

# EXPLORE THE ISSUE BEING INVESTIGATED

## Can Cancer Tumors Be Starved to Death?

One of the most exciting recent developments in the war against cancer is the report that it might be possible to starve cancer tumors to death. Many laboratories have begun to look into this possibility, although it's not yet clear that the approach will actually work to cure cancer. One of the most exciting and frustrating things about watching a developing science story like this one is that you can't flip ahead and read the ending—in the real world of research, you never know how things are going to turn out.

This story starts when a Harvard University researcher, Dr. Judah Folkman, followed up on a familiar observation made by many oncologists (cancer specialists), that removal of a primary tumor often leads to more rapid growth of secondary tumors. "Perhaps," Folkman reasoned, "the primary tumor is producing some substance that inhibits the growth of the other tumors." Such a substance could be a powerful weapon against cancer.

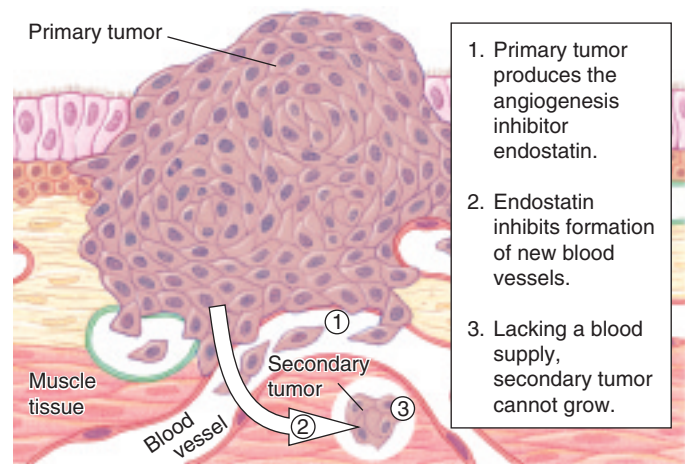
Folkman set out to see if he could isolate a chemical from primary tumors that inhibited the growth of secondary ones. Three years ago he announced he had found two. He called them angiostatin and endostatin.

To understand how these two proteins work, put yourself in the place of a tumor. To grow, a tumor must obtain from the body's blood supply all the food and nutrients it needs to make more cancer cells. To facilitate this necessary grocery shopping, tumors leak out substances into the surrounding tissues that encourage angiogenesis, the formation of small blood vessels. This call for more blood vessels insures an ever-greater flow of blood to the tumor as it grows larger.

When examined, Folkman's two cancer inhibitors turned out to be angiogenesis inhibitors. Angiostatin and endostatin kill a tumor by cutting off its blood supply. This may sound like an unlikely approach to curing cancer, but think about it—the cells of a growing tumor require a plentiful supply of food and nutrients to fuel their production of new cancer cells. Cut this off, and the tumor cells die, literally starving to death.

By producing factors like angiostatin and endostatin, the primary tumor holds back the growth of any competing tumors, allowing the primary tumor to hog the available resources for its own use (see above).

In laboratory tests the angiogenesis inhibitors caused tumors in mice to regress to microscopic size, a result that electrified researchers all over the world. Other scientists were soon trying to replicate this exciting result. Some



**How primary tumors kill off the competition.** Tumors require an ample blood supply to fuel their growth. The growth of new blood vessels is called angiogenesis. Inhibiting angiogenesis offers a possible way to block tumor growth.

have succeeded, others not. Five major laboratories have isolated their own angiogenesis inhibitors and published findings of antitumor activity. The National Cancer Institute is proceeding with tests of angiostatin and other angiogenesis inhibitors in humans. Preliminary results are encouraging. While not a cure-all for all cancers, angiogenesis inhibitors seem very effective against some, particularly solid-tumor cancers.

Gaining a better understanding of how tumors induce angiogenesis has become a high priority of cancer research. One promising line of research concerns hypoxia. As a solid tumor grows and outstrips its blood supply, its interior becomes hypoxic (oxygen depleted). In response to hypoxia, it appears that genes are turned on that promote survival under low oxygen pressure, including ones that increase blood flow to the tumor by promoting angiogenesis. Understanding this process may give important clues as to how angiogenesis inhibitors work to inhibit tumor growth.

So how does a lowering of oxygen pressure within a tumor promote blood vessel formation? Dr. Randall Johnson of the University of California, San Diego, is studying one important response by a tumor to hypoxia—the induction of a gene-specific transcription factor (that is, a protein that activates the transcription of a particular gene) that promotes angiogenesis. Called HIF-1, for *hypoxia inducible factor-1*, this transcription factor appears to induce the transcription of genes necessary for blood vessel formation.