Center for Astrophysics in Cambridge, Massachusetts, is putting Arp's iconoclastic ideas to a simple test. If the ejection theory is correct, he points out, the paired quasars near a galaxy should move across the sky. Using 1998 data from the National Radio Astronomy Observatory's Very Long Baseline Array, Moran is trying to detect the proper motion of one of the quasars apparently associated with a galaxy known as M 106 or NGC 4258, located in the Big Dipper, 25 million light-years from Earth. "We should have results later this year," Moran says, although he reckons that "a null result will probably not satisfy" the true believers.

At 78, Burbidge—a former director of the Royal Greenwich Observatory in England and former president of the American Association for the Advancement of Science—can afford to do unfashionable research. Still, few of her colleagues are willing to follow her down a path that would throw measurements of cosmic distances into turmoil. "She has earned the right to do whatever she thinks best," says an influential U.S. astronomer who asked not to be named. "But 99% of the astronomical community is pretty sure that quasar redshifts are due to the expansion of the universe and tell us distances."

### Largest Structure in the Universe

Astronomers at the Cerro Tololo Inter-American Observatory in Chile have spotted the largest coherent structure in the universe: a supercluster of galaxies measuring almost 600 million light-years across. The real surprise, though, is the supercluster's enormous distance—some 6.5 billion light-years away, where the universe appears as it was 6.5 billion years ago. Theorists have trouble explaining how such huge structures could have formed so early in cosmic history.

Astronomers began piecing together the galactic aggregation about 10 years ago, says Gerard Williger of the National Optical Astronomy Observatories and NASA's Goddard Space Flight Center in Greenbelt, Maryland. Luis Campusano of the University of Chile and Roger Clowes of the University of Central Lancashire, England, had discovered a large group of quasars in that part of the sky. Most astrophysicists believe that quasars are the bright cores of very distant active galaxies. The new observations indicate that the region occupied by the quasar group contains about three times as many distant galaxies as anyone expected to find.

"In fact, we've put some galaxy flesh on the quasar skeleton," Williger says. Most of the galaxies are too distant and dim to be seen directly, but they leave a telltale absorption fingerprint in the light from still more distant quasars that passes through the galaxies' extended gaseous halos on its way to Earth.

Just how big a headache the supercluster will give theorists depends on how much matter is locked up in it, says Piero Rosati of the European Southern Observatory in Germany. "You have to prove there's mass collapsed here; otherwise it wouldn't be really relevant," Rosati says. Rosati and his colleagues have detected other distant, large superclusters by their x-ray emission, a method that gives a direct estimate for the mass of the cluster, he says. Similar techniques might show that the new supercluster is less fearsome than it appears. "If this is just a bunch of galaxies, it may not be that important," Rosati says. "Sheets and superstructures of galaxies are everywhere in the universe."

—GOVERT SCHILLING

Govert Schilling is an astronomy writer in Utrecht, the Netherlands.

SOURCE: R. N. DUBOIS

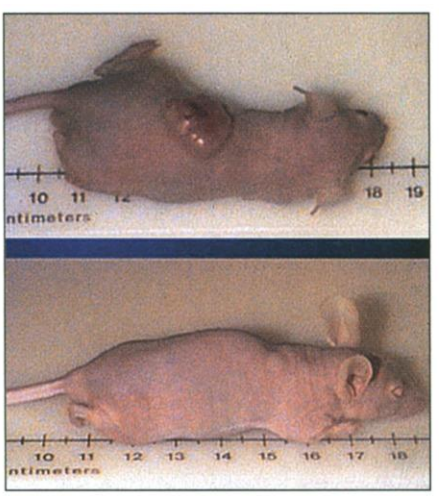
CANCER RESEARCH

# Anti-Inflammatories Inhibit Cancer Growth—But How?

**A debate has emerged about how NSAIDs—nonsteroidal anti-inflammatory drugs—protect against colon and other cancers**

"Prescribing aspirin for cancer" sounds like an exercise in medical futility. But such a treatment may not be pointless after all: Beginning about 15 years ago, evidence began accumulating from both animal work and epidemiological studies on humans indicating that aspirin and related drugs, known as NSAIDs, hinder the development of colon cancer and perhaps other cancers as well.

"NSAIDs protect against cancer—no ifs, ands, or buts," says gastroenterologist Andrew Dannenberg of the Weill Medical College of Cornell University. But, he adds, because aspirin and older NSAIDs can cause potentially dangerous gastrointestinal bleeding, there was "a reluctance to push forward with this [idea] for people with low to moderate [colon cancer] risk." Within the past 2 to 3 years, however, the availability of a new generation of more specific—and therefore safer—NSAIDs has touched off a spate of clinical studies aimed at determining whether these drugs can be used to prevent or treat cancer. Early results suggest they can.



**Protected.** Both mice received transplants of human cancer cells, but treatment of the bottom animal with an NSAID greatly slowed the growth of the cells.

But researchers are deeply divided on whether they exert this potentially beneficial effect by blocking a single enzyme or by stimulating programmed cell death by other routes. The issue is important, because figuring out the mechanism could aid the design of better chemopreventive drugs. Consequently, on 8 January, the National Cancer Institute (NCI) brought many of the leading researchers in the field together in Rockville, Maryland, for a workshop aimed at examining the evidence on both sides.

#### The COX-2 explanation

The surge of interest in using NSAIDs to combat cancer is the outgrowth of the decade-old discovery that the body has two versions of an enzyme called cyclooxygenase. Aspirin and all the other NSAIDs then in use inhibit both versions of the enzyme, but it soon became clear that only one of them, COX-2, is important for inflammation. This enzyme converts a long-chained fatty acid called arachidonic acid to prostaglandins, which in turn trigger inflammatory reactions in the body. The other cyclooxygenase, COX-1, also makes prostaglandins, but they are needed to maintain the stomach lining and normal kidney function. Thus, researchers surmised, inhibition of COX-1 likely accounts for such NSAID side effects as gastrointestinal bleeding. This conclusion led to a new generation of drugs that inhibit only COX-2 (*Science*, 22 May 1998, p. 1191) and that

are now the focus of several cancer trials.

Last spring, the results of the first of these trials was published in *The New England Journal of Medicine*. In this study, a team including researchers at the M. D. Anderson Cancer Center in Houston, St. Marks Hospital in London, NCI, and G. D. Searle in Skokie, Illinois, gave a new NSAID called celecoxib to patients with a rare hereditary condition, familial adenomatous polyposis (FAP). FAP is caused by loss or inactivation of the APC tumor suppressor gene, which leads to the development of numerous precancerous growths, or polyps. Some of these inevitably progress to full-fledged colon cancers. Celecoxib treatment reduced the number of polyps by nearly 30%. NCI's Ernest Hawk says that several more trials of similar new NSAIDs are getting under way for both colon and other cancers.

As described at the NCI workshop, work in several labs has suggested that the drugs' antitumor effects stem directly from their inhibition of COX-2. For example, Raymond DuBois of Vanderbilt University Medical Center in Nashville, Tennessee, and his colleagues found that more than 80% of human colon cancers show much higher expression of COX-2 than the normal cells of the colon lining, suggesting that this overexpression contributes to tumor growth. Work with knockout mice also fingered COX-2. When researchers inactivate the APC tumor suppressor genes of mice, the animals develop numerous polyps in their intestines, as do humans with FAP. By knocking out the COX-2 gene in the FAP mice, a team of Merck researchers significantly reduced polyp formation. Treating the animals with a selective COX-2 inhibitor had the same effect.

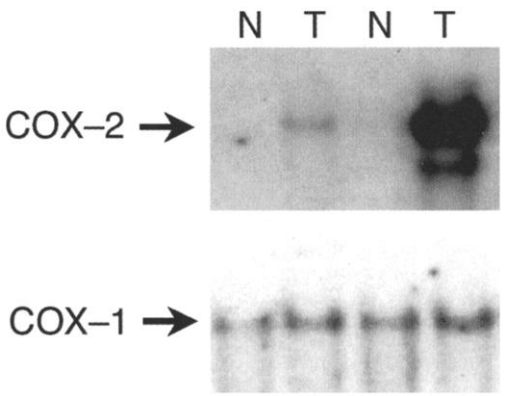
Several other teams have found that COX-2 overexpression may contribute to the development of other cancers as well, including those of the lung, breast, skin, and esophagus. Indeed, new work presented at the NCI workshop by Timothy Hla of the University of Connecticut Health Center in Farmington suggests that COX-2 activity may be all that it takes to induce breast cancer.

Hla and his colleagues attached the COX-2 gene to a regulatory sequence that turns on the gene specifically in breast tissue and then introduced this hybrid gene into mice. The researchers found that the animals, particularly those that had had several litters, began developing metastatic breast cancer. "The data are consistent with the conclusion that COX-2 expression alone is sufficient to induce mammary carcinogenesis," Hla told the workshop participants.

Other findings point to two mechanisms by which COX-2 may foster cancer development. DuBois's team found that it appears to inhibit the form of cell suicide known as apoptosis or programmed cell death, which should otherwise remove damaged or mutated cells. In addition, DuBois's group and a team led by Jaime Masferrer at Pharmacia in St. Louis have evidence that COX-2 activity leads to angiogenesis—the formation of new blood vessels needed to nourish a growing tumor. They also showed that COX-2 inhibitors block this effect.

### Alternative routes

Not so fast, said some other workshop participants, who described ways that the inhibitors might stimulate apoptosis without involving COX-2 at all. For example, I. Bernard Weinstein of Columbia University College of Physicians and Surgeons in New York City has been working with a derivative of the NSAID sulindac produced by Cell Pathways Inc. of Horsham, Pennsylvania. The derivative, called Exisulind, does not inhibit COX-2 yet still has antitumor activity, Weinstein says. His team has shown that it inhibits the growth of human prostate cancer cells in lab cultures and also when transplanted into mice. The data suggest that Exisulind does this by inhibiting an enzyme that breaks down an internal cellular messenger called cyclic GMP, Weinstein said at the workshop. As a result, cyclic GMP builds up in the cell, touching off a series of reactions culminating in cell death.




**A shade of difference.** Human tumors (T) contain much more COX-2 than normal tissue (N), but there is little difference in the COX-1 contents of normal and cancerous tissue.

Work by Kenneth Kinzler, Bert Vogelstein, and their colleagues at the Johns Hopkins University School of Medicine suggests that sulindac itself may stimulate apoptosis through two pathways that don't involve COX-2. In one pathway, they reported, sulindac and other NSAIDs decrease the concentration of an antiapoptosis protein called Bcl-$X_L$. In the other, the drugs counteract the activity of a protein called PPARδ, which protects against apoptosis. Here the NSAIDs may be directly countering the effect of the known cancer-causing mutation, the loss of the APC gene, because PPARδ concentrations go up when that happens.

Finally, Richard Gaynor of the University of Texas Southwestern Medical Center in Dallas reported that NSAIDs interfere with still another cell signaling pathway. This one involves a protein called NF-κB, a so-called transcription factor that regulates the expression of a number of genes, including some that protect against cell death. NF-κB is held in the cytoplasm by another protein called I-κB until an appropriate signal calls for its release. This occurs when an enzyme adds a phosphate group to I-κB, causing it to break down and release NF-κB. Gaynor's team found that sulindac and aspirin both block the activity of the enzyme that phosphorylates I-κB, preventing NF-κB from being set free to exert its antiapoptotic and other effects. "I think this is going to be very complicated and that there will be multiple targets for these [NSAID] agents," Gaynor says.

The COX-2 proponents aren't convinced. They note that most of the experiments pointing to alternate targets involved treatment of cultured cells with what they describe as "industrial strength" NSAID concentrations—tens or even hundreds of times higher than a patient would be exposed to. "A human being never sees anything at that level. It would be incompatible with life," DuBois says. Dannenberg, who organized the workshop with NCI's Victor Fung and Daniel Hwang of Louisiana State University in Baton Rouge, shares that concern. Dosage is a "key issue," he says. "You see all these interesting COX-2–independent effects in [cell culture]. But are they relevant for understanding effects in a human or animal?"

Kinzler concedes that the concentration issue needs to be addressed, although he suspects that because the drugs are given orally, their concentrations may well be higher in the intestine than in the bloodstream, where their concentrations have typically been measured. He also points out that, so far at least, the best evidence that NSAIDs are chemoprotective comes from studies of their effects on colon cancer. "It's a tough question as to what [NSAIDs] do biologically," Kinzler says. But, he adds, the drugs could be working through both COX-2–dependent and –independent pathways, as the two are "not mutually exclusive."

However this debate turns out, say Dannenberg and others, at the very least, the studies finding non–COX-2–related effects of NSAIDs are identifying potential new targets for drugs that can be used to prevent or treat cancer. "A good interpretation of the day is that there are some other legitimate targets [in addition to COX-2] that need to be developed further," says COX-2 camp member DuBois. **–JEAN MARX**

CREDIT: R. N. DUBOIS