Without a blood supply to provide the needed nutrients, neoplasms cannot grow more than a few millimeters. Tumors that lack this ability remain in situ, a steady state in which the number of new cells equals the number of dying cells. But, for unknown reasons, an in situ tumor can suddenly induce new capillary growth, allowing the mass to continue growing and invade adjacent tissue. Evidence shows that some cancers progress due to decreased oxygen availability, or hypoxia. The lack of oxygen triggers a chemical response that in turn creates neovascularization and other processes that allow tumor cells to survive or escape their oxygen-deficient environment.

Once angiogenesis occurs, scores of new capillaries converge on the tiny tumor. According to Hawkins, “…each vessel soon has a thick coat of rapidly dividing tumor cells.” Within months the tumor may grow to a cubic centimeter, containing about one billion tumor cells. To make matters worse, the endothelial cells of the new capillaries release different proteins that can stimulate excess cell proliferation or the cell’s ability to move, increasing the likelihood that cancer cells will leave the primary tumor and migrate into the bloodstream.

It is these qualities of uncontrolled proliferation, lack of adhesiveness, anchorage independence, diminished need for growth factors, the ability to secrete degradative enzymes and induce new capillary growth that are associated with cancer cells’ ability to spread. The spreading occurs irrespective of patients’ activities. It happens while watching TV, cooking dinner, playing with the children, or even sleeping. Avoiding massage will not stop these rogue cells from slipping away from the original tumor. This is not to say that bodyworkers are free to work without inhibition. As shall be seen in later chapters, there are reasons for adjusting the sessions a cancer patient receives, but the adjustments do not center around the potential for metastatic spread. They are, by and large, a result of the patient’s treatment history.

THE SPREAD OF CANCER

Cancer does not spread in a random, willy-nilly way. It is a logical, orchestrated event. Malignant cells spread from the primary tumor by two major processes: 1) direct spreading to adjoining areas, or 2) metastatic spread to distant sites. The dissemination may be by one or both processes, since spread via one route may create access to the other.

DIRECT SPREAD

It is not yet understood why certain malignant masses remain in situ, some are locally invasive but limit their growth to the surrounding tissue without metastasizing, and others become aggressively malignant and metastasize to often distant tissues. Researchers believe...
that tumors are propelled toward invasiveness by another accumulation of genetic transformations.

Direct spread, the penetration and destruction of adjacent tissue, is the result of many factors. Local invasion is enhanced by the ability of malignant cells to stimulate new capillary formation. This greatly increases the tumor’s growth rate. Rapid proliferation produces densely packed, expanding masses of cells that exert pressure on adjacent tissues, forcing fingerlike projections into neighboring areas. Tumors then spread into spaces that separate in response to pressure, such as interstitial or cerebrospinal spaces or the abdominal cavity.

Malignant cells may also invade by secreting enzymes that break down the basement membrane of tissues, resulting in the penetration of body cavities (see Figure 2.1). After spreading into neighboring areas and penetrating body cavities, such as the pleura or peritoneum, cancer cells can attach to the surfaces within the cavity.

**METASTATIC SPREAD**

Fortunately, even if a malignant cell is released due to increased pressure or has slipped away from the primary site, the formation of a secondary tumor is not an automatic outcome. Once a tumor cell has left the parental mass, it must successfully complete a series of steps to establish a metastatic lesion. (A lesion is tissue that is pathologically changed.) The inability to complete any of the following steps will stop the metastatic cascade:

1. Detach from the original tumor
2. Invade the blood system or lymph vessels
3. Survive in the circulatory system and travel to a distant site
4. Arrest in a congenial site
5. Adhere to the endothelial lining of the blood vessels in the new organ
6. Re-invade the distant organ or tissue
7. Establish a blood supply

Despite their many capabilities, it is so difficult for the migrating cells to complete all of these requirements that very few manage to colonize a distant site. The spread to distant sites occurs via two entryways, lymphatic channels or blood vessels. Often, because the vascular and lymphatic systems are interconnected, both are involved.

**LYMPHATIC DISSEMINATION**

For many types of cancer the first evidence of spreading is a mass in the lymph nodes that drain the area where the primary tumor is located. The spread of malignant cells into the lymph nodes is a
A significant occurrence, as lymph nodes are involved in about half of all fatal cancers. Lymphatic metastases indicate the tumor is able to leave the primary site and are predictors that distant metastases are likely to be found. Extension into the lymph nodes can be fast or slow, depending on the tumor. Once malignant cells lodge in lymph nodes they have several possible fates: 1) die of a local inflammatory reaction; 2) wither and die because of a lack of the proper environment; 3) grow into a mass; 4) remain dormant.

At one time, the filtering action of the lymph nodes was believed to be the cause of nodal metastasis. Research, however, has shown filtration to be only a minor influence. Most likely the interaction between physiochemical changes on the cancer cell's surface and the lymph node determines whether and where the cancer cells will lodge in the lymphatic system. Logically, it might follow that the nearby lymph nodes that drain the primary tumors would test positive before more distant nodes. While this sometimes is the case, other metastatic cells bypass local lymph nodes and settle in distant ones, indicating that other influences are at work. Just as blood-borne metastases are not random or completely the result of anatomical flow routes, neither are nodal metastases. Most likely, site specific recognition plays a part in the location of these cancers.

Until recently, researchers were unaware that tumors are able to form new lymph vessels. A protein known as vasoendothelial growth factor-C has been found to stimulate the formation of lymph vessels, a process known as lymphangiogenesis. The formation of new vessels facilitates the spread of cancer to nearby lymph nodes. These new vessels do not, however, appear to spread the cancer to distant sites. Other factors are responsible for that.

**BLOOD-BORNE SPREAD**

The local spread of cancer occurs predominantly through the lymphatic vessels, but spreading to remote organs and tissues is almost always via the bloodstream. Lymphatic metastases are rarely in and of themselves the cause of death in people with cancer. When the spread is to critical distant organs, such as the liver, lung, bone, or brain, cancers are most dangerous.

Tumor cells that enter the blood stream circulate until one of three things happens: 1) they are killed, 2) they are trapped in the capillary bed of another organ, or 3) they invade the blood vessel wall into the tissue of a distant organ. Only the latter group can ever form metastatic colonies. Cells that remain in the blood stream or are trapped inside the tiny vessels of a capillary bed die fairly quickly, often within hours.

It is so difficult for the migrating cells to complete all of the requirements that very few ever manage to colonize at a distant site. It is estimated that fewer than one in 10,000 cancer cells that enter the bloodstream live to reach another organ. Even fewer successfully implant themselves. At every step they must escape the many controls that keep normal cells in place. But, because the process...
occurs over and over for many days, some metastatic growths eventually form.\textsuperscript{10}

While in the circulatory system cancer cells face many threats, such as the mechanical forces of blood turbulence. Hemodynamics has been suggested as a possible factor in that vascular pressure and flow rate may be too high in certain areas, such as skin and skeletal muscles, to allow cancer cells to come to rest there.\textsuperscript{13} On the other hand, tumor cells often adhere to other tumor cells and blood cells, especially platelets. Platelets produce their own growth factors which may help the cancer cells survive in the blood.\textsuperscript{17} Adhering to other cells also helps protect the tumor cells from circulating immune cells and produces enlarged emboli, increasing the likelihood they will arrest in the target organ.\textsuperscript{4,9}

It is hypothesized that the location of over half of metastatic deposits can be predicted from the blood flow route. In this model of prediction, the first organ encountered would be the site of the greatest tumor cell arrest. This might account for the higher number of lung tumors, as the lung is the first organ the shed cells encounter after entering the venous circulation. How, though, do tumors travel past the initial organ and implant farther afield? There is evidence that cells can pass through capillaries smaller in size than themselves,\textsuperscript{18} so it is not enough to passively trap tumor emboli that are too big to pass. Other factors dictate where metastatic colonies will develop.

The ability of cancer cells to flourish at a specific site is dependent on the interactions between the cancer cell and the organ. One characteristic that might make an organ congenial to tumor growth is the presence of specific growth factors found at those sites. Other evidence points toward an idea of adhesive-specificity, where particular cancers bind to certain types of tissue. In part, this happens because they home in to certain sites that contain the molecular address system that matches to the surface of certain tissues or organ. Figure 2.2 illustrates this “lock and key” configuration known as site specific recognition. Migration to these sites appears to be under the influence of chemical messengers that guide the tumor cells to travel in the direction of certain growth factors rather than moving about in hit-or-miss fashion. Some researchers have put forward the idea that the preference for certain metastatic sites may be genetically determined.\textsuperscript{17}

After the tumor cell embolus has arrested, a number of things must happen in order for the sequence to continue. It must adhere to the endothelial lining, and then invade that wall to pass through to the basement membrane surrounding the tissue or organ. Then the metastatic cells must invade that protective wall. This happens either directly through thin-walled capillaries, or by producing enzymes that degrade the basement membrane. Degradation of the basement membrane damages the tissue, which in turn stimulates an inflammatory response. Prostaglandins, one of the substances released during the inflammatory process, causes vasodilation, which increases the permeability of the affected vessels. Cancer cells use these leaky
vessels and the subsequent creation of an inflammatory reaction at the site to further escape from the vascular system.\(^9,17\)

A number of things can happen once cancer cells invade remote tissue. They may die, or lie dormant for years and then grow to a large size long after the primary tumor has been removed, or they may begin growing to a large size immediately. It is not known what causes cancer cells to remain in a dormant stage, or what causes them to eventually become active. Possibly small populations of tumor cells remain in an avascular phase for prolonged periods, until a new biochemical message stimulates them into action. Breast cancer, for example, has been known to metastasize to the vertebrae 30 years later.\(^9\)

The final ability needed to create a new growth is the capacity of the tumor to establish its own blood supply. This is done when the metastatic cell sends a chemical message to the host tissue, such as the lungs, that stimulates capillary growth. Without the ability to perform angiogenesis, the tumor would wilt and die after a short period of time.\(^19\)

**Host Factors**

Exposure to a cancer-causing agent doesn’t mean a person will get cancer. The development of cancer is a complex interaction that is influenced by how often, how long, and how much exposure the person had, and his or her genetic predisposition to developing cancer. The way in which tumors of the same type metastasize varies from one person to the next. This has led some researchers to conclude that factors related to the host contribute to metastatic potential. Besides genetics, diet and other lifestyle choices, the immune system, age, and hormones can determine the way in which the cancer process unfolds.\(^9\)

The capacity of a person’s immune system influences whether and how cancer will develop. Some researchers believe that cancer cells are continually being created in our bodies, and then destroyed, and that it is when the “surveillance system” breaks down that malignancies occur. Stress, age, or certain medications can be the cause of the immune system’s becoming suppressed. In experiments with animals, cancer cells that normally wouldn’t metastasize will do so in animals whose immune systems are suppressed. Human evidence bears this out, too. Immunocompromised individuals are many times more likely to develop cancer than those in the general population.\(^9\)

Surprisingly, certain processes of the immune system, such as inflammation, assist in the establishment of metastatic disease. Some tumors can induce an immune response when their growth causes injury to surrounding tissue. This sets the inflammatory cells of the immune system into motion. Along with the tumor, these inflammatory cells also produce enzymes that degrade the basement membrane of surrounding tissue as well as blood vessels. Tumor cells