have developed, and a combined clinical/laboratory evaluation of family members, using protocols that are tailored to the particular type of cancer manifest in a given family. Laboratory studies include genetic, immunologic, virologic, and other biologic assays which might clarify mechanisms of individual cancer susceptibility.

Malignant melanoma is a cancer that originates in the pigment-forming cells of the skin. Although it was apparent for some time that familial predisposition was greater for melanoma than for other forms of cancer, very little had been done to define specifically why members of high risk families were susceptible to melanoma. Like other types of skin cancer, melanoma appears causally related to sunlight exposure (ultraviolet radiation), although the precise nature of that relationship is unclear. In the past, it was suggested that ordinary moles (nevi) on the skin were melanoma precursors, but that idea had fallen into disfavor.

Impetus towards improving our understanding of melanoma pathogenesis came from two observations. First, many researchers described rapid increases in both the incidence and mortality from melanoma. On a worldwide basis, the incidence of melanoma was noted to have doubled in the previous decade, a trend that continues today. This trend has been related to changes in clothing habits, recreational sun exposure and, possibly, to decreases in atmospheric ozone. Second, clinical and pathology studies of melanoma (pioneered in part by project co-investigator Dr. Wallace H. Clark) resulted in the ability to diagnose melanomas earlier in their natural history, and documented the surgical curability of early melanoma. Therefore, the ability to identify individuals at increased risk of melanoma would have important consequences for the prevention, early diagnosis, and eventual control of this form of cancer.

We undertook a preliminary evaluation of a melanoma-prone family in the hope that a clue to melanoma etiology might become apparent. In our first effort, 25 members of a family with four known melanoma patients (one deceased) were examined. Clinically, the surviving melanoma patients and a number of their healthy relatives were found to have a very unusual pattern of moles (nevi) on their skin. These nevi were larger and more numerous than normal, had irregular outline and pigmentation, and seemed to be found all over the skin, including areas where ordinary nevi are usually not seen, such as the scalp and buttocks. One family member was discovered to have a previously undiagnosed malignant melanoma. When removed, it was an early melanoma of the surgically curable type; and, in fact, that patient is alive, well, and free of melanoma five years later.

The study was then expanded, and careful clinical evaluation revealed that six additional families had the same unusual nevus pattern as we observed in the first. Detailed pathology studies of pigmented nevi removed from family members revealed that these

lesions had a characteristic microscopic appearance that permitted Dr. Clark to distinguish these nevi from other types of nevi. The critical microscopic feature of these nevi is the presence of disordered, faulty growth (cytologic atypia or dysplasia) of melanocytes. Nevi consist of clusters of benign melanocytes, while melanoma is present when melanocytes have become malignant. Dysplastic nevi, therefore, fall in between benign, ordinary nevi and fully developed malignant melanoma, both on clinical and histological grounds. In fact, nevi which are severely dysplastic may be very difficult to distinguish from true melanoma. Thus, it was felt that these special moles represented a precursor state for melanoma. This distinctive clinical/microscopic pattern has been designated the DNS, and is analogous to preneoplastic states in other human cancers, e.g., cervical dysplasia and carcinoma of the cervix, and familial polyposis and colon cancer.

Detailed studies have now been completed, the clinical and histologic features of the DNS have been more sharply defined, and the relationship between dysplastic nevi and familial melanoma has been delineated. Our data strongly support the hypothesis that dysplastic nevi are formal melanoma precursors; these lesions appear to be a special type of mole that is unusually susceptible to malignant transformation. All patients who had new melanomas diagnosed during our study had the DNS (i.e. no *new* HMM were diagnosed in normal family members), and all but one of these new melanomas were of the very early (surgically curable) type. This suggests that careful monitoring of high risk family members, as determined by the presence of the DNS, does facilitate early cancer diagnosis.

Recently, both we and other investigators have described the occurrence of the DNS in nonfamilial melanoma patients as well. This suggests that the DNS may permit recognition of individuals at increased risk of both hereditary and nonhereditary melanoma. These nevi appear to be premalignant lesions, but only a small proportion of them progress to melanoma. Removal of the most abnormal nevi constitutes primary melanoma prevention. In this vein, we have developed extensive written guidelines for the management of persons at increased risk, and a series of educational videotapes for family members and the physicians involved in their care. These materials delineate the characteristics of dysplastic nevi, the melanoma warning signals, principles of skin self-examination, techniques for minimizing sunlight exposure, and recommendations regarding the day to day health care of high risk individuals. They will be available soon through the National Audiovisual Center, Washington, D.C.

The work summarized here has been conducted in collaboration with Dr. Clark and Dr. David E. Elder, of the Pigmented Lesion Clinic, Hospital of the Univ. of Pennsylvania; Drs. Kenneth H. Kraemer and Margaret A. Tucker, and Mary C. Fraser, RN, of NCI. As part of this project, we are collaborating with several laboratories to study in vitro immune function, chromosome structure, and repair of cell damage caused by ultraviolet radiation. Other studies include a statistical analysis to determine how HMM and the DNS are inherited, electron microscopy of dysplastic nevi, and development of a color atlas detailing the clinical features of these lesions.

Continued work is expected to enhance our ability to prevent and control malignant melanoma, while simultaneously clarifying the developingal biology of this important human cancer.

Human Hybridomas to Study Human Diseases—Carlo Croce, Wistar Institute of Anatomy & Biology

Human melanoma cells can be used to produce human hybridomas secreting antiviral antibodies and autoantibodies.

We have selected human myeloma cell lines deficient in hypoxanthine phosphoribosyltransferase (HPRT) to be used to produce human hybridomas secreting human monoclonal antibodies. At first we selected patients who had very high titers of antibodies against viruses. One of these patients, a 19-year-old girl with subacute sclerosing panencephalitis (SSPE) that is caused by a measles virus infection of the central nervous system, had extremely high titers of circulating antibodies specific for measles virus. We obtained 10 ml of peripheral blood from this patient and we purified her blood lymphocytes. By using polyethylene glycol we fused the HPRT deficient human myeloma cells with the peripheral lymphocytes and we selected the hybrid cells in HAT selective medium in which only the hybrid cells can grow.

Hybrids (hybridomas) were obtained in most of the wells in which the fusion cell mixture was distributed. Culture fluids derived from the wells were tested for their ability to immunoprecipitate radiolabeled measles viral proteins. The cells in the wells were also cloned and the culture fluids of the clones were also tested for their ability to immunoprecipitate the radiolabeled viral protein. Hybridomas were found that produced antibodies against the nucleocapsid (NP) of measles virus. Such hybridomas were found to secrete new heavy and light immunoglobulin chains.

Subclones of hybridomas secreting antimeasles virus antibodies were also tested for their ability to secrete antiviral antibodies. Monoclonal antibodies capable to immunoprecipitate the NP protein of measles virus were produced by the hybridoma subclones. Since the human myeloma cell lines and the related human hybridomas are capable of growing in an ascitic form in nude mice it is possible to produce

extremely high quantities of human monoclonal antibodies. We have extended these observations to the study of human autoimmune diseases. We have hybridized lymphocytes derived from patients with myasthenia gravis, Greaves disease, and insulin independent diabetes with the human myeloma cells in order to clone the autoantibodies responsible for the diseases. At present we have obtained hybridoma cells derived from the fusion of human myeloma cells and hyman lymphocytes from a patient with diabetes that produce monoclonal antibodies against the insulin receptor.

This procedure can be used to clone and produce large quantities of human autoantibodies responsible for the development of certain human autoimmune diseases. The development of antiidiotype antibodies specific for these cloned autoantibodies might result in a cure for certain human autoimmune diseases, such as Greaves disease, myasthenia gravis, rheumatoid arthritus and insulin independent diabetes.

Immunization Against Chemical Carcinogens—Frederick Moolten, Dept. of Microbiology, Hubert H. Humphrey Cancer Research Center at Boston Univ.

If certain poisonous substances, such as tetanus or diphtheria toxins, are slightly altered to render them harmless, and are then injected into a person or animal, they stimulate the production of antibody molecules which can neutralize the virulent forms of these toxins if they are later encountered. This is standard public health practice for immunization against tetanus and diphtheria, but can similar immunization procedures be developed to protect against a different group of poisonous substances—those that cause cancer?

Past experiments have demonstrated that some of these carcinogens, when linked to certain proteins and then injected into animals, could stimulate the animals to make antibodies, but these experiments provided no evidence that the antibodies could inhibit the cancer-causing actions of the chemicals. To investigate this latter possibility, we have immunized animals with 5-fluoro-12-methylbenzanthryl-7-acetic acid (FMBAAA), a substance belonging to the polycyclic aromatic hydrocarbons class of chemicals. Many PAHs are ubiquitous in our environment, generated either by natural processes, or as a byproduct of human activities, such as cooking, combustion of fuels, and smoking of tobacco.

A substantial number of these environmental PAHs are potent carcinogens. FMBAAA, on the other hand, is a synthetic PAH that we chose for our studies because it contains a fluorine atom which appears to render it noncarcinogenic. In our initial experiments, we found that when FMBAAA, conjugated to a protein—bovine serum albumin—was used to immunize guinea pigs, the antibodies that the guinea pigs produced could react not only with FMBAAA but also with carcinogenic PAHs. When the antibodies were mixed with animal cells grown in culture in the laboratory, they protected the cells against the toxic effects of a potent synthetic PAH carcinogen, dimethylbenzanthracene. Further experiments were then done in whole animals. Mice were given the FMBAAA-bovine serum albumin complex by stomach tube, and were then fed the PAH carcinogen benzopyrene. The immunized mice were found to possess antibodies in their gastrointestinal tracts which could bind the benzopyrene. Since benzopyrene is one of the carcinogens in tobacco smoke and polluted air, other mice were immunized via the respiratory tract, and then exposed to benzopyrene instilled into their nostrils. The respiratory tract tissues of the immunized mice were found to contain less benzopyrene than was found in unimmunized mice given identical quantities of the carcinogen.

Since all of these studies suggested the possible ability of immunization to protect against PAH carcinogens, we have begun long term experiments to test directly whether immunized mice exposed to these carcinogens develop fewer tumors than control mice that received no immunization or were immunized with irrelevant substances.

The experiments are slow and difficult because only very low doses of carcinogens (not greatly exceeding quantities found in the environment) can be used if the capabity of the antibodies to neutralize the carcinogen is not to be exceeded. As a result, there is little tendency for tumors to develop even in unprotected mice. To some extent, this difficulty can be circumvented by the use of tumor promoters. The use of promoters is particularly efficacious in enhancing the incidence of PAH induced skin cancers in mice. Our first protection experiment utilized this approach.

We applied repeated miniscule doses (25 nanograms) of dimethylbenzanthracene to the skin of mice in alternation with the promoter, tetradecanoyl phorbol acetate. Some of these mice had been immunized with the FMBAAA-bovine serum albumin conjugate (i.e., the antigen which we knew could induce antobodies capable of binding dimethylbenzanthracene). Other mice served as controls; they were either unimmunized, or were immunized with bovine serum albumin alone, or with a mixture of bovine serum albumin and FMBAAA (when the FMBAAA is not conjugated to the albumin, it does not induce antibodies).

The experiment has yielded encouraging results. After 40 weeks, the control mice developed small but significant numbers of skin tumors (averaging 0.47-0.54 tumors per mouse), while the mice immunized with the FMBAAA-bovine serum albumin conjugate developed significantly fewer tumors (0.23 tumors per mouse, an incidence similar to that observed in

mice that were not exposed to dimethylbenzanthracene, but only to the promoter).

It thus appeared that immunization reduced the ability of dimethylbenzanthracene to induce skin tumors in these mice. Further experiments with larger doses of carcinogen will now be needed to assess the full extent of the protection that immunization can afford. In addition, protection of organs other than the skin will warrant investigation, and attempts to develop immunization regimens capable of conferring protection against other types of carcinogens present in the environment will be desirable.

It is premature at present to consider studying immunization of this type in humans, but such a possibility may deserve consideration in the future if further animal experiments demonstrate that immunization against environmental carcinogens is safe and that it protects the animals against naturally occurring tumors.

Selenium, Chemoprevention, and Breast Cancer—Daniel Medina, Baylor College of Medicine

In the past three years, we have investigated the effects of supplemental selenium on the induction of mouse mammary cancer. Our initial experiments confirmed an earlier observation by Schrauzer and his associates that a nontoxic dose of selenium added to the drinking water inhibited the mammary tumor incidence by 80 percent in mice carrying the highly oncogenic mammary tumor virus. Successive experiments demonstrated that selenium inhibited mammary tumor formation in three different strains of mice treated with chemical carcinogens. The percent inhibition of tumor incidence ranged from 42 to 85 percent depending on the dose of carcinogen and the mouse strain.

The mouse mammary tumor system is unique since it is characterized by a discrete morphological lesion which is a precursor to mammary tumors. These precursor lesions are termed preneoplastic to indicate that they are cell populations altered from normal but have not obtained the unique properties of progressive growth, a property possessed by neoplastic cell populations. Thus, the experimental animal model system offers the advantage of defining in a precise manner which stage in a multiple stage model of tumor formation is sensitive to selenium mediated inhibition.

In a series of experiments, we examined whether selenium inhibited the induction and/or expression of preneoplastic lesions which are induced by viral and chemical carcinogens. In these experiments, the mice were terminated before the appearance of mammary tumors and the mammary glands examined for discrete morphological lesions using a dissecting microscope. In three different strains of mice, selenium supplementation to the drinking water decreased the incidence of mice with preneoplastic lesions from 60 to 17 percent. Conversely, selenium supplementation did not inhibit the growth rate of established mammary tumors induced by viral and chemical carcinogens.

The potential benefits of firmly establishing the basis for selenium chemoprevention of cancer through an understanding of its mode of action are significant since it will help us understand the findings of epidemiological studies which have suggested an inverse correlation between crude environmental selenium levels and human breast cancer. It is reasonable and prudent to view the ultimate control of cancer as resulting from a combination of approaches. Within this context, chemoprevention may serve as one of the magic bullets in the armamentarium used to fight cancer.

Carcinogenesis and Cancer Prevention—Joseph DiPaolo, Chief, Laboratory of Biology, NCI Div. of Cancer Cause & Prevention

The identification of factors that lead to transformation is important to somatic cell genetics and to developing information critical to planning interventive measure to block or interfere with transformation leading to neoplasia, reverse the transformation process or eliminate or protect against carcinogenic risk...

One aspect of prevention of human cancer is the identification of potential human carcinogens. Fresh Syrian hamster cells respond to a number of organic and inorganic chemical carcinogens. A positive correlation of over 90 percent exists between carcinogenic activity of these compounds and their ability to produce transformation. Approximately 125 chemicals have been tested with the Syrian hamster quantitative bioassay system including such chemicals as vinyl chloride, beryllium, arsenic, asbestos, and bisulfate. Transformation can be inhibited or enhanced by biological modifiers or chemical treatment. Lymphotoxin, a lymphokine produced by mitogen or antigen stimulated lymphocytes, inhibits tumor cell growth in vivo and in vitro.

Guinea pig cell transformation is characterized by extended preneoplastic stages in vitro; the susceptibility of morphologically transformed cells to lymphotoxin develops during the penultimate stage or concomitantly with the ability of the cells to produce tumors. With the Syrian hamster embryo cell model, transformed colonies are recognizable four days after carcinogen treatment. Reduction in morphological transformation frequencies by lymphotoxin six days after carcinogen treatment is proportional to lymphotoxin concentration. Since transformation is equally diminished when lymphotoxin is present for the first three of six days post carcinogen, lymphotoxin irreversibly inhibits the first morphologic recognizable step of carcinogenesis.

We have also established a model for a carcinogenesis study using a readily available, well charac-

terized, virus free human diploid cell strain, MRC-5 cells derived from fetal male lung. Several chemical carcinogens and ultraviolet irradiation induced in vitro anchorage independent growth and in vivo lethal multicellular infiltrative growth of human MRC-5 cells.

In order to obtain reproducible results, it is imperative that cell growth is blocked just prior to DNA synthesis. A single carcinogen insult eight hours after release of MRC-5 cells from the metabolic block is followed within four-five weeks by formation of colonies in semi-solid agar medium. The anchorage independent MRC-5 cells, moreover, when injected intracranially into immunologically deficient homozygous nude mice, six-seven weeks post carcinogen exposure, produce progressive neurological dysfunction five-six weeks later accompanied by lethal multifocal multicellular infiltrating lesion.

Intracranial injection of non-treated MRC-5 cells did not induce abnormal changes in neurological function or affect the lifespan of the nude mice. The present investigation demonstrates for the first time carcinogen induced anchorage independent growth and in vivo lethality of a well characterized human diploid fibroblast cell strain and indicates the potential value of MRC-5 cell transformation as a new model for the study of carcinogenesis in human cells.

NEW PUBLICATIONS

"Cancer Staging Worksheets," developed by Scripps Memorial Hospital Cancer Center. Available in packages of 25 for each of 25 sites, in three part carbonless sets (medical records, tumor registry, physician), from Johnson Forms Management, P.O. Box 945, San Diego 92112. $8 per package, $10 with institution or group name imprint. Write for order forms.

"Community Cancer Programs in the United States: 1980-81," the delegate roster of the Assn. of Community Cancer Centers. Edited by Lee Mortenson and Celia Berdes. One page for each member institution includes names of delegate representatives, description of the cancer program for each. Single copies, $20; five to 10, $17.50; 11-20, $15; library discount 50 percent. ACCC Roster, 11600 Nebel St., Rockville, Md. 20852.

"Cancer Among Black Populations," edited by Curtis Mettlin and Gerald Murphy. Proceedings of the International Conference on Cancer Among Black Populations held at Roswell Park Memorial Institute May 5-6, 1980. Alan R. Liss Inc., 150 Fifth Ave., New York 10011. $24.

"Cancer Signals and Safeguards," edited by Gerald Murphy, with contributions from Roswell Park Memorial Institute scientists. PSG Publishing Co., Littleton, Mass. $22.50.

"Psychosocial Aspects of Cancer," edited by Jerome Cohen, Joseph Cullen and Robert Martin. Raven Press, 1140 Avenue of the Americas, New York 10036. $25.

"Advances in Polyamine Research," edited by Claudio Caldarera, Vincenzo Zappia and Uriel Bachrach. Raven Press, $55.

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, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

RFP NCI-CP-FS-11018-77

Title: *Support services for radiation and related studies*

Deadline: *May 18*

The Div. of Cancer Cause & Prevention of NCI, Environmental Epidemiology Branch, is seeking technical (non-professional) managerial and clerical support for its radiation studies program.

Prospective contractors must have experience and expertise in all phases of radiation studies, such as, the design of data collection documents, abstracting, interviewing, keying and editing data, recoding, tracing of members of established cohorts, procuring death certificates, creation and manipulation of computer files, and generation of basic statistics.

Personnel required include four full time permanent persons—one data collection manager, one programmer/analyst, one computer programmer and one coding/abstracting supervisor. The contractor must have or be willing to establish, at the time of submission of a proposal, permanently established offices within 50 miles of the NIH off-campus Landow Bldg., 7910 Woodmont Ave., Bethesda, Md. 20205, in which the Environmental Epidemiology Branch of NCI is located.

A mandatory requirement for small business subcontracting is included in this RFP.

Contract Specialist: Patrick Williams
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The Cancer Letter _Editor Jerry D. Boyd

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