If the cardiologists can do it, so can we

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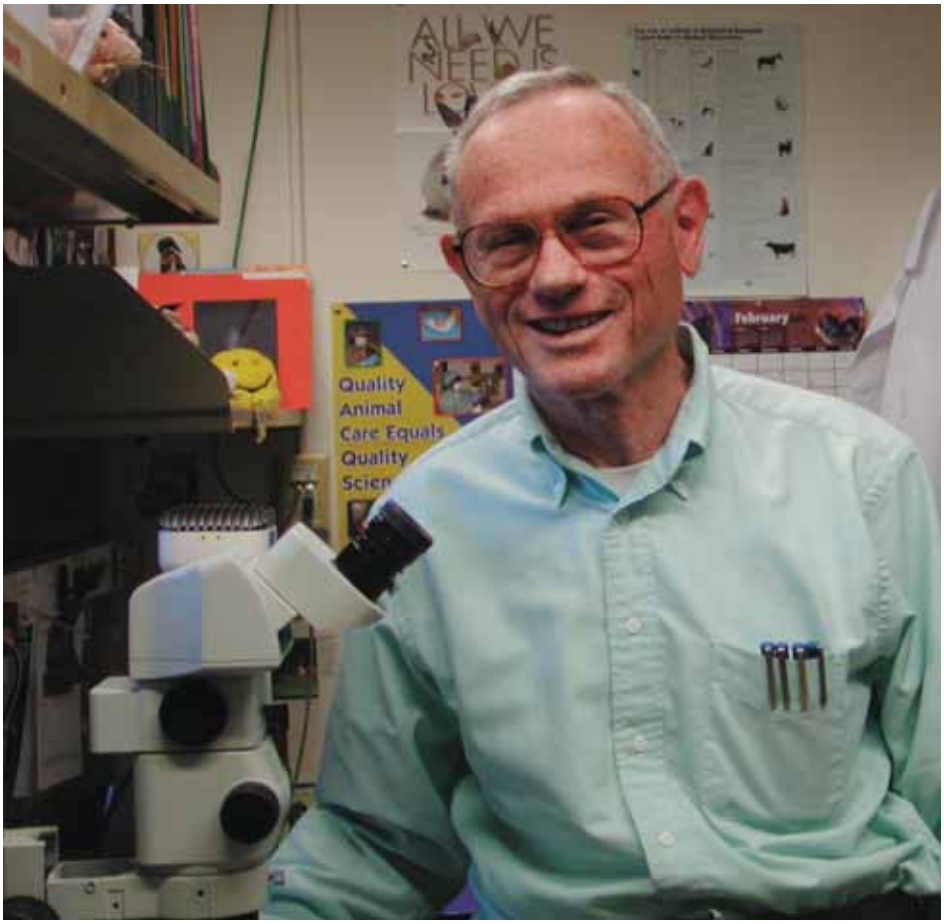
Michael Sporn believes the best bet for controlling cancer is to pick up the warning signs and nip it in the bud. A pot of gold awaits any drugs company that can come up with a Lipitor for cancer, says Sporn, and easy-to-use biomarkers would already be on the market had one-tenth of the research dollars poured into chemotherapy been invested in proteomics.

From his fifth floor office at Dartmouth Medical School, in the bucolic town of Hanover, New Hampshire, Michael Sporn, the man who coined the term "chemoprevention," is still waging his own version of the war on cancer. That it is one largely devoid of research dollars and ignored by pharmaceutical companies has left him frustrated, but undaunted. There is no greater motivation for him to keep at it than the fact that many of his good friends and colleagues have already died from carcinoma and, he says, "hundreds of thousands more like them are slipping through the back door every day."

The answer, he believes, is not to be found in diet and lifestyle changes, the subjects that often come to mind when the word 'prevention' arises, and which are largely the focus of the US National Cancer Institute's prevention programme. "We're not going to fix this dietarily," says Sporn. "Living well and eating well isn't going to make cancer go away. Vitamin C has been a failure. Vitamin D hasn't been much better, and low-fat diet hasn't worked either." Sporn's ideas, in fact, are less about preventing the disease than identifying people at the early stages of malignant cell differentiation and nipping that process in the bud with drugs. "This is a nasty disease that involves genetic dysfunction, and we need some real medicine to deal with it," he says.

His model is based on what cardiologists have done to reduce mortality from heart disease: identify people when they're first showing signs of trouble – high blood pressure or cholesterol – and medicate them before they're too sick to save. His favourite graphic shows two simultaneous curves – one downward slope, indicating decreased mortality from heart disease over the years, superimposed upon a flat line reflecting the static mortality from cancer. "Lipitor is a classic chemopreventive agent," says Sporn. "Pfizer may not want to call it that, but that's what it is."

Granted, cancer is more complex than heart disease. Chemoprevention studies are prohibitively long and expensive; pharmaceutical companies are averse to the risk of treating so-called 'healthy' patients with any medication that might cause lawsuit-worthy side-effects; and, perhaps most challenging, there are as yet no easy



biomarkers for cancer. "You put someone on 20 mgs of Lipitor, measure their cholesterol that day and then again in three months, and you can tell them their cholesterol and blood pressure are down," says Sporn. Not so with cancer.

Not, says Sporn, because it's impossible, but because little effort has been made. "For all the molecular biology that has been done on cancer, there hasn't been much of a crash on biomarkers," he says. "The bottom line is that the dollars are simply not there, even though chemoprevention would be more cost-effective. Meanwhile, we still have three hundred thousand useful lives being snuffed out every year. And you can only trot out Lance Armstrong so much. Sometimes," he admits, "my frustration over the lack of progress wakes me up at night."

Serendipity

Sporn's path to becoming an advocate for cancer chemoprevention was serendipitous. Born in 1933, he spent his childhood "smack in the middle" of New York City, which he didn't much enjoy. "I didn't like the general pushiness of it," says Sporn, who lived all over the city, and worked as a delivery boy for a florist in his free time. College was Harvard University, where pushiness took the form of grade competition. He didn't like that either. It wasn't until the summer of his second year in college that he started to get a sense of what he *did* like. "I went to Cornell and took a summer school class in comparative anatomy with an anatomist named Perry Gilbert," he says. "It was a formative experience."

Gilbert, famous for his expertise in shark

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anatomy, had a reputation as a mentor to students. He kept a card on each one he taught over the course of his career, complete with their picture, exam scores and personal details. This was a different world to Sporn. "When I was at Harvard, there was never any meaningful personal interaction between professors and students," he says. Gilbert, on the other hand, loved to be with his students, and was known to roll up his sleeves and help them with dissections. "He even took the class on a picnic," says Sporn. The experience gave Sporn a life-long taste for congenial and idealistic research environments that would guide every step of his career.

Because of his experience with Gilbert, he turned down Harvard Medical School, opting, instead, for the University of Rochester, the first medical school to be founded after the Flexner Report of 1910, which changed American medicine by creating a higher standard for modern medical education and effectively closed two-thirds of the US medical schools. Rochester was exactly what Sporn wanted. "It was a very strong, very holistic, integrated place," says Sporn. "And a very nurturing one." Research was encouraged, but never allowed to become separate from reality – the basic science part of the school was separated from the hospital only by a set of double doors. Students and teachers, basic scientists and clinicians, shared a cafeteria.

Nor was the school simply about producing doctors every four years. "Somewhere along the line, various faculty members would tell you to take a year out and do research," says Sporn. When his turn came, he took 15 months out to study with the British psychiatrist and theoretician Ross Ashby, one of the founding fathers of cybernetics. "He was totally uninterested in anything by way of the laboratory, but he let me do whatever I wanted," says Sporn. "So I was exposed to a really world class theoretician and at the same time I was allowed to sow my wild oats in the lab. I was learning how to work in a laboratory and given total freedom to explore things."

He returned to Rochester "totally bitten by this way of life." He finished his last two years of medical school, at which point two "absolutely wonderful" faculty members, John Romano and George Engel, both professors of psychiatry and long-time collaborators themselves, helped him and a friend of his get a $50,000 grant from the National Institutes of Health (NIH) to set up their own lab and do basic research. He still can't believe his luck. "We had no preliminary data, no nothing. We were just a couple of bright kids with a dream of doing research." Together, he and his partner did some of the first papers on amino acid metabolism in the brain, showed that the brain can make its own urea, and did one of the first studies on the biochemical basis of memory.

When the money ran out, Romano and Engel helped Sporn and his lab partner get jobs as research associates at what was then the biggest research Mecca in the US – the NIH.

In the US in the early '60s, if you wanted a research career, NIH was where you wanted to be. The public, and the government, placed an enormous trust in the power of science, and the money flowed freely. "The sky was the limit," says Sporn, still marveling over it after all these years. "Jim Shannon, the director, would go down to Congress and ask for money for something, and they'd say, 'You're not asking for *enough* money, doctor, you need *more*.' There was no political interference, either. We might as well have been living in a magical land of Oz, divorced from the world of politics." Like Rochester, the labs and the wards of the NIH were separated only by a hallway, reinforcing the ideal of lab-to-bedside medicine, and the scientists were all part of one big community. "No one even knew what institute anyone else was in."

From 1960 to 1964, Sporn worked on the

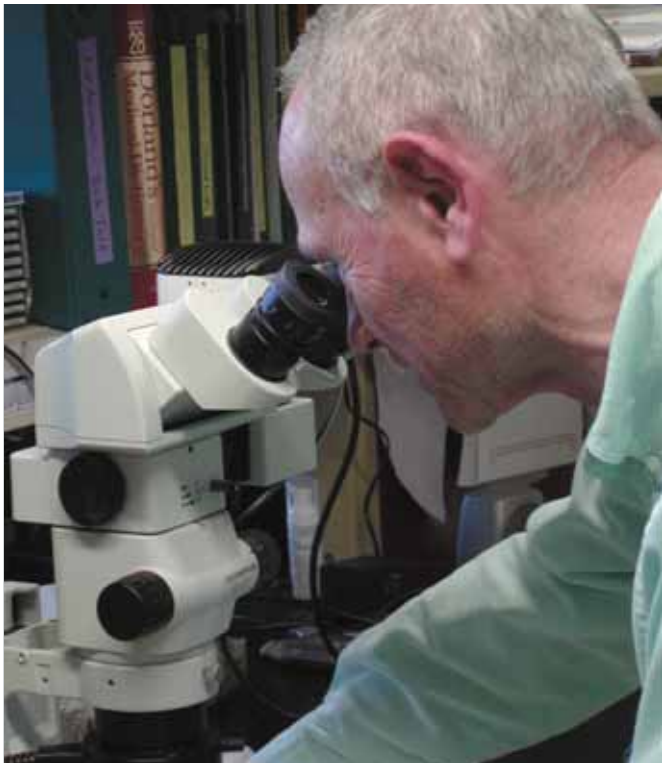
nucleic acids of brain cells at the Neurology Institute. Though he had once imagined a career as a general practitioner, those four years changed that for good. "If I had any thoughts of going back into clinical medicine, they were gone," he says. When his four years were up, he decided he wanted to stay. The problem, by then, was that Vietnam had changed everything. Even young doctors who hadn't envisioned research careers were competing for spots at the NIH because it was part of the Public Health Service, and working there meant you didn't have to go to war.

The challenge of cancer

To make matters worse, there was a hiring freeze on. Sporn went to every institute director at the NIH in search of an opening, with no luck. "A freeze was a freeze," says Sporn. Then, one night, at a poker game, one of his co-workers overheard something about a new carcinogenesis programme the National Cancer Institute (NCI) had managed to set up on a contract basis. And they *were* hiring. He'd never given any serious thought to doing cancer research before. But he jumped at the opportunity, not only because he needed the job, but because he'd started to feel an urge to do something more clinically applicable. "I knew there was a big challenge in cancer," he says.

He knew because his wife, Kitte, a paediatric nurse at the NIH, took care of many cancer patients. Nightly, she regaled him with stories of children dying of leukaemia, before the era of platelets and supportive therapy, and patients struggling to overcome "kamikaze" maxillofacial procedures and hemi-pelvectomies. "Kitte took care of one patient without a face," he says. One Sunday morning, he'd met one of her patients, a young, pale, girl named Debbie, who, he knew, would inevitably die. "She was like a poster child for everything the NIH was trying to do," he says.

This was 1964, two years after Rachel



Carson, a former marine biologist with the US Fish and Wildlife Service, set off a public firestorm with *Silent Spring*, a book that argued that the pesticide DDT was killing fish and wildlife, and raised speculation that chemicals in the environment might have a negative effect on the human population, as well. The NCI was as interested as anyone in sorting out the connection between chemicals and cancer. As for Sporn, it was no big leap, he says, to go from studying the nucleic acids of brain cells to studying the nucleic acids of rat cells that had been exposed to common carcinogens like Azo dyes, such as butter yellow, or the chemical aflatoxin which is the product of a mold that often grows on spoiled grain, and acetyl amino fluorine (AAF).

"The popular hypothesis back then was that chemical carcinogens caused cancer by binding

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to key protein targets," he says. "We did some of the first studies that showed that chemical carcinogens would bind to DNA and cause dysfunction." They also showed that the non-carcinogenic analogues of those chemicals *didn't* bind to DNA. "The greater the carcinogenicity of a substance, the higher the level of DNA binding," says Sporn.

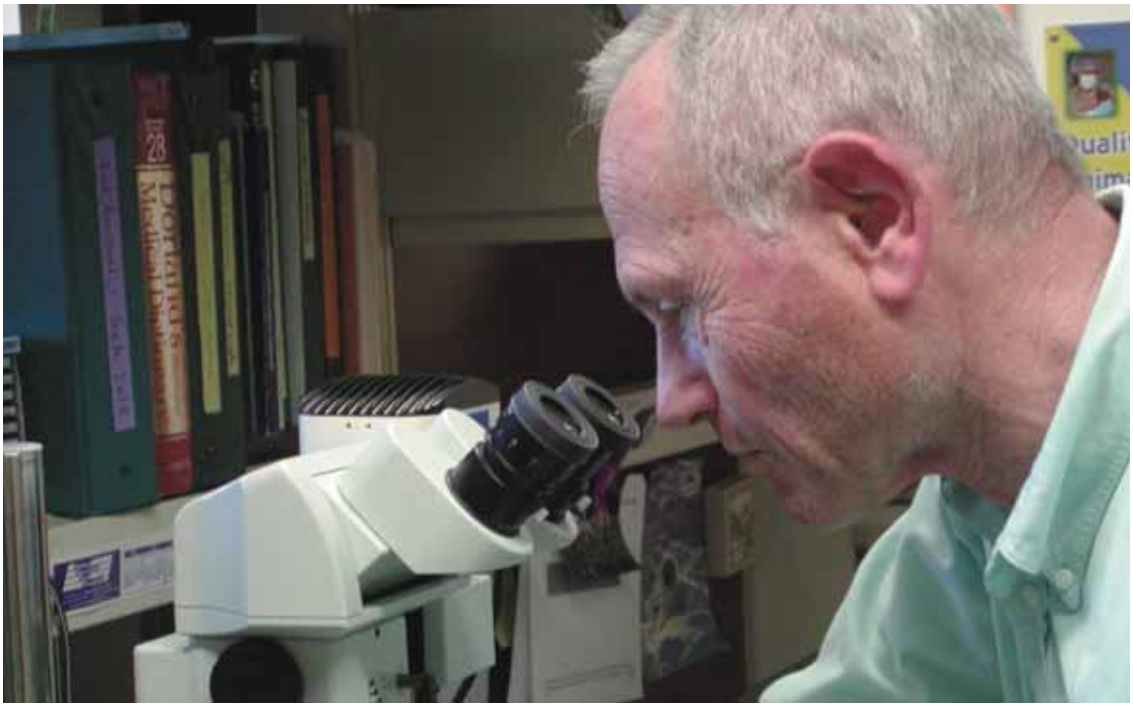
Six years passed, and as intellectually exciting as the research was, it still didn't feel terribly helpful to the patients Kitte was caring for. "I started thinking, where is this going," he says, "what does it mean?" Then Umberto Saffiotti, an Italian pathologist, became director of the NCI carcinogenesis programme. Saffiotti had a research interest in vitamin A. He'd done hamster studies that showed that vitamin A could suppress carcinogenesis. He asked Sporn to look into vitamin A and lung cancer. Sporn knew little about either, but he started reading up, and discovered that vitamin A acts more like a hormone than a vitamin. "It controls the differentiation of almost all the epithelial tissues in the body," he says. He was also stunned by another, earlier, discovery: the histology of tissues in rats with vitamin A deficiency resembled the histology of early carcinogenesis in humans.

"It got me really excited," says Sporn. If one could control or reverse early abnormal differentiation, vitamin A could be a true preventive tool at a very early stage. But there were two major problems: First, high doses of vitamin A caused toxicity. And second, natural forms of vitamin A didn't necessarily reach target tissues, such as the lungs, where one wanted to prevent cancer. "I got the idea to make synthetic analogues of vitamin A, for which we coined the new term, 'retinoids'," says Sporn. He set up a collaboration, first with Hoffmann-LaRoche and then with Johnson and Johnson, and also set up a new programme for chemists throughout the country to make new retinoids. "In those days, there were no patents at the NIH and no MTAs [material transfer agreements, which allow one party to perform research using the materials of another party]." They tested several hundred vitamin A analogues on well over twenty thousand hamster tracheas. It quickly became clear, he says, that a number of the analogues could reverse the abnormal differentiation.

Early results

By 1976, they had their first animal data. "We could take lesions in hamster tracheas that resembled those of heavy smokers and reverse them," he says. Further work showed similar success in animal models with cancer of the bladder, oesophagus, colon and breast. "We would screen an agent first in an organ culture system, and if it looked really promising, then we'd do the preliminary animal experiment, and then we'd do full-blown carcinogenesis studies," he says. Some of the agents they worked with, including one retinoid for clinical prevention of breast cancer that was tested in Italy, got very good results. And some have even gone on to be widely used – but almost always in the context of treatment, never in chemoprevention.

"Drug companies are not very interested in this," says Sporn. "They're terrified of liability suits." It's an issue that frustrates him, he says, because, rationally speaking, he doesn't see the difference between someone with high cholesterol, or blood pressure, and someone with severe dysplasia (abnormal epithelial cells), seen on biopsy or in cytology smears. The latter group, he says, are no healthier than the former. But the concern is that the risk of dosing this seemingly healthy group with chemopreventive drugs might outweigh the benefit. Sporn doesn't think that's the case, and cites the outstanding success of tamoxifen and raloxifene in preventing breast cancer as examples. "Those



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drugs are old, we can do much better than that now," he says, but acknowledges that more work needs to be done to prove it and to develop even safer agents. "We're not ready to put chemopreventive agents in the cornflakes yet."

In 1995, Sporn decided to leave the NIH for Dartmouth, returning to a part of the country he and his wife love. "I have roots that go way back to this part of the world," he says. He spent five summers away at camp there, a respite from the New York City he was never comfortable in. He and his wife spent their honeymoon at nearby Mount Washington, and they used to take ski trips here with his two boys, Tom and Paul, when they were kids. In 1975, he and Kitte bought an old farmhouse out in the countryside, with an eye toward moving there some day.

But another reason for the move was also to get back to chemoprevention work, which he'd drifted from a bit in his last ten years at NIH, and do something "totally off the wall." And by that he means studying triterpenoids, a family of mildly anticarcinogenic and anti-inflammatory chemicals that occur in a wide variety of plants, including rosemary. Upon getting interested in them, Sporn promptly did exactly what he did with vitamin A – he asked a bunch of chemists to make him as many analogues as they could come up with. Although this time, he didn't have to ask drug companies and chemists across the country – he just had to go across the street to Dartmouth's chemistry department, where he asked Gordon Gribble, a professor of chemistry, and Tadashi Honda, an associate professor, to come up with over 300 derivatives. "They're all home brewed," he says.

One of the most exciting things to come out

"I believe that essentially all the common forms of epithelial cancer are preventable"

of the research thus far, he says, is the revelation that triterpenoids have multiple functions. They're markedly anti-inflammatory, anti-proliferative, can induce apoptosis, and are cytoprotective. "We think they'll be useful for both chemoprevention and chemotherapy," says Sporn. In fact, the US Food and Drug Administration (FDA) has approved two of them for phase I trials in leukaemia and end-stage solid tumours, studies which are due to start soon at MD Anderson, Dana Farber and possibly the NIH. "Nothing ever goes into prevention first," he sighs.

An act of faith

He does think the field will gravitate to his point of view, eventually. Not that chemoprevention will replace the other treatment modalities, but rather be the first step in approaching someone at risk. "It's something of an act of faith, but I believe that essentially all the common forms of epithelial cancer are preventable, if we can get at the solutions in the early states of abnormal differentiation and prevent progression," he says. There are problems that need to be solved first, of course.

Drug companies need to shed their fear of liability, and see that cancer chemoprevention drugs can be just as profitable for them as drugs like Lipitor, he says. To assuage them about liability issues, Sporn envisions an insurance pool which could protect both corporations and individual physicians against specific liability, and which could be funded by a tiny surtax on preventive drugs.

Easy-to-use biomarkers, obtained from nothing more complicated than a blood sample, are needed to make chemoprevention studies more economically feasible. And the FDA needs to be persuaded to let drug companies use them. "If a tenth of the budget that has been put into chemotherapy had been put into development of proteomics I think we would have a blood test," he says.

On the day that we last spoke, Sporn was, as he said himself, in a very optimistic mood. He and his colleagues at Dartmouth had figured out a way to detect tiny amounts of tumour in an anaesthetised mouse lying spread-eagled in an NMR (nuclear magnetic resonance) machine. "We have this huge amount of technology we've developed to do all these studies, but I don't think they've ever been applied to prevention before," he says. "We detected a tumour less than a millimeter across."

When he's not doing research, he spends time doing what the teachers he once revered did for him – leaving his office door open so that he's always available to his students, and working one-on-one with them when they need him. He's hopeful that his students, in the not-so-distant future, will finish the job he's started.

"There are a huge number of drugs we can make as preventive agents and we have to find a way between support from the government, the private sector, big Pharma and the oncology community to see that they get developed for chemoprevention," he says.

"If it's going to happen, it needs to be a co-operative effort."

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