**Meeting Report**

Vitamins and Cancer Prevention

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A meeting took place from October 30 to November 1, 1991, at the Pennington Biomedical Research Center, a new facility of Louisiana State University located in Baton Rouge, Louisiana. The meeting focused on the mechanisms of action and the epidemiology of vitamins with cancer prevention potential. The meeting was opened by George Bray, Director of the Center, who outlined the goals of the new center, which include nutritional research in diabetes, cardiovascular diseases, cancer, behavior, public health, and clinical food sciences. A number of programs have recently been initiated, while others are in different phases of planning. Donna Ryan, Associate Executive Director of the Center, welcomed the participants in the name of Mervin Trail, Director of the newly established Louisiana State University Cancer Center.

The keynote speaker, Peter Greenwald (National Cancer Institute, Bethesda, MD), called attention to the increased awareness in the scientific community of the role of nutrition in cancer causation, reflected by the marked increase in funding of nutrition research by the National Cancer Institute, covering studies of dietary patterns and food groups (approximately $30 million in 1991), single-nutrient chemoprevention (approximately $37 million), and nonnutrient chemoprevention (approximately $21 million). He illustrated a number of research activities funded by the institute, emphasizing their prevention aspects, and referred to the fact that recent research continues in several fields, from epidemiology to molecular biology. An example of this interaction is the model of colon carcinogenesis developed by Vogelstein and co-workers, the multistep, multifactorial nature of which illustrates the many opportunities for prevention research. He noted the need to fund nutrition research adequately; budget allocations are not commensurate with research needs and opportunities for progress, given that 35% of cancers are attributed to diet.

Session I on the mechanisms of action of vitamins in cancer prevention, was chaired by William Pryor (Louisiana State University, Baton Rouge, LA). He described the cascade of chemical reactions related to oxidative stress and its likely role in carcinogenesis. He also emphasized the role played by antioxidants in maintaining the delicate balance that tends to prevent free radical injury to cell membranes, proteins, and DNA. He described some of the biomarkers that can be used to assess oxidative stress in clinical trials and related studies.

He pointed to a growing feeling by the scientific community that recommended daily allowances of antioxidant vitamins are suboptimal in light of their role in preventing cancer, heart disease, cataracts, and other chronic diseases. Adrienne Bendich (Roche Vitamins and Fine Chemicals, Nutley, NJ) discussed the many immune functions that require antioxidant vitamins and pointed to the fact that a common denominator of many carcinogenic influences (i.e., smoking, UV light, age) is some degree of down-regulation of the immune system. The role of vitamin B6, ascorbic acid, folic acid, and β-carotene in enhancing the immune response was discussed.

John Bertram (University of Hawaii, Honolulu, HI) presented evidence that the ability of retinoids and carotenoids to inhibit carcinogen-induced neoplastic transformation in 10T1/2 cell cultures is strongly correlated with their ability to up-regulate intercellular gap junctional communication. In other studies enhanced junctional communication was shown to be associated with enhanced growth control. Together these results lead to the proposal that retinoids and carotenoids function as cancer-preventive agents by increasing the ability of adjacent nontransformed cells to suppress the growth and transformation of carcinogen-initiated cells. Both types of compounds increased expression of the gap junction gene connexin 43 in 10T1/2 mouse cells and in human keratinocytes and dermal fibroblasts, suggesting a unifying mechanism of action for these chemopreventive agents in epithelial and mesenchymal cells.

Session II on epidemiology was chaired by Pelayo Correa (Louisiana State University Medical Center, New Orleans, LA), who emphasized the consistency of international epidemiological investigations in reporting that the frequent ingestion of fresh fruit and vegetables reduces the risk of cancer. Some of the mechanisms of action are not well understood, and nutrients as well as nonnutrients may play a role, but sufficient data have accumulated to justify intervention research. Epidemiological studies showing a prominent role for antioxidant vitamins, especially vitamin C in Louisiana, were reported in the presentation and covered in more detail in a poster prepared by Elizabeth Fontham (Louisiana State University Medical Center, New Orleans, LA). JoAnn Manson (Harvard Medical School, Boston, MA) reviewed available cohort studies that show consistently protective effects for β-carotene-containing foods but less clear results for other vitamins. Larry Kolonel (University of Hawaii, Honolulu, HI) summarized epidemiological studies of cancer of the lung, prostate, bladder, thyroid, and endometrium and malignant melanoma in the multiethnic population of Hawaii. This population laboratory allows evaluation of the cross-cultural consistency of the findings. Although specific protective effects of any given vitamin were detected in subsets of the data, the most significant and constant finding was seen when all fresh
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vegetables were analyzed as a group. The Hawaiian experience indicates that these foods have a substantial potential for cancer risk reduction: 29% for \( \beta \)-carotene in the case of lung cancer in males and 40% in women; for all vegetables the corresponding figures are 34% and 47%.

Session III on the use of vitamins in precancerous lesions was chaired by Donna Ryan (Pennington Biomedical Research Center, Baton Rouge, LA). She provided the clinical perspective. She commented on the strong influence of the society at large (as opposed to the scientific community) in adopting vitamin use for the prevention of cancer and chronic diseases. She provided examples of chemoprevention trials of precancerous lesions. She pointed to new ways in which chemopreventive agents may have antineoplastic potential, as in the case of tretinoin, which induces terminal differentiation of neoplastic cells, resulting in complete remission of acute promyelocytic leukemia. The results in general forecast an expanded role for vitamins in cancer prevention and chemotherapy. Harinder Garewal (University of Arizona College of Medicine, Tucson, AZ) provided an overview of studies of retinoids, carotenoids, and vitamin E in oral leukoplasia. \( \beta \)-Carotene at 30 mg/day was successful, producing a 70% response rate in an initial study. A similar response rate is being observed in a follow-up trial of longer duration, which is now underway. Two posters corroborated the finding. Richard Brandt (Medical College of Virginia, Richmond, VA) and co-workers reported a 60% partial or complete resolution of oral leukoplasia in patients from Virginia who received antioxidant vitamins. S. Tomia and co-workers (University of Genoa School of Dentistry, Genoa, Italy) reported a 44% objective response rate in patients receiving 90 mg/day of \( \beta \)-carotene. Douglas Heimburger (University of Alabama, Birmingham, AL) reported on ongoing trials using bronchial epithelium-related end points, showing that retinoids and a combination of folic acid and vitamin B\(_2\) reduce the severity of bronchial metaplasia and atypia. He illustrated the bias toward the null hypothesis resulting from the statistical regression to the mean and gave examples of techniques to minimize it. Current trials are utilizing end points that are presumably earlier and more sensitive than classical histopathology, such as ploidy, micronuclei, DNA adducts, epidermal growth factor, cytokeratins, and others. Because of the poor prognosis of lung cancer, greater emphasis should be placed on chemoprevention research. A poster by Geert van Poppel and co-workers (TNO Toxicology and Nutrition Institute, Zeist, the Netherlands) reported on the value of intermediate end points in the chemoprevention of lung cancer. Smokers given \( \beta \)-carotene had counts of micronuclei which were 27% lower than those of the placebo group. John DiGiovanna (National Cancer Institute, Bethesda, MD) reported on the treatment of xeroderma pigmentosa patients having multiple skin cancers with doses of isotretinoin (0.5 mg/kg/day) that were 4 times lower than in previous trials. The frequency of new cancers decreased in five of seven patients treated. Charles Butterworth (University of Alabama, Birmingham, AL) utilized case-control studies of cervical dysplasia to examine the interaction between folic acid deficiency and other etiological factors. He reported that patients infected with papilloma virus have a 5 times greater risk of dysplasia if they are in the two lowest tertiles of RBC folate content. These findings suggest that folate deficiency facilitates the incorporation of human papilloma virus genomes into the host's DNA at folate-sensitive fragile sites. A significant reduction of cervical cancer could be achieved through improved nutritional intake of folate. Further information on the role of folate was provided by Bret Lashner (University of Chicago, Chicago, IL), who studied the development of dysplasia and carcinoma of the colon in patients with ulcerative colitis. Patients with colon cancer had significantly lower folate levels. Folate supplementation decreased the incidence of dysplasia. Patients with ulcerative colitis are frequently treated with sulfasalazine, a competitive inhibitor of folic acid. The evidence of the role of folic acid deficiency in colon carcinogenesis needs to be further elucidated, but ethical considerations have led to universal supplementation with folic acid in patients treated with sulfasalazine.

Session IV on vitamins C, E, and B\(_6\) was chaired by Larry Machlin (Roche Vitamins and Fine Chemicals), who reviewed the complex functions of these vitamins as antioxidants, blockers of nitrosation reactions, enhancers of immune response, participants in detoxifying reactions, and protectors of cell membranes. Synergistic interactions, food sources, and doses were reviewed. Most Americans are ingesting less than the recommended daily amounts of these vitamins. George Sobala (St. James University Hospital, Leeds, United Kingdom) reported on studies of the dynamics of ascorbic acid excretion into the gastric cavity and its relationship to gastritis and possibly gastric neoplasia and preneoplasia. Ascorbic acid injected i.v. is rapidly secreted into the gastric juice, and this secretion is blocked by *Helicobacter pylori* infection. Ascorbic acid levels in gastric juice are low in the presence of atrophic gastritis, but total nitrosocompound levels are not elevated. Ascorbic acid appears to play an important role in gastric physiology, and its deficieny at the level of the gastric mucosa may have a role in carcinogenesis, as previously postulated. Gladys Block (University of California, Berkeley, CA) reviewed the literature evaluating the anticarcinogenic role of vitamin C. She noted that nature has packaged several antioxidant vitamins in the same foods and that what is selected for reporting in epidemiological studies often depends on the interest of the investigators. The epidemiological evidence for a protective role of vitamin C is very strong for non-hormone-dependent cancers, especially those of the stomach, esophagus, oral cavity, and pancreas. All recent analysis of breast cancer studies found a significant protective effect for breast cancer. She commented on the inadequacy of the intake of antioxidant vitamins in large segments of the U.S. population. Twenty-five percent of the population ingests less than 40 mg/day of vitamin C. Very low serum ascorbate levels (at or below 0.3 mg/dl, near the scurvy range) are found in 10% of white females, 15% of white males, and 20-30% of black men. Clement Ip (Roswell Park Memorial Institute, Buffalo, NY) discussed the effects of the different tocopherols on experimental carcinogenesis. Vitamin E prevents carcinogen-induced oral cancer in hamsters and 7,12-dimethylbenz(a)anthracene-induced breast cancer in rats on a high-fat diet. Vitamin E is a powerful antioxidant that may potentiate the activity of other anticancer agents such as selenium. Paul Knekt (Research Institute for Social Security, Helsinki, Finland) reviewed the epidemiological evidence for vitamin E in human...
cancer and pointed out the difficulties in adequately evaluating the intake of this vitamin. A large nested case-control study in Finland demonstrates an excess of cancer in patients who had low serum values of vitamin E at the beginning of the study. The excesses were mostly in cancers of the stomach and pancreas as well as melanoma. There were no excesses in tumors of the ovary, breast, and endometrium. Metaanalysis of epidemiological studies have shown excess cancer of all sites, as well as lung and colorectum, in subjects with low intake. The largest case-control differences are seen in nonsmokers. Chemoprevention trials are ongoing. Gerald Litwack (Jefferson Cancer Institute, Philadelphia, PA) discussed the role of vitamin B6 in inhibiting glucocorticoid binding to DNA.

The last session on vitamin A and β-carotene was chaired by Norman Krinsky (Tufts University, Boston, MA), who reviewed the experimental work on the prevention of cancer with vitamin A and carotenoids, some of which lack pro-vitamin A activity. In addition, carotenoids are effective in preventing genotoxicity or malignant transformation in cell culture systems. Richard Moon (IIT Research Institute, Chicago, IL) presented data on inhibition by vitamin A and retinoids of experimental tumors of the breast, lung, and urinary bladder. Hormonal manipulation combined with retinoid administration worked synergistically in inhibiting mammary carcinogenesis. Tom Moon (University of Arizona, Tucson, AZ) reported on ongoing clinical trials that have shown a response to retinoid administration of approximately 70% in actinic keratosis, 50% in keratoacanthoma, and 100% in basal cell carcinoma. Encouraging responses have also been reported for cervical dysplasia and bladder tumors. He emphasized the need for additional chemoprevention research, which is feasible in human populations and promises to throw light on the mechanisms of carcinogenesis in humans. The last formal presentation was by Regina Ziegler (National Cancer Institute), titled "Does β-carotene explain why reduced cancer risk is associated with vegetable and fruit intake?" She described methods of evaluating the independent effects of dietary constituents, the intake of which is moderately correlated, such as carotenoids, ascorbic acid, folate, and fiber. She commented on ongoing efforts in this direction utilizing existing large representative data sets, liquid chromatography to separate individual carotenoids, and updated food composition tables. She also emphasized potential for prevention, which may reduce the risk of cancer by 15–30% overall and 30–50% in populations with inadequate diets.
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