time to spend with his four children and six grandchildren.

LeMaistre departs M. D. Anderson at what he considers "the most exciting time in the history of cancer. We are on the verge of pushing so many fundamental basic science discoveries to the bedside that will either improve cancer therapy or prevent cancer. All the fundamental tools are emerging to do this."

In particular, he cites developments in the identification of molecular markers for cancer, which ultimately may lead to more effective therapies and to new approaches to prevention.

Though he leaves open the possibility of continued involvement in cancer control, LeMaistre clearly envisions a low-profile role in the future.

"I'll be involved to the extent that I can be of help," he said. "I'm not actually a crusader. I have great confidence that an informed public will make the right decisions. I might remain involved in education and in trying to get the facts, as they really are, to the public."

If he could write his own epitaph, LeMaistre would offer a simple assessment of his life.

"I've been blessed. That's all," he said. "When you have the opportunities that I've had, that's far more than anyone has a right to expect. Every one of them has been different, and each one has been enjoyable."

To his successor, John Mendelsohn, M.D., former chairman of medicine at Memorial Sloan-Kettering Cancer Center in New York, LeMaistre has only a few simple insights to offer.

"Remember that the accomplishments of this institution have always been a team effort. To be part of a team is essential. Be a leader, if that is appropriate," said LeMaistre.

— Charles Bankhead

Is Chemoprevention Overrated or Underfunded?

Researchers in the field of diet and cancer seem to repeatedly prove the adage, "an ounce of prevention is worth a pound of cure." Diet studies spanning the last 15 years presented at the most recent American Association for Cancer Research meeting in Washington, D.C., led to the same conclusion as an earlier landmark report: one-third of all cancer deaths are avoidable by changes in diet.

But trying to isolate the exact substances in food that are beneficial is not easy — as shown by the mixed results of chemoprevention trials. Some investigators believe that the best way to proceed is food supplementation trials — giving people kale and carrots, rather than beta carotene pills. But others question whether chemoprevention trials are worth the time and money, because the lack of intermediate biomarkers that predict cancer has made them long and costly.

Dramatic Shift

The association between diet and cancer deaths is well established. There has been a dramatic shift in the focus of cancer prevention in recent years, however, from an emphasis on the adverse effects of fat and other dietary components, to the importance of the positive effects of fruits and vegetables.

"The most compelling evidence of the last decade has indicated the importance of protective factors, largely unidentified, in fruits and vegetables," said Walter C. Willett, M.D., Dr. P.H., chairman of the Department of Nutrition at Harvard School of Public Health, and a speaker at AACR's symposium on nutrition and cancer in April.

Willett amassed diet data accumulated since the 1981 landmark report on cancer deaths in the United States by Doll and Peto. Doll and Peto estimated that 35% of cancer deaths in the United States were avoidable by changes in diet, but added that this percentage might be as low as 10% or as high as 80%. Willett, reviewing studies from the intervening 15 years, came up with a similar estimate — about 32% of cancer deaths are avoidable by changes in diet — but within a narrower range, 20% to 42%.

Both reports list avoidable deaths by organ site and calculated identical percentages for all sites, with the exception of colon and prostate. Willett estimated that 70% of colon cancer deaths are linked to diet, compared with Doll and Peto's estimate of 90%, because of clear evidence since 1981 that physical activity plays an important protective role in colon cancer. (Red meat and animal fat appear to be the dietary culprits most strongly associated with colon cancer).

As for the prostate discrepancy, in 1981 there was not enough evidence to link diet and prostate cancer, so Doll
and Peto made no estimate. Studies since then led Willett to conclude that as many as 75% of prostate cancer deaths are avoidable by diet. Animal fat and beef show high correlations to risk of prostate cancer.

Aside from the differences for colon and prostate cancer, Willett’s estimates for all other sites are identical to the 1981 report. Both predict that at least half of the cancer deaths for several organs — colon, breast, prostate, pancreas, endometrium, and gall bladder — can be prevented by dietary changes. In the United States, however, diet doesn’t seem to play a significant role in lung, bladder, cervical, or esophageal cancers.

**Fruits and Vegetables Protect**

The research that changed the focus to fruits and vegetables was summarized by another AACR speaker, Lee Wattenberg, M.D., a professor of laboratory medicine and pathology at the University of Minnesota Medical School in Minneapolis, in his American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. He noted that a series of papers published in the early 1990s unanimously demonstrated the strong protective effect of both fresh vegetables and fruit against many cancers.

The first of these publications, by Steinmetz and Potter in 1991, reviewed 137 studies of diet and cancer and found the strongest protective evidence for raw vegetables against upper digestive tract cancers. In 1992, Block et al. carried out a similar review of 200 studies with essentially the same results.

The most convincing evidence, however, came from a pooled analysis in 1994 by Negri et al. of a group of case-control studies with a total of 8,077 cancer cases and 6,147 controls. The power of this work rests in the clear dose-response relationship, and in the separate analysis of the effects of fruits versus vegetables. The study showed a strong dose-related protective effect of vegetable consumption against epithelial cancers of the digestive tract, and a weaker, but still clearly protective, effect against hormone-related cancers — breast, endometrium, and prostate. Fresh fruit was strongly protective against cancers of the digestive tract, bladder, and prostate, but not against cancers of the breast and endometrium.

These data contributed to the initiation of a series of chemoprevention trials to test the protective effects of selected vitamins and minerals present in fruits and vegetables. Another AACR speaker, Frank L. Meyskens, M.D., director of the University of California Irvine Clinical Cancer Center, reviewed trials that involve several relatives of vitamin A, (including beta carotene, 13-cis-retinoic acid, retinol, alpha tocopherol, retinyl palmitate), vitamins C and E, folic acid, and a handful of minerals. Of the more than 40 phase II/III trials initiated, about 15 are complete, with mixed results.

In trials using beta carotene or retinol to prevent new skin cancer lesions in patients with prior skin cancer, neither was effective. In contrast, retinol at the same dose produced a 25% decrease in first squamous cell cancers of the skin in patients with actinic keratoses, a precancerous skin condition.

In trials for the treatment of colon polyps, fiber and vitamins successfully suppressed polyp formation in familial adenomatous polyposis patients, whereas a cocktail of vitamin C, alpha tocopherol, and selenium given to patients with resected colon polyps had no

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**Estimates of cancer deaths avoidable by dietary change**

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<tr>
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<tr>
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<td>20-42</td>
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effect on later polyp formation. Folic acid had no effect as an intervention agent for the precancerous condition of cervical intrepithelial neoplasia, where there are abnormal cells on the cervical surface.

Chemoprevention trials for lung cancer have also been mixed — three negative and one positive trial. Smokers in Finland taking beta carotene showed an 18% increase in lung cancer incidence. Similar results were reported in the latest CARET study, whereas using beta carotene in the Physician’s Health Study showed no effect (see News, Feb. 21). One positive study was reported in which patients with early stage lung cancer were treated with high doses of vitamin A.

In summarizing the trials, Meyskens claimed that we will not know whether micronutrients have a role in reversing malignancy until the year 2000 when the first generation of vitamin and mineral studies is complete.

For future trials, he strongly advocated combinations of low-dose multimicronutrients instead of a single chemical, as well as food supplementation studies.

“Supplementing the diet with fruits and vegetables that we know are beneficial may in the long run be more productive than spending a lot of years and money trying to dissect the precise ingredients, or combination of ingredients, in fruits and vegetables that are protective,” said Meyskens.

No Good Biomarkers

But the major limitation in the development of micronutrients as chemoprevention agents, Meyskens believes, has been the unavailability of intermediate biomarkers for cancer. Because the endpoint of chemoprevention trials is incidence of cancer, many years of study with large populations makes phase III trials very long and expensive. Although several molecular markers of premalignancy are under intense study — p53 gene mutations or protein accumulation, loss of chromosome 9p, ras mutations, aneuploidy (an abnormal number of chromosomes), and certain retinoic acid receptors — none have been proven as predictors of cancer.

“So far a validated marker predictive for subsequent cancer development is not available for any cancer,” said Meyskens. Michael B. Sporn, M.D., professor of pharmacology and medicine at Dartmouth Medical School, Hanover, N.H., wholeheartedly agrees and added, “The cardiovascular research community, by contrast, has been uniquely successful in establishing significant biomarkers to direct the development of a large pharmacopeia of chemopreventive agents, which have contributed significantly to the decline in cardiovascular death rates.”

But Sporn sees the lack of cancer biomarkers as part of a larger failure to see cancer as a preventable rather than a treatable disease. He argues in the May 18 issue of The Lancet that the process of carcinogenesis in epithelial cancers — lung, breast, prostate, ovary, and pancreas — entails an accumulation of genetic mutations over the course of 20 to 30 years, the result of a failure in communication between epithelial and underlying stroma cells.

“We have a unique opportunity to suppress the disease in its early stages, since the unraveling process is so prolonged before invasion and metastasis,” continued Sporn. “And we know that many preneoplastic lesions disappear spontaneously without pharmacological interventions.”

Like Meyskens, Sporn advocates the use of multiple chemopreventive agents, and believes that clinical chemoprevention is still in its infancy, receiving a disproportionately low level of funding in both academia and the drug industry.

Other physicians not only decry the low level of funding for chemoprevention at the National Cancer Institute — about 5% of its $2.1 billion budget for fiscal year 1996 — but believe that more chemoprevention trials are not the answer to reducing cancer deaths. Charles B. Simone, M.D., a medical oncologist, was so struck by the data published by the National Academy of Sciences, U.S. Department of Health and Human Services, and NCI, estimating that 80% to 90% of all cancers could be prevented by lifestyle changes, that he formed his own clinic, Simone Protective Cancer Center in Lawrenceville, N.J., to educate his patients.

For now, the greatest weapon for achieving NCI’s stated goal of a 50% reduction in cancer mortality by the year 2000 (compared with 1985 deaths), may be to heed the advice of Willett, Wattenberg, and Meyskens: avoid smoking, stress, sun, workplace carcinogens, and alcohol, and pursue fruits, vegetables, activity, and lean-ness. Please pass the broccoli.

— Nancy J. Nelson