The formation of new blood vessels, termed angiogenesis, is important in development, ovulation, wound repair, and tumor growth (1). Various key steps in angiogenesis have been defined and include cell migration, invasion of tissues, proliferation, and formation of a new underlying basement membrane matrix. Tumor cells use similar mechanisms when forming metastases except that tumor cells do not synthesize a basement membrane matrix. When tumors reach a certain critical size, they require a blood supply to allow further rapid growth (2). Various stimulators of angiogenesis have been found to increase tumor growth and metastases (1, 3). In addition, tumors produce a number of angiogenic factors and the levels of some of these factors in the urine are being proposed as predictors of cancer growth and progression (4). The importance of the vascular supply to tumor growth has also been shown by blocking either the activity of angiogenic factors with antibodies or by blocking their receptors for these factors on endothelial cells. Recently, therapeutic strategies aimed at the tumor-induced vessels have been found to have success in animals in reducing tumor growth and metastases (5). The main advantage of using antiangiogenic factors as therapeutic drugs for cancer is that such an approach would be effective against all solid tumors unlike the many cancer treatments in current use which are stage- and tumor type–specific. Some antiangiogenic factors are currently in clinical trials but must await further testing (6). Many of these drugs being tested are protease inhibitors, cytokines, and steroids (1). Some of these antiangiogenesis inhibitors under study also affect tumor cells since tumor cell growth, metastases, and angiogenesis involve some common mechanisms. For example, these processes can all be affected by protease inhibitors (7).

In this issue of *The Journal*, Volpert and colleagues (8) find that a clinically approved drug, Captopril, which is used to manage hypertension and congestive heart failure, has the unexpected beneficial side effect of reducing angiogenesis and tumor growth in rats. Captopril was an excellent choice to test for antiangiogenic activity because it had been found to reduce arthritis, diabetic retinopathy, atherosclerosis, and cancer, which are angiogenesis dependent. How Captopril functions is not known. The demonstration of the antiangiogenic activity as a beneficial side effect in an already approved drug in clinical use could mean a quick route to treatment of many diseases including cancers that depend on an external blood supply, Kaposi's sarcoma, etc. The timeliness of the finding is exciting.

Many drugs in clinical use should be further examined for additional beneficial activities that may have important and unexpected uses. The public generally focuses on the bad side effects of drugs and fails to recognize good "side effects" or other activities. Some drugs have been found to have multiple activities. Examples of already known drugs with such multiple possible uses include aspirin, minoxidil, retinoic acid, etc. Aspirin has been used as a pain killer and recently has been found to reduce cancer and vascular disease. Retinoic acid was used initially to treat acne and has an additional use in reducing wrinkling. The antihypertensive drug minoxidil is currently popular because it can restore hair growth in certain people. These are examples of some drugs with more than one activity. Others likely exist that have not yet been identified and need to be extensively tested.

Hynda K. Kleinman and M. Lourdes Ponce
Cell Biology Section
National Institute of Dental Research
National Institutes of Health

References

1. Cockerill, G.W., J.R. Gamble, and M.A. Vadas. 1995. Angiogenesis: models and modulators. *Int. Rev. Cytol.* 159:113–160.
2. Folkman, J. 1990. What is the evidence that tumors are angiogenesis dependent? *J. Natl. Cancer Inst.* 82:4–6.
3. Kibbey, M.C., D.S. Grant, R. Auerbach, and H.K. Kleinman. 1992. The SIKVAV site of laminin promotes angiogenesis and tumor growth. *J. Natl. Cancer Inst.* 84:1633–1638.
4. Nguyen, M., H. Watanabe, A.E. Richie, and J. Folkman. 1993. Elevated levels of the angiogenic peptide basic fibroblast growth factor in urine of bladder cancer patients. *J. Natl. Cancer Inst.* 85:241–242.
5. Folkman, J. 1995. Angiogenesis in cancer, vascular, rheumatoid and other diseases. *Nat. Med.* 1:27–31.
6. Harris, A.L., S. Fox, R. Bicknell, R. Leek, M. Relf, S. LeJeune, and L. Kaklamanis. 1994. Gene therapy through signal transduction pathways and angiogenic growth factors as therapeutic targets in breast cancer. *Cancer Res.* 74: 1021–1025.
7. Moscatelli, D., and D.B. Rifkin. 1988. Membrane and matrix localization of proteinase: a common theme in tumor cell invasion and angiogenesis. *Biochem. Biophys. Acta.* 948:67–85.
8. Volpert, O.V., W.F. Ward, M.W. Lingen, L. Chesler, D.B. Solt, M.D. Johnson, A. Molteni, P.J. Polverini, and N.P. Bouck. 1996. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. *J. Clin. Invest.* 98:671–679.

J. Clin. Invest.

0021-9738/96/08/0599/01 $2.00
Volume 98, Number 3, August 1996, 599