The terminology of cancer: One of the more confusing aspects of neoplasia is its arcane terminology. This is due to the recognition of cancer for 2,500 years. Even if there was a poor understanding of what it represented, physicians sought to categorize ugly growths, resulting in a terminological mini-maze for students. In truth there is no perfect term for “cancer.” Indeed it is hard to define cancer in a short sentence, since it is not a single disease. The best definition of cancer you will see is that of the British oncologist Willis who in 1952 offered the following:

“A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change.”

This distinguishes neoplasia from hyperplasia, since the latter wanes once the inductive stimulus has disappeared. Cancer does not, since it is the result of a permanent genetic damage that, at least initially, is not lethal to the affected cell. Willis’ definition says nothing about the appearance of neoplastic tissue, which in some cases may look confusingly normal, or resemble inflammatory or reparative responses. Some terms used on oncology (the science of studying tumors) follow.

Neoplasia is arguably the best, and means “new tissue.” It encompasses both benign and malignant masses. A perfectionist might argue that an exuberant scar or a fetus also represent “new tissue”. Cancer, literally a crab, by definition means a malignant neoplasm – the Greeks recognized that malignant skin tumors were firmly attached and, when advanced, extended into and were anchored by underlying tissue. A tumor, mass or growth connotes a clinical swelling, and are common synonyms for neoplasia. In some cases they prove to be something else, such as an abscess or a granuloma masquerading as cancer.

More specific and clinically meaningful terms are benign and malignant. A benign mass, often identified by the suffix –oma, is generally well-differentiated and not life-threatening. It resembles its tissue of origin, tends to compress rather than invade local tissue, never metastasize, and has low rates of mitosis. By contrast, a malignant mass is less well differentiated (i.e., cells tend to be anaplastic), has a high mitotic rate, tends toward pleomorphism (cells vary in size and shape), and tend to grow more rapidly. Rapid growth is one reason why ulceration or necrosis in a tumor is a warning sign of possible malignancy. As an aside, my mother, an avid gardener, developed a small ulcer on her leg when in her 50s. She saw a doctor, who reassured her that it was probably nothing - but had her in for surgery the very next day. He removed what proved to be a cutaneous squamous cell carcinoma associated with sun exposure; it was only then he told her that this rapidly ulcerating mass was suspicious for a SCC. One unequivocal sign of malignancy is metastasis: spread from the tissue of origin to another location. Most malignant tumor falls into two broad categories. If they arise from tissue derived from any of the three embryonic germ layers, they are carcinomas. If instead they derive from mesenchymal components, such as connective tissue, bone, cartilage, or muscle, they are sarcomas. So one of the
major tumors arising from mammary gland tissue is called a simple mammary adenocarcinoma – the suffix *adeno-* means it originated in a gland. And a tumor arising from fibrous connective tissue is called a fibrosarcoma. Combination tumors, with both epithelial and mesenchymal components occasionally occur (in dogs most commonly in mammary tumors), and are called * carcinosarcomas.*

An important part of the job of a diagnostic or surgical pathologist is to establish whether a mass removed from a patient is a neoplasm, whether it is benign or malignant, whether removal is complete or not, and the likely prognosis. You occasionally see on television a man in a white coat tell a patient, usually a woman: “You have 6 weeks to live.” In truth, determinations of life expectancy after a diagnosis of cancer are not this precise. And having given you some broad guidelines for the distinction between benign and malignant tumors, it would be remiss of me not to point out that there are cases where this distinction is so clear cut. For example, there is a fast growing round cell tumor we see in young dogs (<3 years old), sometimes called “button ulcers.” Histologically they contain moderately pleomorphic round cells derived from a subset of the antigen-presenting cells (dendritic cells). Mitotic figures can be bizarre. If a slide of such tumor, called a *cutaneous histiocyтома,* was shown to a human pathologist it is likely she would diagnose a malignant histiocytic tumor. This is one reason why human pathologists should attempt diagnosis of disease in animals – and equally why it is unethical for veterinary pathologists to examine tissues from human patients. Another tumor that histologically looks malignant yet rarely if ever metastasizes, is an *extramedullary plasmacyтома.* Histologically these are moderately pleomorphic and contains large ("giant") cells. Its behavior is distinct from malignant plasmacytomas in animals and human patients, which are true killers. Some tumors that look histologically low-grade, yet are clinically aggressive: one such is the lugubriously named *histologically low-grade yet biologically high-grade fibrosarcoma of the canine mandible and maxilla.* One skill of the diagnostic pathologist, medical or veterinary, is to be aware of distinctions between histological appearance and likely biological behavior. Unfortunately, they are not always the same

**Grading and staging:** A clinician “stages” a tumor, and a pathologist “grades” them. One nice thing about working as a surgical pathologist is the need to work closely with clinicians; in an ideal world, a combination grading-staging system has clinical and prognostic significance. Together, the goal is to box in the type of tumor most accurately so that it can be treated appropriately. This becomes important in clinical trials: one has to be sure that all tumors being treated are in the same class. Currently, in veterinary medicine, this is done by a combination of grading and staging. Grading is easy when the choice is between the two ends of the spectrum: the challenge is that gray zone in the middle. Typically in veterinary medicine it is done on a 1, 2 and 3 scale. This assumes one or more groups have published credible Kaplan-Meier curves showing that there is a biological meaning in terms of long-term survival and the histological grade. Criteria typically used are size and location of the mass (bigger implies worse prognosis), along with histological features such as pleomorphism, anaplasia, tissue necrosis, and mitotic rate. Long established in human medicine, and increasingly important in veterinary medicine, is the use of **immunohistochemistry** to better characterize the antigenic content of tumors, particularly undifferentiated masses. The detection of estrogen/progesterone receptors is established as a prognostic tool in human medicine for breast cancer, signaling which ones are likely to respond to anti-estrogen therapy. **Molecular profiling** is increasingly important as a medical tool in human medicine,
and is likely to become so in small animal oncology in the near future. It is based on the use of microarray technology, where mRNA extracted from patients’ tumors is analyzed to determine which genes are up- or down-regulated. Ideally these should be a small number (10 – 100) of genes of proven prognostic significance. The FDA has approved several such gene-expression signature devices for use in breast cancer treatment in people. They are used as a guide for prognosis, the most beneficial treatment, quantifying disease burden, and monitoring early recurrence. In tumor staging, the TNM system is used, with T meaning tumor, N meaning lymph node, and M meaning metastasis,. The tumor is typically staged as 0, I, II, III or IV, based on a number between 1 to 4 assigned to T, N and M. So a stage 0 might be a carcinoma in situ, a stage I means it invaded a little into tissue of origin, stage II means it has invaded that tissue extensively, stage III means it has spread to local lymph nodes, and IV means extensive metastasis throughout the body. Staging takes into account the size of a tumor, how deeply it penetrates, whether it has invades adjacent organs, how many lymph nodes have metastases and whether there is spread to distant organs.

The causes of cancer: There are, as you should now know, eight recognized causes of disease. In addition to neoplastic, these are trauma/physical; age-related; nutritional; intoxication; infectious; genetic/developmental; immune-mediated. Each of these can also cause cancer, although their relative importance varies with species. Trauma/physical causes include burns, solar and x-irradiation, and foreign body material. We occasionally see sarcomas (most commonly, fibrosarcomas) at sites of microchip implants and associated with foreign body material such as aluminum adjuvants in vaccines. Rarely, cotton swabs left in patients are the sites of subsequent neoplasms. It is unclear whether this is response to inflammation and/or repair, or another process. Age-related causes are obvious: most cancers occur in the second half of life in people and dogs, presumably as a consequence from swimming in a sea of inhaled and ingested carcinogens. At least two factors are involved: the accumulation of somatic mutations over time, and some age-related decline in immune competence/surveillance. That is not to say that neoplasia does not affect children or young animals. Cancer is the second most common cause of death among children between 1 - 14 years in the United States, surpassed only by accidents. These tumors tend to a specific subset of tumors seen later in life – and one rarely sees carcinomas in children. The common childhood cancers are the leukemias, primitive neoplasms of nervous system, and soft tissue sarcomas. One of the big successes in oncology has been the increased ability to treat and control childhood cancer. Currently the 5-year survival rate for such children is 81% (1999 – 2005), compared to 58% in earlier decades (1975 – 1977). One price paid for this is the high rate of post-treatment complications (including secondary cancer) in cancer-survivor children later on in life. Infectious forms of cancer, particularly the retroviruses, are important and relatively common causes of cancer in young animals (domestic chickens; cats; dairy cattle). It has been recognized from Virchow’s time that chronic infections can predispose to neoplasia – so we see tumors as a sequel to Helicobacter pylori infection (gastric neoplasia) and some forms of viral hepatitis. Nutritional risk factors – I hesitate to call them causes – include high-fat diets and, in people, alcohol. According to one estimate, obesity is a factor about 1/5 of all human cancers. There is little information available about genetic forms of neoplasia in animals, but in people it is estimated that <10% of cancers are due to predisposing inherited mutations. Some have been important as providing clues about what has gone wrong, such as mutations in tumor suppressor genes and defective DNA repair syndromes.
Immune-mediated forms of cancer are most clearly seen in immunosuppressed patients, particularly those that received organ or tissue transplants. According to one estimate, after 20 years of immunosuppressive therapy some 40% of recipients developed cancer.

The components of a neoplasm: Tumors typically have three major components: the tumor population, its supporting fibrous connective tissue matrix, and the blood supply. Interestingly, most tumors lack a nerve supply, which is why they are largely painless – pain, which is often present, is due to effects on adjacent tissue. Often there is a fourth: an inflammatory response, due either to tumor antigens or the presence of necrosis, or both. The vascular supply is the source of considerable interest from a biological and treatment standpoint, since this is often the basis for metastatic spread and may represent a good target for treatment, assuming there was a way to selectively destroy the tumor’s blood supply. The connective tissue component is of interest since some tumors evoke little connective tissue, whereas others induce an excessive response. These are called scirrhouss or desmoplastic reactions, which can be clinically useful as a clue to the nature of a mass. Some tumors, such as intestinal and gastric adenocarcinomas in dogs and cats, evoke such a scirrhous response that when they examined histologically they consist mostly (up to 90%) of the host’s fibroblastic response. The white, scarred gross appearance may lead the clinician-surgeon to mistake these grossly as non-neoplastic, ulcerative lesions.

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