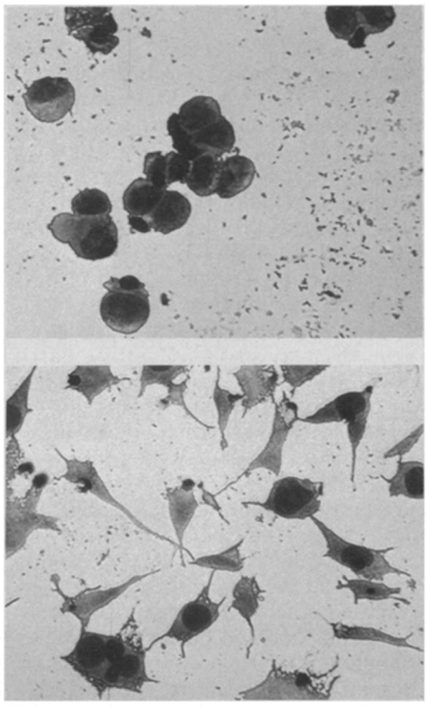
Stopping the deadly invasion of cancer

Cancer cells breaking loose from the original tumor can travel to other sites in the body and multiply into satellite tumors called metastases. These uncontrolled invasions complicate an already serious situation, affecting both treatment and prognosis. During a seminar last week at the National Institutes of Health (NIH) in Bethesda, Md., scientists discussed novel ways being studied to stop the spread of malignant cells — methods they say may someday help lower cancer mortality.



Liotta/NCI

Cultures of human breast cancer cells (above) radically change shape (below) after researchers add autocrine motility factor, a metastasis-promoting substance made by malignant cells.

Lying under the epithelial cells that cover different organs in the body is a scaffolding called the basement membrane, a thin layer of connective tissue that essentially fills space between cell layers and serves as a barrier against invasion. But when the basement membrane is disrupted by malignant cells, metastasis into the underlying tissue occurs. NIH scientists say they are making inhibitors of different substances used by cancer cells to penetrate the basement membrane's defenses, with the hope that such inhibitors may eventually be used as cancer therapy.

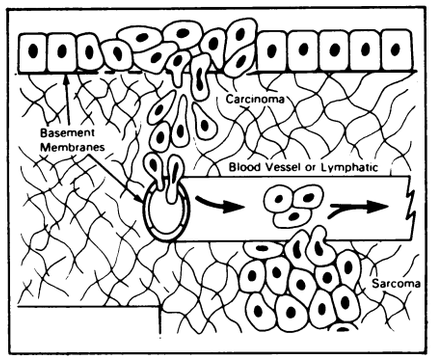
Of special interest among the substances used by metastasizing cells are laminin, fibronectin and autocrine motility factor. A team led by George Martin at the National Institute of Dental Research, for example, is concentrating on laminin, a protein unique to the basement membrane and important in the normal, ordered growth of epithelial cells. But laminin has a dark side as well: Malignant cells have increased numbers of laminin receptors on their surface and become invasive after attaching to the laminin in basement membranes. This binding also increases the release of collagenase IV, an enzyme that further degrades the once-protective membrane.

In the Nov. 20 SCIENCE, Martin and his co-workers reported that a synthetic compound mimicking part of the laminin structure can inhibit melanoma cell migration in mice and cell cultures — most likely by competing with the basement membrane's laminin for the laminin receptor on the cancer cells, and thus preventing the interaction between the cells and the basement membrane. More recently, the scientists have used antibodies against collagenase IV to reduce the tumor cells' attack on the basement membrane. Preliminary studies in mice show that metastases are suppressed "some 70 percent" in animals treated with the antibody, says Martin.

"Studies have shown that it only takes two or three passes through the bloodstream for all tumor cells to be eliminated by the immune system," he says. "So if you stop metastases from forming during this time, you can stop metastasis. There's a great deal of excitement about this [approach]. But people are worried, because lots of enzymes [in metastasis] also are involved in so many things like digestion, that [using antibodies against some enzymes] could be toxic."

At the National Cancer Institute (NCI), researchers led by Kenneth Yamada are dissecting the activities of another substance vital to metastasis. Fibronectin is one of a family of proteins responsible for a cell's ability to adhere to other cells or other structures, a process important to normal cell migration and metastasis alike. Yamada's group has used fibronectin mutants to pinpoint a small area responsible for fibronectin's binding to cells. By synthesizing this active area, the scientists designed an agent that competes with native fibronectin and inhibits its effects on cultured cancer cells.

Using a mouse melanoma model, Martin Humphries and Kenneth Olden from NCI and Howard University Cancer Center in Washington, D.C., are finding that treatment with the synthetic fibronectin fragment provides "a striking protection" from metastasis, says Yamada. He says that, in the latest test completed, all eight mice treated with the substance at the time of injection with melanoma cells are still alive 14 months later, while the eight untreated animals died of melanoma within six weeks. Like Martin's synthetic laminin, however, the fibronectin is short-lived in the body. And included in the possible side effects of any drugs based on fibronectin, says Yamada, are ineffective blood clotting and slower wound healing, both of which rely on cell adhesion.



Yamada/NCI

During metastasis, malignant cells leave their primary tumor and move through layers of tissue into the circulation system. After traveling through the blood or lymph vessels, the cancer cells start new tumors elsewhere in the body.

Another NCI group is taking a somewhat different research approach by looking for genes that influence metastasis. While some genes were found to enhance metastasis, Lance Liotta and his co-workers recently found and cloned a naturally occurring suppressor gene that seems to *inhibit* the process. Patricia Steeg of that group has just discovered similar suppressor genes in four rat and mouse tumors and in human breast cancer cells, says Liotta.

Last fall, Liotta and others reported in the Sept. 17 NATURE that tumor cells secrete a substance the scientists called autocrine motility factor (AMF). The factor binds back onto the cells' surfaces and induces the formation of long "feet" extending from the cells, followed by cell movement. The newly described substance has since been found in greater amounts in the urine of patients with invasive bladder cancer than in patients with noninvasive cancer or without cancer. Liotta told SCIENCE NEWS that he and others are working on a compound that inhibits a key step in the chemical pathways needed for AMF's activity.

None of these potential agents would work against the primary tumor, say the scientists. But, says Martin, "if one could stop that metastatic process, one could control the disease [in many cases]." Antimetastasis agents, according to Liotta, could possibly be used to prevent metastases formed by the "showers of tumor cells" liberated into the blood during surgery, and by the spread of ovarian cancer into the abdominal cavity.

Martin said in an interview that the first clinical trials of these agents may be planned within six months. But, he says, more basic research must be done first to determine whether they are legitimate therapy candidates or "just another thing that's been overpromised."

— D.D. Edwards