

## John Baron, M.D.: The A-B-Cs of preventing cancer

By Roger P. Smith, Ph.D.

The building blocks of a career are sometimes as simple as A-B-C. In the case of epidemiologist John Baron, M.D., make that A for aspirin, B for beta-carotene, and C for calcium. From work on these and other substances, he's built a national reputation in cancer-prevention research.

Considering that Baron had no family role models who were doctors or mathematicians, it may seem surprising that he pursued a career in epidemiology—for it's a discipline that combines mathematics and medicine to study the transmission and control of disease. But he had an aptitude for math that he parlayed into a bachelor's degree, with honors, in intensive mathematics at Yale. He went on to gain admission to a doctoral program in mathematical statistics at Stanford. The Vietnam War interrupted his Ph.D. studies in 1969, however. The late 1960s and early 1970s were turbulent times for draft-eligible men. Of the small group of Baron's peers at Stanford, "one accepted a direct commission in the Army, one went to Canada, one was already in the Navy, . . . and one decided to try to become too fat for the draft," Baron recalls.

Baron met his own military obligation by becoming a commissioned officer with the U.S. Public Health Service: he served as a statistician with the National Center for Health Statistics. He loved being financially independent for the first time. He loved the excitement of living in a city like Washington, D.C. But most of all, he loved his work in the Public Health Service. So much so that he began questioning whether he wanted to finish his doctorate.

Stanford had already awarded him a master's degree in mathematical statistics. So it was the right time, he says, "to think about whether or not I wanted to spend the rest of my life standing by a blackboard doing abstract math. Although I actually enjoyed it, I thought I might like to do something a little more physical and a little less cerebral."

He decided that medicine struck the right balance and enrolled in the University of Michigan Medical School. After earning his M.D. in 1976, he did a year of internship at Michigan and then came to DHMC, where he completed a residency in internal medicine and was chief resident in 1979-80.

During Baron's year as chief resident, the chair of medicine, George Bernier, M.D. (who is now a professor and dean emeritus of the University of Texas Medical Branch in Galveston), suggested that Baron consider a two-year fellowship in epidemiology as a Milbank Scholar at Oxford University in London. Baron's wife, clinical psychologist Karen Nielsen, Ph.D. (also a member of the DMS faculty), was ecstatic about the idea of being able to spend two years in London, so off they

went. While there, Baron collected a second master's degree, this one in epidemiology, from the London School of Hygiene.

In Oxford's heady atmosphere—surrounded by world-class statisticians and epidemiologists—Baron started looking at several questions, including whether oral contraceptives increase the risk for breast cancer. Another question, one that continues to occupy him today, involved some unusual effects of cigarette smoking. An unexpected and,

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at the time, unwelcome finding emerged—that cigarette smoking seemed to protect against breast cancer. In cases like this, statisticians try to "massage" the data to make sure that the analy-

sis is correct. But try as they might, the effect wouldn't go away.

After a period of both soul- and literature-searching, Baron began to think about other effects of smoking, such as its ability to substantially increase the amounts of certain liver enzymes that break down drugs and other foreign chemicals in the body. The same enzymes have a limited ability to act on some naturally occurring substances, such as steroid hormones. Perhaps smokers with a revved-up complement of these enzymes were metabolizing their own estrogens at faster rates than nonsmokers were, and in so doing they lowered their risk for estrogen-related problems such as breast cancer. This hypothesis was strengthened when Baron found evidence in the literature that cigarette smoking also decreased the risk of endometrial cancer, which is a strongly estrogen-sensitive malignancy.

But further study indicated that cigarette smoking does not decrease the risk of breast cancer after all. It does, however, alter the physiology of women in such a way that their bodies behave as if they were in a state of relative estrogen deficiency. Baron has been studying that phenomenon for more than 20 years and has thus acquired a reputation as an expert on smoking and hormones.

It is a controversial line of research. Smoking presents such a horrific risk not only for lung cancer, but also for several other forms of cancer, that researchers are reluctant to suggest that it might have any kind of health benefit, let alone any antitumor effect. But, says Baron, "smoking involves exposures to hundreds of chemicals, and it would not be particularly surprising, even if the vast majority of them were carcinogenic, that some of them might reduce the risk of other diseases." For example, smoking is associated with protection against pulmonary hypersensitivity reactions, such as farmer's lung and pigeon breeders' pneumonitis, he explains.

Upon returning to DMS, Baron found several kindred spirits, including fellow epidemiologist Robert Greenberg, M.D. Baron started working with Greenberg, who was just launching a skin-cancer chemoprevention trial using beta-carotene. Although beta-carotene looked promising as a cancer preventative—people with a lot of the

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vitamin in their blood didn't seem to get cancer—the skin-cancer trials showed no effect from beta-carotene. The study still made an important contribution, however, because the scientific world at that time had begun to act as if the sun rose and set on that nutraceutical (a nutraceutical being any chemical compound in food, including vitamins and additives, that offers health benefits).

After a year, in a strange twist, Greenberg took a one-year sabbatical and wound up in the same

department, and even at the same desk, that Baron had just vacated in Oxford. They continued to collaborate even during the year apart. Greenberg (who later served as director of Dartmouth's Norris Cotton Cancer Center) had gone to considerable trouble to put together a multicenter consortium to study skin cancer, and it seemed natural to use such a well-oiled machine to do other studies.

Within a few years, Baron and Greenberg were able to show that antioxidants—compounds that protect against cell damage inflicted by molecules called oxygen-free radicals—didn't work for colorectal tumors. But something as simple as taking calcium supplements actually does. (See page 10 for details of his latest such finding.)

Baron, who says he's proud of his smoking research, "coined the phrase 'antiestrogenic effects of smoking,' which has sort of caught on," he explains. "I'm also proud of the chemoprevention work with colon cancer. . . . Dartmouth now enjoys a well-deserved reputation as one of the leading centers for cancer chemoprevention in the world." Baron has contributed substantially to that reputation. He was the director of the cancer epidemiology and chemoprevention programs at DHMC's Norris Cotton Cancer Center for almost 10 years, and he was also the founding director of Dartmouth's Clinical Trials Center.

"Finally," Baron continues, "I'm proud to have been a mover in getting the bioinformatics group here and up and running. They have proven to be a tremendous resource not only for chemoprevention, but for the entire institution."

Baron, whose CV lists more than 200 original articles—an especially impressive number given the fact that epidemiological studies generally take years to complete—as well as dozens of other publications, has also served on regional and national committees and groups, including as a senior reviewer for the U.S. Surgeon General's Report on Cigarette Smoking in 2002. He is on the verge of launching a new chemoprevention trial for colon cancer, building on his success with



JON GILBERT FOX

**During his more than 25 years at Dartmouth, epidemiologist John Baron has applied his aptitude for math and his interest in medicine to the prevention of cancer.**

calcium. This study will include both calcium and vitamin D supplementation. In the future, he might add aspirin to the regimen, a substance he and his colleagues have shown to be protective against colorectal adenomas.

Baron's many interests include orthopaedic epidemiology, too. Dartmouth is uniquely positioned for such studies because of the existence of the massive health-claims databases used in the preparation of *The Dartmouth Atlas of Health Care*.

Consistent with the discovery of the antiestrogenic effects of smoking, Baron's research has shown that women smokers also tend to be more prone to osteoporosis, a condition characterized by a decrease in bone mass and strength.

**B**aron's first large grant, in fact, was to study osteoporotic fractures—an estrogen-related problem that is made worse by smoking. His work attracted the attention of a group at Harvard that wanted to study the epidemiology of total hip and knee replacements and confirm the incidence of post-replacement adverse events—such as infection, dislocation, or death. When Baron and a DMS colleague manipulated their databases, they found that insurance claims for such events appeared to be uncommon nationwide. Furthermore, claims correlated inversely with hospitals' and surgeons' procedural volumes. The analysis validated the value of hip and knee replacement in terms of a vastly improved quality-of-life for the recipients.

Outside of work, Baron enjoys spending time with his wife of 27 years, as well as with his two daughters, who are both in college. He has tried to find time over the years for a couple of hobbies, too: music and woodworking. He helped to found the Yale Symphony Orchestra as an undergraduate and went on to play (tuba and double bass) in classical groups in graduate school and during his stint in the Public Health Service. He hasn't been involved in music lately, though. His double bass stands in a corner of the Barons' dining room, but his wife has never heard him play it. "If I were to pick up music again, it would be as a blues bass guitarist," he says.

After coming to Dartmouth, Baron discovered the woodworking shop in the Hopkins Center for the Arts, and that's the pastime that has occupied him in recent years. He is currently working with a professional cabinetmaker in White River Junction, Vt., on a drop-leaf desk that, he says, "is slowly taking shape."

In woodworking—just as in epidemiology—it takes a lot of time and attention to detail to get things right. ■