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Young Takes Over Centers & Community Oncology, Says Biggest Problem Is Getting Adequate Funds

Robert Young started his new job this week, as associate director of NCI's Div. of Cancer Prevention & Control and director of the Centers & Community Oncology Program. He faces a wide range of issues and problems which have been developing over the past couple of years, some of which have

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In Brief

Hellman To Leave Memorial This Fall For Position As Dean, Vice President At Univ. of Chicago

SAMUEL HELLMAN will leave his position as physician in chief of Memorial Hospital this fall to become dean of the Univ. of Chicago School of Medicine, vice president of the university, and head of the Div. of Biological Sciences. "I'm very excited about the opportunity in Chicago, but I will be sad to leave Memorial, in terms of the institution itself," Hellman said. "It's a great research institution." Thomas Krizek, professor and chairman of the Dept. of Surgery at Chicago, has been acting dean. Hellman joined Memorial as physician in chief in July, 1983, after heading Harvard's Joint Center for Radiation Oncology. MSK President Paul Marks said a search committee will look for "the very best person we can find" to replace Hellman. "I think it is an extremely attractive opportunity for someone, made more so by Sam in his five years here." . . . **"THERAPEUTIC PROGRESS** in Urological Cancers" is the subject of an international symposium June 29-July 1 in Paris. Presentations will be made on ultrasound in early detection of prostatic cancer, and treatment of prostatic, bladder, renal and testicular cancer. The symposium is sponsored by the American Urological Assn. in collaboration with various European societies, EROTC, World Health Organization and SUNY (Buffalo). Contact AUA, 6750 West Loop South, Suite 900, Bellaire, TX 77401. . . . **GIFTS TOTALING** $1 million to the Susan G. Komen Alliance for Breast Disease, Treatment, Research & Education will be used to fund a chair in breast cancer research at the Univ. of Texas Southwestern Medical Center in Dallas. . . . **"CANCER UPDATE"** with reports on what is new in prevention, detection and treatment will be presented by the Providence Cancer Center at its annual cancer symposium April 29 in Portland, OR. Contact the center, 4805 N.E. Glisan, Portland, OR 97213, phone 503/230-6014.

Young: Where Centers Program Sits Should Not Influence Its Value

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placed on hold while the search for a new AD was being conducted. Those issues and problems include:

*Location within NCI of the Centers & Community Oncology Program. This has been debated for more than two years, with center directors pushing for either a move of the program out of DCPC and into NCI Director Vincent DeVita's office, or into a new division created especially for it. They feel they will never get a fair shake from a division whose mission primarily is cancer control and cancer prevention. They think centers deserve more visibility.

DeVita is considering a reorganization that would combine much of DCPC with the Div. of Cancer Etiology, leaving Centers & Community Oncology, with its Research Facilities Branch, Centers Branch and Community Clinical Oncology Program in another division. This division might also include the organizational headquarters for the Organ Systems Program, the Research Training Branch, and possibly elements from other divisions.

*Guidelines for recognition as a comprehensive cancer center. For the first time in about eight years, centers other than the 20 now officially recognized as comprehensive are asking about achieving that status for themselves. DeVita has asked the National Cancer Advisory Board, which wrote the original guidelines, to review their applicability now and determine if they should be modified or rewritten.

*Research facilities (construction/renovation). NCI's authority to award grants for construction and renovation of cancer research and clinical facilities has not been adequately funded since the mid-1970s, if it ever was. The latest review, by a panel convened by NIH, determined that institutions involved in biomedical research needed $2.5-3 billion over seven years to repair and expand the infrastructure (**The Cancer Letter**, March 4). The reauthorization bill introduced last week by Sen. Edward Kennedy would establish an NIH wide construction program, with no dollar limits except for the first year, $150 million. NCI would retain its separate construction authority, but for that to mean anything, Congress would have to be sold on funding it separately.

*CCOPs. The 52 awards made last year in the recompetition are coming up for continuation funding. Their reports on first year activities were due April 1; continuation awards will be made by June 1. If any of them are not performing up to standard, cutting them off might be one of Young's first unpleasant decisions.

Sometime during Young's first year on the job, recompetition for CCOP III will have to get under way. More decisions: Keep, drop or expand the cancer control requirement? Seek more money to increase the number of CCOPs? Add other new requirements? Bring the program closer to the cooperative groups by moving it to the Div. of Cancer Treatment, which administers the groups through its Cancer Therapy Evaluation Program? Or move CTEP to wherever Centers & Community Oncology lands?

DeVita, DCPC Director Peter Greenwald, the NCI Executive Committee and the NCAB all will be involved in those decisions, but whatever they are, Young will have to live with them.

*Organ systems. If administration of the program remains with Centers & Community Oncology, the new arrangement in distributing the grant portfolio around to other divisions, and taking over the tasks of the Organ Systems Coordinating Center, will have to be developed.

*Personnel. Several key positions are being filled on an acting basis. Permanent appointments will have to be made.

All of those are issues which can be resolved by the appropriate persons as required, Young believes. Some of them may not be as critical as they seem: "In my view, we need to do the kinds of things that will help centers achieve their goals. I'm not sure that where we sit will influence that very much."

The NCAB Centers Committee is working on most of the issues involving centers, and will meet later this month (April 26, in Chicago), to set the stage for a workshop to be held during the summer to develop final recommendations for presentation to NCI and the full Board. The committee will have an analysis of a survey in which individuals and organizations were asked to submit their views of what cancer centers, their missions and their organization should be.

Young said he is confident the NCAB will develop recommendations which will help the program go forward.

As for all the other problems and issues, they take second place to the issue of funding. He said he was especially con-

cerned that there is no money for facilities in the current fiscal year. "There are applications of high merit which have been reviewed and could be funded," Young said. "These grants have a tremendous multiplier effect, always generating a lot more money than NCI puts in."

Adequate funding for center core grants is also a concern, with centers again facing cuts from recommended levels, and possibly some cut entirely unless the budget is increased.

Young's previous job at NCI was chief of the Medicine Branch in the Div. of Cancer Treatment's intramural Clinical Oncology Program. DeVita called him one of the 10 outstanding cancer clinical investigators in the country when he announced the appointment. Young is particularly noted for development of new therapies for ovarian cancer and lymphoma.

Jerome Yates, Young's predecessor at director of Centers & Community Oncology, also is a clinician (and in fact returned to that role, as head of clinical research at Roswell Park Memorial Institute). During his six years at NCI, Yates frequently commented that he missed the contact with cancer patients.

Young intends to maintain that contact, and will continue to be involved with clinical research at the NIH Clinical Center, he said.

Reagan Reappoints Longmire To Third Term On President's Cancer Panel

President Reagan announced last week that he intended to reappoint William Longmire as a member of the President's Cancer Panel. The new term will expire Feb. 20, 1991.

This is Longmire's third three year appointment to the Panel, the first coming in 1982. The President last year named Chairman Armand Hammer to his third three year term, which will expire in 1990. The third member of the Panel, John Montgomery, received his second appointment in 1986, with the term to expire next year.

When their present terms expire, all three members will have served on the Panel longer than anyone previously had. The first chairman, Benno Schmidt, served two terms. Lee Clark, also a member of the first Panel after it was created by the National Cancer Act of 1971, served two terms.

Longmire, 74, is professor of surgery emeritus at the UCLA Medical Center.

HPV Vaccines Would Be Valuable And Are Feasible, Workshop Concludes

Human papillomavirus vaccines would be "highly valuable" and their development is feasible, although targeted development is premature at this time, a workshop convened to consider prospects for such vaccines and related immunotherapies concluded.

The workshop, held last fall, was sponsored by the Biological Carcinogenesis Branch of NCI's Div. of Cancer Etiology and by the Microbiology & Infectious Diseases Program of the National Institute of Allergy & Infectious Diseases. Hilary Koprowski, director of Wistar Institute and chairman of the DCE Board of Scientific Counselors, was cochairman of the workshop along with King Holmes, Univ. of Washington, cochairman for NIAID.

A report on the workshop was presented at the last meeting of the DCE Board by Alan Schreier, program director for DNA virus studies in the Biological Carcinogenesis Branch. The report follows:

Stage Is Set

Since the recognition that human papillomavirus (HPV) infection may have strong etiological association with anogenital carcinomas, e.g., cervical and penile cancer, the possibility of vaccines against papillomaviruses has been raised as one of the ultimate goals of research. Dramatic advances have recently occurred in knowledge of these viruses which may have set the stage for the development of vaccines and related immunotherapies. For example, specific HPV types have been found to be usually associated with severe dysplasias and cervical carcinomas (HPV types 16, 18, 31, 33, 35, 39 and 45); whereas, other types are found usually associated with condylomas (genital warts) and mild dysplasias (types 6, 11, 42, 43, and 44)).

Certain viral genes (the E6 and E7 genes in HPV 16) and their protein products have been implicated in the maintenance and possible development of transformed cells. Viral proteins such as E6 and E7 have recently been produced in the laboratory via recombinant DNA technology. Thus, NCI and NIAID staff cosponsored this workshop to assess whether it was time to actively promote the development of vaccines and related immunotherapies and, if not, to determine the barriers to such development.

Several prominent issues involved in the

development of HPV vaccines and immunotherapies were identified by the staff and posed to the workshop participants. Speakers at the workshop provided background information on these issues. Drs. King Holmes, Richard Reid and Richard Reichman presented data on the epidemiology and current and experimental treatments of papillomavirus associated diseases. Dr. Bettie Steinberg gave an overview of the basic biology of these viruses. Drs. Anthony Faras and Felix Wettstein provided information on current vaccine work and animal models. Dr. Gerald Quinnan of FDA discussed regulatory issues and Dr. Thomas Broker gave a summation. The workshop concluded with a general discussion led by Dr. Koprowski. Summarized below are the views of the workshop participants on the issues.

Are papillomavirus vaccines desirable?

Safe and effective papillomavirus vaccines would be highly valuable. In the U.S., the incidence of invasive cervical cancer (14,000 new cases a year) is greater than the incidence of leukemia in women (11,000 cases a year). This annual incidence continues in spite of the widespread use of pap smear screening. In some developing countries where pap smear screening is uncommon, cervical cancer rates can be five times greater than the U.S. rate and can exceed the rates for all other female cancers including breast cancer. A vaccine would be particularly useful in such countries.

Control of the putative oncogenic sequelae of papillomavirus infection is only one reason for a vaccine. The "benign" papillomavirus lesions, genital warts or condylomas, are considered to be a sexually transmitted disease. About a million new cases requiring treatment are diagnosed each year in the U.S. About 20 percent of the cases are resistant to conventional therapy.

The workshop participants felt that the initial goal for papillomavirus vaccines should be the prevention of condylomas and mild dysplasias. Reduction in cancer rates would then come as a future benefit. Condylomas and mild dysplasias were targeted first because they are early manifestations of HPV infections and are significant public health problems in their own right. Their incidence also appears to be increasing. Conversion of condylomas and dysplasias to carcinoma has a probable latency of five to 20 years and requires additional cofactors. Thus, the testing of a vaccine using the endpoint of carcinoma or severe dysplasia is not practical. The significant personal and financial costs of treatments for condylomas and dysplasias and of frequent pap smears also argues for the development of vaccines. However, even if a safe and effective vaccine were available, a number of issues need to be addressed before a vaccination program could be started. First, it is not clear who should be vaccinated: only females, or males and females? Just high risk populations or the general population? At what age should vaccination occur? In childhood? Adolescence? These are issues that arise with all vaccines against sexually transmitted disease agents.

What basic science questions need to be resolved before the rational development of vaccines and immunotherapies can commence? What types of vaccines would be desirable?

Workshop participants overwhelmingly agreed that targeted development of HPV vaccines was premature at this time. The best ways to prepare HPV vaccines are not known due to limited knowledge of the host immune response to papillomaviruses. In humans, anogenital lesions start as genital warts, either flat or exophytic, and then may progress to various levels of dysplasia. These lesions then either stabilize or regress with relatively high frequency. Past studies in animals and in human patients have implicated the cellular immune system in this stablization and regression. Failure of the immune system is probably an important factor in the subsequent progression of dysplasias to carcinomas.

Since regressions occur in human dysplasias as well as in at least one animal system (cottontail rabbit papillomavirus induced lesion in the natural host), it may be feasible to induce both immunity in uninfected individuals and regression in patients. However, many questions need to be answered. The viral and cellular epitopes involved in the initiation of the cellular immune response have not been characterized. Only the E6 viral protein has been suggested as a possible mediating protein due to its partial localization in the cellular membrane. The role of humoral antibodies to viral antigens in the progression (through the masking of epitopes) or regression of lesions has not been defined. Preliminary studies have identified specific antibodies to the viral capsid proteins in condyloma patients; however, they appear to be absent in patients with vulvar carcinomas. Some of these cancer patients appear to have antibodies to the E7

and possibly other HPV proteins. These results suggest possibly different host responses to early vs. advanced disease. An additional complication is the multiplicities of genital HPV types which may require the production of specific vaccines if group specific immunogens cannot be found. The answers to these questions will determine the potential types of HPV vaccines, and their routes and schedules of administration. Few of the needed immunological studies have been performed to date due in part to the lack of purified viral proteins.

What work is currently being done on human and animal papillomavirus vaccines?

Only animal vaccines have been investigated. In 1962 Evans and Ito showed that a partial immunity to the cottontail rabbit (or Shope) papillomavirus could be induced in native rabbits by the administration of a crude vaccine extracted from warts on infected rabbits. A similar vaccine has been used to protect cattle herds from bovine papillomavirus induced warts on the udders of cows. The efficacy of the cattle vaccine varies substantially from lot to lot due to the heterogeneity of the source material.

Live, attenuated animal papillomavirus have not been developed due to the lack of in vitro propagation systems. Both human and animal viruses cannot yet be grown in cell culture. Recently, a subunit vaccine for bovine papillomavirus (BPV) has been developed. Both the major (L1) and minor (L2) capsid genes of BPV have been cloned and expressed in bacteria. Both proteins produced specific antibodies but the L1 generated antisera was better able to neutralize BPV in vitro. Subsequently, the L1 protein was used as a vaccine against wart disease in cattle and was found to be up to 90 percent effective as judged in direct challenge studies.

How will HPV vaccines be tested? What regulatory issues need to be addressed for FDA approval of HPV vaccines?

Workshop participants strongly felt that the development and testing of HPV vaccines for both scientific and regulatory purposes would require extensive use of animal models. Model vaccines can be developed and tested by direct challenge in animals. Human vaccines could be initially tested for safety and antigenicity and possible for efficacy if an animal were found that could be infected by the human virus.

The most widely used animal model currently is the bovine papillomavirus type 1 due to the availability of both large quantities of virus from cattle warts and an in vitro cell transformation assay. However, the disease created by this virus, a fibropapilloma, does not resemble the human disease which is purely epithelial in nature. The best known animal model for papillomavirus associated human neoplastic disease is the cottontail rabbit papillomavirus host system. This virus produces purely epithelial lesions which have a similar progression/regression profile as human lesions. In addition, the genes in the rabbit virus which have been implicated as potential transforming genes are the same as those identified in human viruses, namely E6 and E7. The virus rabbit model has been underutilized in the past few years.

Very recently, two simian papillomaviruses (SPV 1 and SPV 2) have been identified from the rhesus and colobus monkeys, respectively. These primate virus host systems may potentially be better models of human genital disease. Both the rhesus and colobus viruses produce cutaneous warts; however, the rhesus virus was also found associated with a penile carcinoma that had metastasized. The colobus virus has significant homology with human papillomavirus types 5, 8, and 12 which are associated with a rare squamous carcinoma of the skin. Experiments were described in the workshop to test whether rhesus monkeys are susceptible to infection by HPV type 11, the only human virus that currently can be produced in sufficient quantity in the laboratory for such studies.

These studies are in progress. Worshop participants strongly recommended the promotion of more studies using animal models.

*The Board of Scientific Counselors approved the concept of new grants to support development of HPV animal models (***The Cancer Letter***, March 4). The RFA to solicit those applications is being written.*

How effective are current therapies for HPV infections and dysplasias?

Conventional treatment modalities for genital condylomas and dysplasias generally involve destruction or removal of the infected tissues. The various procedures include cryosurgery, podophyllin treatment, electrocautery, laser surgery and biopsy excision. With these treatments, approximately 80 percent of the cases of condylomas and mild dysplasias can be controlled. The remaining 20 percent of cases represent a therapeutic challenge. A new ablation treat-

ment with the CO_2 laser combined with adjuvant treatment with a topical 5-fluorouracil cream appears to give good results with these resistant cases. Conventional treatments usually remove only the clinically visible lesions. Extensive fields of latent or subclinical infection are often found in both treated and untreated patients. This in part explains the high recurrence rate of warts after treatment and the difficulty in preventing its spread as a sexually transmitted disease.

Recently, interferons have been used experimentally to treat HPV lesions. Initial studies using various types of interferons which were injected intralesionally have shown that up to 50 percent of injected warts resolve within 16 weeks. Further studies of interferon and other immune modulators such as interleukin, either single or in combination, were recommended. In addition, recent work on antiviral drugs prompted by the AIDS epidemic has led to the development of many candidate drugs. The workshop participants recommended that such drugs be tested for antipapillomavirus activity. An appropriate screening assay needs to be developed to test the drugs, but, if one were found, it could become another therapeutic option.

In summary, the workshop participants made a number of recommendations on how NCI and NIAID could promote the development of HPV vaccines and immunotherapies. Although targeted studies leading to HPV vaccines were felt to be premature, they strongly recommended more basic studies of the host immune response to papillomavirus infections and their oncogenic sequelae in both humans and animal models.

Such studies are needed for the rational design of vaccines and immunotherapies. The Biological Carcinogenesis Branch is actively promoting immunological studies through the encouragement of collaborations between current grantees and established immunologists. Animal studies were particularly stressed since they can also be used for vaccine development and testing by direct viral challenge.

In the therapeutic area, continued exploration of immune modulators as a treatment modality should be encouraged as well as the investigation of new antiviral drugs. Specific resources that may be needed by investigators in the future include purified viral proteins and antibodies specific to these proteins.

Good News For Women Who Booze-- CDC Finds No Breast Cancer Increase

Recent epidemiologic studies implicating consumption of alcoholic beverages as an etiological factor in breast cancer stimulated an effort by the Centers for Disease Control to take a new look at the data. The finding, as reported at the American Cancer Society Science Writers Seminar: There appears to be no increased risk of breast cancer with alcohol use.

Susan Chu of CDC said the new study examined breast cancer and alcohol association from the CDC cancer and steroid hormone study, a multicenter, population based, case control study.

Cases were 3,252 women aged 20-54 with newly diagnosed breast cancer identified between August 1981 and Dec. 1982 through population based tumor registries. Controls were 2,971 women selected by randomly phoning households from the same geographic areas as the cases. Participants were interviewed in their homes using a pretested, standard questionnaire focusing on reproductive and contraceptive histories, use of medical care, and personal characteristics and habits.

"We found no increased risk of breast cancer with alcohol use," Chu said. "Women who drank any alcohol had a risk of breast cancer of 1.0 compared with nondrinkers. Risk estimates did not increase appreciably with the amount of alcohol consumed: risk estimates for women drinking 8 to 14, 15 to 21, and 22 drinks or more per week were 1.1, 1.0, and 1.1; respectively. None of these risks were statistically significant. There were no notable differences by type of beverage (beer, wine, or hard liquor) or within specific risk factor subgroups (e.g., younger vs. older women).

"Although some previous reports agree with our findings, several recent, well designed cohort studies have demonstrated increased risk, even at moderate levels of alcohol intake. We have difficulty explaining our discrepant finding.

"We carefully examined several sources of bias. Although potentially present, biases were unlikely to have completely masked a true association. Probably the most serious limitation of our study is the lack of exposure time data, i.e., when alcohol use first began and the total time of alcohol use. Since many risk factors for breast cancer seem to exert their effects at

relatively young ages, the effect of drinking at younger ages needs to be explored. Although most studies have used average number of drinks or grams of alcohol per day or week to assess dose response, a more appropriate measure of dose may include total years of drinking. Future investigations specifically designed to examine the relationship of alcohol consumption and breast cancer should include detailed exposure histories of alcohol consumption throughout a woman's life.

"The consistency of an association between alcohol consumption and the risk of breast cancer among several recent cohort studies is compelling. Although the increases in risk were small, suggestions of dose response effects were evident in all the studies. However, the magnitude and dose response effects were not consistent over all subgroups within and between the studies.

"In light of negative findings by us, as well as others, and the absence of an established biological mechanism to explain the role of alcohol in the etiology of breast cancer, conclusive statements or general recommendations concerning the relationship between alcohol consumption and breast cancer seem premature. Further studies are needed, with more refined measures of lifetime alcohol consumption and careful consideration of other factors related to alcohol consumption which may explain the positive findings."

William Fletcher, professor of surgery at the Univ. of Oregon, reported his studies in management of advanced breast cancer which questions current accepted practices involving use of tamoxifen.

"We have demonstrated that patients with advanced breast cancer treated by total endocrine ablation (oophorectomy and adrenalectomy) followed by chemotherapy when and if necessary live three or more times longer than such patients treated by chemotherapy alone.

"Breast cancer patients whose disease is progressing on the antiestrogen tamoxifen will respond to stopping the tamoxifen and removing the ovaries and adrenal glands or removing the ovaries and suppressing the adrenal glands with aminoglutethimide.

"The entiestrogen tamoxifen can cause an increase in endogenous estrogen which then overcomes the beneficial effect of the tamoxifen.

"The mechanism by which the endogenous estrogen increase occurs is stimulation of the adrenal gland to put out dehydroepiandrosterone (DHEA). DHEA is a steroid molecule which is then changed into estrogen by the enzyme aromatase which occurs in liver, muscle and fat. The affinity of estrogen receptor in the breast cancer tissue is approximately 10 times that of tamoxifen so that even a slight increase in the endogenous estrogen can overcome the beneficial effect of tamoxifen.

"These findings indicate that much more study is required of the impact of tamoxifen on the neuroendocrine system.

"Patients on tamoxifen should be followed by serial determinations of at least DHEA and estrone. Patients whose disease is progressing on tamoxifen should have the drug stopped and be considered for total endocrine ablation/suppression.

"Clinical trials utilizing tamoxifen should be designed in such a way that any possible deleterious effect of the tamoxifen would become apparent early in the course of the trial."

Describing the study on which he based the above conclusions, Fletcher said:

"We subjected 287 consecutive patients with metastatic carcinoma of the breast to total endocrine ablation followed by chemotherapy when and if they needed it. Median survival of all patients was over 40 months which compares very favorably with the 13.5 months which can be expected from the time of recurrence with any combination of chemotherapy. ER positive patients enjoyed a median survival of over 60 months and ER positive premenopausal patients had a median survival of over 70 months. A number of these patients are still alive and have never been on chemotherapy.

"Our second major contribution has to do with the effect and mechanism of action of tamoxifen. Some patients are made worse by the initiation of tamoxifen therapy which is generally believed to indicate that the patient does have a hormone sensitive tumor and that if you continue to treat them they may get better. Such is not the case. Most patients who are made worse by tamoxifen live only a few months. If, however, these patients are withdrawn from tamoxifen and subjected to a total endocrine ablation or suppression, they uniformly respond for prolonged intervals.

"To determine why this happens we measured the DHEA, estrone, and estradiol follicle

stimulating hormone, and the luteinizing hormone in 16 patients initiating or on tamoxifen therapy. We found that somehow by blocking the estrogen receptor in the central nervous system the adrenal gland was stimulated to pour out massive amounts of DHEA. This is a steroid precursor molecule which can then be changed by the enzyme aromatase in muscle, fat, liver and even the tumor itself into estrogen.

"We believe that this is the mechanism which stimulates the cancer in some patients started on tamoxifen. As you know, the NCI consensus conference recommended that postmenopausal ER positive patients be placed on tamoxifen. There is also a large number of cooperative group clinical protocols which call for tamoxifen in each arm of the study. Since tamoxifen may have a survival disadvantage for some patients, protocols should be designed so that this would become apparent. Moreover, we need to measure at least DHEA and estrone in such patients.

"Should the DHEA and estrone rise and the patient's clinical condition deteriorate, they almost certainly will respond to discontinuing tamoxifen, removing the ovaries, and suppressing or removing the adrenal glands.

"We are currently studying the effect of the potent synthetic progestational agent megestrol acetate (megace) on patients with metastatic breast cancer. It appears to work in an opposite fashion to tamoxifen. It lowers DHEA and therefore circulating estrogens, presumably through an effect on the pituitary or the hypothalamus.

"In summary, we believe that we have made some important strides in unravelling an enormously complex subject which is of vital interest to anyone who has or is involved in the management of hormone sensitive cancer."

Gary Stoner, Medical College of Ohio, reported on studies which indicate that ellagic acid is a natural inhibitor of chemically induced cancer.

"Our laboratory has been investigating the ability of ellagic acid (EA), a naturally occurring plant phenol found in various fruits and nuts (such as strawberries, grapes and Brazil nuts), to inhibit chemically induced carcinogenesis. More specifically, we have been studying EA's inhibitory effects on carcinogenesis induced by at least three classes of chemicals: polycyclic aromatic hydrocarbons (PAH), nitrosamines and aflatoxin.

"Initial studies, by other investigators, suggested that EA might protect against chemically induced cancer, since it was shown to have an exceptional ability to inhibit PAH induced mutations in bacteria and in mammalian cells. We examined the effect of EA on the DNA damaging effects of PAH in cultured mouse lung tissue and found that EA inhibited both the metabolism and DNA damaging effects of PAH by as much as 45-70 percent. Subsequently, EA was shown to inhibit PAH induced lung cancer in mice. In addition, we observed that EA inhibited the ability of PAH to induce DNA damage in cultured human lung tissue by 24-77 percent, indicating that EA could also act as an inhibitor of PAH induced lung cancer in man.

"In a separate study, we tested EA for its effect on the ability of the nitrosamine NBMA to induce genetic damage and cancer in the rat esophagus. NBMA was chosen for the study since it is found in the diets of Chinese living in regions where there is a high incidence of esophageal cancer. In tissue culture, EA inhibited the ability of NBMA to induce genetic damage in the rat esophagus, although the inhibition was not as extensive as with the PAHs. For the in vivo studies, rats were randomized into groups of 30 and placed on semipurified diets containing EA two weeks prior to, during, and seven weeks after treatment with NBMA. The rats were harvested at both 20 and 27 weeks. Histopathological analysis of esophageal lesions showed that EA inhibited the induction of preneoplastic lesions, as well as the formation of papillomas and carcinomas. EA also inhibited the ability of NBMA to induce genetic damage in cultured human esophagus, suggesting that it could be an inhibitor of nitrosamine induced human esophageal cancer."

EA also inhibited the mutagenicity of aflatoxin on both rat and human lung tissues, Stoner said.

Responding to a question from a hopeful writer, Stoner said that EA, although present in grapes, is not in grapejuice or wine.

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