Conducting clinical cancer prevention trials in Bangladesh, Dr. Baron has made three trips there in the pat 12 months.

Finding New Ways to Prevent and Treat Cancer

"Cancer is truly a worldwide phenomenon, but I don't think that means that it's inevitable," explains Dr. John Baron, professor of medicine and of community and family medicine at Dartmouth Medical School (DMS) and an investigator in the Cancer Epidemiology and Chemoprevention research program at Norris Cotton Cancer Center.

Dr. Baron, who provided a perspective on the global burden of cancer as part of the Dartmouth Community Medical School program, *Cancer, Nutrition and the Environment,* has been a leader in epidemiological research and cancer prevention for 25 years. His research has been varied and extensive, in the US as well as in Scandinavia, other parts of Europe, and South Asia.

"The fact that cancers vary a lot in their geographic distribution is one important piece of evidence that it is preventable. For example, if breast cancer is more prevalent in North America than in Asia then we can learn how to be more like Asians with respect to the disease—perhaps we can reduce the incidence of breast cancer or largely avoid it in this country."

Testing Simple Interventions

Dr. Baron recently returned from Bangladesh (his third trip there in the last 12 months), where he has been sharing his expertise in conducting clinical cancer prevention trials. "I helped a colleague of mine there get funding for the trial," he says. "The study we've launched is building on an existing National Cancer Institute (NCI) supported study of people with varying degrees of arsenic exposures."

Bangladesh's low-lying geography and monsoon climate make it susceptible to flooding. "As a result, the country historically had a largely surface water supply and had a lot of trouble with diseases like cholera, until the 1960s and 70s when some of the international health organizations helped to put in wells," Baron explains. "Then, about 15 years ago, it was discovered that some of the ground water from the wells was badly contaminated with (naturally occurring) arsenic."

It's now estimated that there are more than 10 million people with high levels of arsenic contamination. "There are some characteristic skin lesions that are very specific for arsenic, and those lesions are thought to be a marker for increased risk of skin cancer," he says. "And if experience can be extrapolated from other parts of the world like China, these people will also be at increased risk for lung, bladder, and kidney cancers, and probably at increased risk for heart disease, diabetes, and hypertension."

Our goal is to see if providing Vitamin E and Selenium can help reduce cancer risks," says Baron. "Vitamin E is an anti-oxidant, and it's thought that one of the mechanisms for the cancer risk associated with arsenic has to do with oxidative damage. And Selenium, as it turns out, is a mineral that can be used to treat acute arsenic toxicity. What we're dealing with, though, is chronic exposure accumulated over decades, so we don't know if will prove effective in this case."

Targeting Colorectal Cancer

Testing the effectiveness of simple, cheap interventions like those being studied in Bangladesh has been a hallmark of Baron's research. He has been following an intriguing line of investigation using similar techniques to study chemoprevention of colorectal cancer.

For more than 20 years, Baron has been leading a series of large, NIH-funded studies conducted jointly by doctors and researchers from Norris Cotton Cancer Center at DHMC and at a number of other institutions across North America. "Our work has focused on finding out how to prevent adenomatous polyps—benign growths in the large bowel that are fairly common for people in their 60s and may turn into cancer," says Baron, who has been involved in all four trials, and served as a principle investigator for three of them.

"We've tested antioxidants, calcium, aspirin, and folic acid (a B vitamin)," he explains. "Of the four, calcium and aspirin worked. And with both, we saw about a 35 percent reduction in high-risk adenomas and about a 20 percent reduction for all adenomas including ones that aren't so worrisome. In our current trial, we want to see if vitamin D adds something to the effectiveness of calcium."

Crossing Many Disciplines

Dr. Baron isn't yet able to pinpoint exactly why some agents prove effective and others don't. "We certainly have some ideas, but it gets very complex at the biochemical level," he says. "With cancer prevention you need to find agents that are very safe but produce enough of an effect to be helpful."

"But it's fascinating trying to find the answers. My line of work is great because it stands at the intersection of disciplines like clinical medicine, prevention, statistics, biology, and genetics. Integrating them into a single picture and research program is really fun."

Third Annual
Great Issues in Medicine
and Global Health Symposium

Cancer • 2006

Linking our Food Choices to Cancer Risk

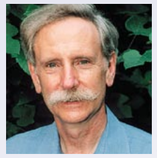
Chances are, if you went to see Dr. Walter Willett speak at DHMC Grand Rounds on November 17—part of the Third Annual Great Issues in Medicine and Global Health Symposium on Cancer—you came away with some different ideas about what constitutes a healthy diet.

Dr. Willett—professor of Epidemiology and Nutrition and chairman of the Department of Nutrition at Harvard School of Public Health, and professor of Medicine at Harvard Medical School—is considered to be one of the world's foremost authorities on the long-term health consequences of food choices.

In his presentation, *The Effects of Diet on the Occurrence of Cancer and Other Major Diseases*, Willett shared findings based on 30 years of research about diet and long-term health. His study results have at times differed from what gets reported by media and is promoted by other sources of health information for the public.

Shaking Up the Food Pyramid

One of the best examples of Willett's research conflicting with conventional wisdom is the US Department of Agriculture's (USDA's) Food Guide Pyramid. He has asserted that the USDA pyramid was built on "shaky scientific ground," putting too much emphasis on guidelines like limiting all fats, promoting large amounts of starch (like bread and pasta) in the diet, and encouraging several servings of dairy products per day as a means of combating osteoporosis.



Dr. Walter Willet's research has revealed associations between dietary factors and diseases like cancer.

"Until very recently, reduction of total fat in the diet was the centerpiece of dietary advice," says Willett. "Unfortunately, replacing fat with carbohydrate does not reduce risk of heart disease. But changing the type of fat in the diet can greatly reduce risk of heart disease."

To help people make better choices about what they eat, Willett and his colleagues at the Harvard School of Public Health have created their own evidence-based guidelines, called the *Healthy Eating Pyramid*. Major distinctions between their version and the USDA's include: placing daily exercise and weight control at the base; replacing processed carbohydrates with whole grain foods; substituting plant oils ("good fats") for saturated and trans fat; limiting milk and cheese consumption (and recommending calcium supplements); and placing foods like white rice, white bread, potatoes, white pasta, and sweets at the very top to be used sparingly.

Eating What's Good for You

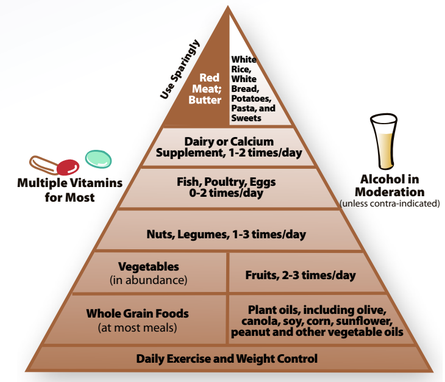
Dr. Willett first became a critic of the USDA's Food Guide Pyramid after serving as a principle investigator in the well-known Nurses Health Study. The study, one of the largest ever conducted on the long-term effects of diet, scored participants on their body mass, food choices, and exercise habits, and used the data to accurately determine their risk of heart disease.

He employs a similar, easy-to-use system, called the "Body Score," in a new book co-written with best-selling cookbook author Mollie Katzen—*Eat, Drink and Weigh Less, A Flexible and Delicious Way to Shrink Your Waist Without Going Hungry.*

The book emphasizes nine basic "Turning Points" or gradual changes to help people achieve and maintain a healthy weight while reducing their risk of chronic diseases: eating plenty of fruits and vegetables; eating more good fats; upgrading your carbohydrates; choosing healthy proteins; staying hydrated; drinking alcohol moderately; taking a multivitamin every day; being more active; and eating mindfully through each day.

Dr. Willett's epidemiological studies—using both questionnaire and biochemical approaches—reveal a wealth of associations between dietary factors and diseases like cancer, e.g., links between the intake of red meat and colon cancer, alcohol and breast cancer, cruciferous vegetables and reduced risk of bladder cancer, and lycopene and a decreased risk of prostate cancer.

"With careful attention to the foods we eat, combined with not smoking and regular physical activity, we find that over 80 percent of heart attacks and over 70 percent of colon cancers could be avoided," says Willett.



Healthy Eating Pyramid

What's in *Your* Drinking Water?

In 1994, when Dr. Joshua Hamilton and his colleagues at Dartmouth Medical School (DMS) began studying arsenic, they were one of the few research groups focused on the metal as an emerging environmental health issue.

"We realized early on that the problem was more complex than any one scientist or discipline could tackle, so we formed this collaborative group and got a grant from the National Institutes of Health," explains Hamilton, who as professor of Pharmacology and Toxicology at DMS has served as principle investigator on the grant for 12 years.

"Today, arsenic is considered the single greatest environmental chemical of concern regionally, nationally, and worldwide," says Hamilton, who spoke recently at a special evening program entitled, *Cancer, Nutrition and the Environment*. The program was part of the Third Annual Great Issues in Medicine and Global Health Symposium on Cancer, held November 15-17 at DHMC and Dartmouth College.

Recognizing Low-Dose Risks

Arsenic has long been recognized as the "king of poisons and the poison of kings" for its fatal effect when administered in high doses. But not until fairly recently has medical research shown that long-term exposure to low doses can pose a significant threat to human health.

"We first learned about this from epidemiology studies in places like Bangladesh and Taiwan," Hamilton explains. "UNICEF had gone in and dug wells so that people wouldn't drink the surface water, which contained cholera and other diarrheal diseases. What they didn't know was that the geology in those areas has a lot of arsenic in it, so the ground water became contaminated. Now, two or three decades later, we're seeing huge increases in a host of disease risks."

"Our group and others have done studies here in the US (in New Hampshire, the Southwest, and the Rocky Mountains) and large parts of South America—in areas that have similar natural formations of arsenic in rock," he says. "And our research has shown that people drinking even lower levels of arsenic in the Western World also carry these very high risks of disease that include several forms of cancer, heart disease, diabetes, and reproductive or development problems."

Interfering With Hormones

Dr. Hamilton and his team were the first to report in 2001 (in rat cell line studies) that even at extremely low levels, arsenic acts as an endocrine disruptor—an important factor in its ability to increase risk of disease. "What we've found is that arsenic can interfere with the ability of hormones to signal properly," he explains.

A number of other animal studies have confirmed the group's molecular study findings. "We've got a fish model that involves a species indigenous to the coast of New England that can transition back and forth between fresh and salt water," says Hamilton. "This ability is completely regulated by the hormones that we study. So, if arsenic is an endocrine disrupter it should block their ability to transition, and it does—we're seeing clear indications that this hormone interruption is important."

Most organic chemicals like pesticides or PCBs either work to mimic a hormone or block it, says Hamilton. "Arsenic does neither of those things," he explains. "At low doses it actually enhances hormone signaling, and at slightly higher doses it suppresses hormone signaling. We think we may actually see an entirely different pattern of diseases in higher dose areas such as Bangladesh or Taiwan, than in lower dose areas like those in the US and South America."

Raising the Bar on Safety

In 2001, the US Environmental Protection Agency adopted a new standard for arsenic in drinking water at 10 parts per billion (ppb), replacing the old standard of 50 ppb. "While clearly a step in the right direction, it hasn't solved the problem," he says. "Public water systems were given 7-14 years to reach compliance. We're also starting to worry whether 10 ppb is low enough to offer a protective margin."

And, in areas like New Hampshire, half the population gets its water from private wells which are not regulated by the EPA or the State. "Of the households we've surveyed, about one in five has an arsenic level that we would consider unacceptable," says Hamilton, who is a member of the Epidemiology and Chemoprevention Research Program at the Norris Cotton Cancer Center.

"That's why we encourage anyone who uses a well to get their water tested for arsenic—the State added it to its standard battery of tests at our urging about five years ago. If it's high, we recommend that they either purchase a point-of-entry filter system or use bottled water for drinking and cooking."

Gene-Environment Interactions

Dr. Hamilton believes that understanding the interplay between environmental, lifestyle, and genetic factors will be the hallmark of cancer research in the next 10-20 years.

"We need to try to tailor our understanding to individual risk rather than drawing blanket statements," he says. "There are some key things that we can all do to reduce our cancer risk: stop smoking, eat a healthy diet, and get our wells tested for arsenic."