Second Edition

Canine and Feline Geriatric Oncology

Honoring the Human-Animal Bond

Alice Villalobos
with Laurie Kaplan

WILEY Blackwell

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To Dr. Gordon H. Theilen, mentor, teacher, researcher, colleague, and inspiration to many creative leaders who helped develop the rapidly growing, multidisciplinary field of veterinary oncology. I dedicate this book to Dr. Theilen, my great mentor, who guided me, a student oncophile, through his visionary and first mock residency program in veterinary oncology at UC Davis, School of Veterinary Medicine, from 1969 to 1972. Dr. Theilen has continued to advise and inspire me with his wonderful courage, character, and generosity over the years. Dr. Theilen was the first President of the Veterinary Cancer Society and a notable international forefather in veterinary cancer medicine and research. We celebrated his 80th Birthday in May of 2008 at the Theilen Tribute Symposium, where the Veterinary Cancer Society gave him the first Theilen Tribute Award for lifetime achievement in oncology. I thank Dr. Theilen for giving us an autobiographical account of his illustrious career in his book, *The Boy with the Wounded Thumb*, EditPros LLC, Davis, CA 95616, 2017.

To Antonio and Alicia Villalobos, my wonderful parents, who held on to each other and their five children with amazing love and courage through thick and thin for 65 years. Their strength, encouragement, and example in dealing with the joys and adversities of life and aging will live as long as their family has life.

I also dedicate this book in honor of the late Dr. Johan de Vos of the Netherlands, who was an inspirational leader for European and veterinary oncologists, worldwide.

Contents

Foreword

The amount of information that applies to contemporary veterinary geriatric oncology is mounting at a frenetic pace. It is generated from the hard work of thousands of clinical researchers and authors of scientific publications in oncology, hematology, gerontology, radiation oncology, internal medicine, surgery, immunology, nutrition, sociology, epidemiology, and research in all related fields. This book draws from the texts and the milieu of references available. Instead of reprinting material, the author delivers applied knowledge to individual cases. For more in-depth detail, readers are referred most notably to the following general references used for this book, listed alphabetically by title:

- AAHA Guidelines on Managing Cancer in Dogs and Cats is an excellent summary. www.aaha.org/professional/resources/oncology.aspx 2016.
- AAHA/AAFP Pain Management Guidelines for Dogs and Cats: an Implementation Toolkit. www.aaha.org/professional/resources/pain_management.aspx 2015.
- AAHA/IAAHPC End of Life Care Guidelines and Implementation Toolkit: 2016.
- www.aaha.org/professional/resources/end_of_life_care_guidelines.aspx
- AVMA Animal Health Studies Database. Offers a centralized source for clinical trials.
- https://ebusiness.avma.org/aahsd/study_search.aspx
- AVMA Guidelines for Veterinary Hospice Care, 2015
- www.avma.org/KB/Policies/Pages/Guidelines-for-Veterinary-Hospice-Care.aspx
- *Being Mortal: Medicine and What Matters in the End*, by A. Gawande, Metropolitan Books, Henry Holt and Company, NY, 2014.
- *BSAVA Manual of Canine and Feline Oncology*, 2nd and 3rd edns, eds J.M. Dobson and D.B.X. Lascelles. Quedgeley, Gloucestershire, England: British Small Animal Veterinary Association, 2003 and 2011.
- *Cancer Control: Journal of the Moffitt Cancer Center*. Geriatric Oncology, Guest ed. L.Balducci. Vol. 1, No. 2, March 1994.
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- *Cellular and Molecular Immunology*, 8th edn, by A.K. Abbas, A.H. Lichtman, and S. Pillai. Saunders/Elsevier, 2014, 554 pp.
- *Clinical Oncology*, 3rd edn, by M.D. Abeloff, J.O. Armitage, J.E. Neiderhuber, M.B. Kastan, and W.G. McKenna. Philadelphia, PA: Churchill Livingstone, 2004.

- *Comprehensive Geriatric Oncology*, 2nd edn, eds L. Balducci, G.H. Lyman, W.B. Ershler, and M. Extermann. Oxon, UK: Taylor & Francis, 2004.
- *Feline Oncology*, by G. Ogilvie and A. Moore. Trenton, NJ: Veterinary Learning Systems, 2001.
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- *Managing the Veterinary Cancer Patient*, by G. Ogilvie and A. Moore. Trenton, NJ: Veterinary Learning Systems, 1995.
- *Palliative Care: Transforming the Care of Serious Illness*, eds D.E. Meier, S.L. Issacs, and R.G. Hughes. San Francisco, CA: Jossey-Bass/Wiley, 2010, 452 pp.
- *Small Animal Clinical Oncology*, 3rd, 4th, and 5th edns, by S.J. Withrow, E.G. MacEwen, R. Page, and D.M. Vail. Philadelphia, PA: Saunders, 2001–2007, 2013, Elsevier.
- *Tumors in Domestic Animals*, 3rd edn, ed. J. Moulton. Berkeley, CA: University of California Press, 1990.
- *Tumors in Domestic Animals*, 4th edn, ed. D. Meuten. Ames, IA: Blackwell Publishing Professional, 2002.
- *Veterinary and Comparative Oncology*, journal eds. D. Argyle and D. Thamm, Wiley Blackwell, all issues.
- *Veterinary Cancer Medicine*, 2nd edn, eds G. Theilen and B. Madewell. Philadelphia, PA: Lea & Febiger,1987.
- *Veterinary Oncology Secrets*, by R. Rosenthal. Philadelphia, PA: Hanley & Belfus, 2001.
- *Zoobiquity: What Animals Can Teach Us About Health and the Science of Healing,* by B. Natterson-Horowitz and K. Bowers. Knopf, 2012.

Disclaimer: Geriatric patient oncology care and client communications are ultimately the attending doctor's responsibility. Author and publisher shall not be liable for any loss related to the use of information in this textbook. Readers are encouraged to check and verify doses and schedules and current information or consult with specialists. Some excellent resources available online include:

- www.vetcancersociety.org
- https://ebusiness.avma.org/aahsd/study_search.aspx (clinical trials database)
- http://www.lib.ncsu.edu/vetmed/boards/ACVIM/oncology: 2017 Residency reading list
- *How the Immune System Sees and Destroys Tumors*, Jeffrey S. Weber, MD, PhD, Moffitt Cancer Center, Tampa, Florida. https://www.youtube.com/watch?v=3hlGq-3F1uQ
- World Small Animal Veterinary Association, 2014. Guidelines for Recognition, Assessment and Treatment of Pain, *Journal of Small Animal Practice*. http://www.wsava.org/sites/default/files/jsap_0.pdf
- https://clinicaltrials.gov/ct2/results?term=oncology&Search=Search (information on five thousand – mostly NIH – clinical research studies
- http://pubmed.gov/ (full text biomedical articles dated back to 1966)

- www.oncology.medscape.com (provides current information on human oncology)
- www.VIN.com Veterinary Information Network (interactive exchange)
- www.veterinarypartner.com (VIN's client information resource)
- www.csuanimalcancercenter.org
- http://www.vsso.org/ (the Veterinary Society of Surgical Oncology)
- www.veterinaryoncologyconsults.com (clinician consults with Dr. Anthony Moore)
- http://csu-cvmbs.colostate.edu/vth/diagnostic-and-support/argus/pet-hospice/Pages/default.aspx (pet hospice resource)
- www.argusinstitute.colostate.edu (the Argus Institute for Families and Veterinary Medicine counseling support featuring a *Making Decisions* booklet)
- http://pet-loss.net/emotions.shtml (about pet loss grief by Moria Anderson Allen, M.Ed.)
- http://www.griefhealingblog.com/2010/09/is-pet-loss-comparable-to-loss-of-loved.html (is pet loss equivalent to loss of a loved one?)
- www.clinicaltrials.gov (clinical trials resource)
- www.petloss.com (grief support, rainbow bridge, and Monday candle ceremony)
- https://rainbowsbridge.com/Grief_Support_Center/Grief_Support_Home.htm (pet loss support)
- www.PetCureOncology.com (stereotactic radiation information from Neil Mauldin, DVM, ACVIM, ACVR)
- http://www.modianolab.org/cancer/cancer_lymphoma.shtml
- http://www.modianolab.org/cancer/cancer_osteosarcoma.shtml
- https://www.mycancergenome.org

Preface

Dr. Alice Villalobos with Neo

Laurie Kaplan with Bullet

C*anine and Feline Geriatric Oncology* distills out the most important useful information needed by veterinary practitioners and teams to deal with geriatric cancer patients and their carers. Veterinarians contact me daily to fill in the gaps left between the lines in their textbooks. When I was lecturing in Beijing, the head of oncology at the Agricultural University told me that she slept with my book for three months and that it helped her with her students, clients, and patients. During the World Veterinary Cancer Congress, in Brazil, an oncologist, who translated the First Edition, said that she knew my mind and another oncologist said, "We see our books walking, when we see you and Dr. Theilen." In Portugal, a surgeon told me that he had my textbook right next to his Ettinger! Drs. Mark Gendizer and Virginia Quelch said their staff uses the book often.

This Second Edition text draws from an overwhelming deluge of information that overloads practitioners in the rapidly growing field of oncology and end of life care. We have new technology and information from genomics, proteomics, metabolomics, immunogenomics, immuno-oncology (onco-immunology), and nutrigenomics. Researchers may use artificial intelligence to extract information and find the keys to open the gates of many cellular pathways and map the molecular biology of specific tumors. Data would be used to suggest which drugs and immunotherapies would be best to use for the cancer patient for precision therapy.

These technological keys are guiding better diagnostics, earlier detection of cancer, and the development of targeted therapies and immunotherapy. Bioengineering technology enhances the capabilities of radiation therapy, interventional therapy, and electrochemotherapy (electroporation) as new and improved weapons to battle cancer. Further advances in medical technology and research will allow us to extend the health and longevity of our geriatric oncology patients with combinations of newer, less toxic, targeted therapy such as small molecules and vaccine therapy from the growing field of immuno-oncology.

Tumors are organized into five large categories, according to tissue of origin: carcinomas, sarcomas, blood cancer, nervous system tumors, and miscellaneous/unknown. Tumors are also organized by location: skin, head and neck, chest, abdomen, and bone and blood (lymphoid). Sorting tumors with this perspective may assist practitioners with the initial decision-making process, to improve the diagnostic approach and expedite treatment plans.

This text is a unique reference for veterinary students, interns, residents, attending doctors, and nursing personnel challenged with the rigors of decision making and caring for geriatric oncology patients. It is a helpful resource for highly motivated pet owners. Its greatest contribution may be in the fields of end of life care (Pawspice), communication, attachment, the human–animal bond, decision making, bioethics, and philosophy. The H5M2 Quality of Life scale helps the veterinary team guide carers through the maze of decision making for their geriatric pets in Pawspice and hospice care.

Cases are presented that highlight issues in geriatric oncology and in the management of interpersonal relationships with various types of clients. This multilevel approach offers readers scientific subject matter, mixed with cases overlaid with situated knowledge harvested over many years of experience. Victory and frustration are inherent in the management of elderly oncology patients and readers are cautioned to recognize and avert compassion fatigue with uplifting self-care as a key wellness strategy.

This tour through geriatric oncology blends elements of attachment, the human–animal bond, end of life Pawspice, and hospice care with compassion. All facets of practice are woven into the reality of applying cancer therapy with empathy, adjusted for variable client preferences and financial situations. This is what veterinary teams do every day in practice. This book is a comprehensive resource for those learning how to do it better.

May this second edition help you negotiate the ebb and flow of emotions as senescent cancer patients and their deeply bonded families challenge and enrich your career.

Acknowledgements

This Second Edition of *Canine and Feline Geriatric Oncology* culminates my lifetime contribution to the veterinary profession. This book would not exist if it were not for the persistence of publisher-editor and book mentor Mr. Dave Rosenbaum. When Dave was with Iowa State Press, he and Bernie Rollin, PhD, coaxed me to step out of the "trenches" and take the time to write a much needed, different type of textbook. David insisted that the book be written in my own personal style. He awakened a sense of duty in me to give back to my profession. Dave asked me to share the wisdom and humility that 35 years in the trenches battling cancer had conferred upon me. Now it has been 45 years, and I am still in the trenches, soaring with hope for a new era in oncology. In the 1980s, we decreased FeLV infection and related lymphomas in cats by testing, elimination, quarantine, and vaccination. Thanks to brilliant research, we hope to help dogs with early detection and prevention of their most common cancers in the 2020s.

Thinking back to my roots, I thank my parents, siblings, and the good Sisters of St. Joseph of Carondelet for their teaching skills at St. John's Hyde Park and St. Mary's Academy in Los Angeles. I thank my botany teacher, Mr. Charles Luger, at El Camino Junior College. He replaced a stolen textbook and encouraged me to pursue my goals. I thank the late professor Julius Sumner Miller for his Einstein-like expertise in teaching college physics on a practical level. I thank Oscar Schalm and the amazing faculty at UC Davis Veterinary School in the late 1960s and 1970s. I thank my world class oncology mentor, Dr. Gordon Theilen, the first President of the Veterinary Cancer Society. This second edition is rededicated to him along with my beloved parents, Antonio and Alicia Villalobos.

I sincerely thank Dr. Frank Lux, who encouraged me to partner with him to open Coast Pet Clinic/Animal Cancer Center in 1974. Coast expanded rapidly into a 24-hour, 12 doctor, 70 staff member clinic, with four satellite cancer consultation clinics. I thank the late Dr. Bill Zontine, ACVR, who was my veterinary "dad" practice mentor. I am grateful for the friendship and encouragement of the late Drs. Greg MacEwen and Art Hurvitz, who inspired me with their brilliance and work at the Animal Medical Center in New York. I thank my founding colleagues, officers, and members of the Veterinary Cancer Society, who forged the specialty of oncology with unwavering dedication. I genuinely thank Dr. Sue Cotter of Tufts University and Angel Memorial for 45 years of friendship, guidance, and faith in me on and off the slopes. I thank the late Dr. Hal Snow, Drs. Jane Turrell and Alain Theon of UCD for their encouragement and enthusiasm in radiation oncology. I profoundly thank Ira Lifland, my best friend and unbelievably supportive husband since 1982. Ira fills my life with his love and intense multilevel support. In 1983, Ira, Hal, Jane, clients, and friends helped me build the first dedicated radiation therapy facility in private practice in the US after the banks declined to give me a loan for such an unheard of animal service adventure. These friends, along with my associates, interns, and the referring doctors of Southern California, helped me to pioneer one of the first comprehensive oncology services in private practice.

I thank Drs. Frank Lux, Curtis Willauer and Don Wood for their surgical oncology skills. I thank the following veterinary organizations for their energizing effect, while I learned, networked, and lectured at their meetings: VCS, American Association of Human-Animal Bond Veterinarians, Society for Veterinary Medical Ethics, ABROVET, ONCOVET, WVCC, AAHA, AVMA, ACVIM, NAVC, WVC, OVMA, CVMA, SCVMA, the late Dr. Bob Pensinger's Veterinary Post Graduate Institute, Sierra Veterinary Medical Association, and the National Academies of Practice.

I deeply thank my clients, John Peel and Laurel Hunt for nominating me for the 1999 Bustad Award, which ignited my career track into the science of the human–animal bond.

Thanks to editors Brian Hutchins, Marilyn Iturri, and Ken Niedziela at *Veterinary Practice News*, who managed my two columns: *Oncology Outlook*, *The Bond and Beyond*, and *Dr. Alice At Large*. I thank the legendary Dr. Robert Miller (RMM) for his mentorship and for starting the SVMA, which joyfully blended collegiality and skiing. I thank my mentors, Dr. Gordon Theieln of UC Davis, and the late Dr. Bill Zontine.

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honoring the human–animal bond, the glue that holds us all together, and the SVME for centering me in bioethics. Special thanks to Dr. Dani McVety, for fleshing out my concept of "ethics fatigue" as separate from compassion fatigue for our profession to ponder. I thank colleagues who found their calling; to minister to end of life patients; to improve quality of life and palliative care; to provide Pawspice, hospice, and home euthanasia. Admiration and thanks go to the amazing leaders of the International Association of Animal Hospice and Palliative Care. Your collaborative efforts are fulfilling my dreams! And most importantly, I give heartfelt thanks to all pet carers who ask our profession to help their aging pets when threatened by cancer's fatal agenda.

Introduction

My people are destroyed from lack of knowledge.

Hosea 4:6

This book attempts to blend didactic oncology with end of life care for geriatric pets in a way that demystifies it for veterinarians and patient families. I accepted the provocative invitation to write this book in order to light a high-touch fuse for end of life care. This Second Edition rekindles the text, to fan the flames that now burn brightly in this arena. This book may serve as a torch or guiding beacon for veterinarians and staff to engage geriatric cancer patients as highly valued sentient beings. It may help prioritize honoring the humanity of the human–animal bond, as we deliver our modern medicine.

My career as a "trench oncologist" began in 1972 in battles and skirmishes against cancer at the forefront of the rapidly growing field of veterinary oncology. This work is intended to be a force for change, to fuse the art of our high-tech medicine with high-touch empathy and compassion.

Since cancer kills half of our aging patients, it is the single disease responsible for ending the life of millions of highly valued dogs and cats. Cancer breaks hearts in the companion animal community on a routine basis. The human–animal bond has emerged into a respected, life-enriching relationship in our contemporary society. The human–animal bond is validated and celebrated as a viable, healthy relationship, one that often takes a priority position in millions of people's daily routines, lifestyles, and economic choices. People purchase pet-friendly vehicles, motor homes, and homes so that their companion animals can share their lives and be with them as much as possible.

Pet owners are caregivers (carers). The word "family" is used broadly in this text to describe any situation that includes a pet. Family and carers can include singles, partners, and people with or without children who share the human–animal bond with pets. Carers have created the demand for dog parks, dog beaches, dog hiking paths, pet-friendly hotels, and pet service businesses, and a demand for more expertise in end of life care. While carers are at work or on vacation, they hire pet sitters to care for and entertain their animals. Doggie day care and high-end boarding facilities are geared toward quality care and pampering pets.

Today's enlightened carers willingly feel that they are their pet's parents and, figuratively (not legally) speaking, their guardians. Pet carers actively try to learn more about the emotions, thoughts, consciousness, and behavior of their pets. Carers are convinced that their pets think, have emotions, feel happy, sad, lonely, upset, stressed, and painful when injured or sick, and manifest grief when a companion animal or person dies. Carers want and need relief for their pet's ailments because their own quality of life is impacted negatively when a beloved pet is suffering. Pet carers need, demand,

and deserve compassion and understanding from their veterinarians, along with quality medicine and surgery.

When carers want something for their pets, they search the Internet and ask Siri, Google, or Bing. They seek services from specialty veterinarians, complementary and alternative treatments, and a wider growing attaché of pet care services (rehab, acupuncture, massage) to find comfort, help, and relief for their ailing pets.

Veterinarians contribute not only to the well-being and health of their patients; they have an equally large responsibility for supporting the well-being of the family. Until veterinarians fully appreciate this part of their role in society, they will continue to fall short of their obvious and central role in promoting the health and happiness of society through their pets. One of this book's two key themes is that veterinarians must reach out as much to pet carers as to the pet. Providing the best medicine is achieved when carers are educated to understand their pet's needs.

Pets age within a mere 10 years. Pet aging happens so quickly that most families are unaware that the routine activities of daily living may place too much demand on an older pet. Carers will often present their senior pets for examination when the pet is exhibiting only mild symptoms or non-specific preliminary signs of aging, illness, or cancer. Carers are concerned, but they do not understand the value of a thorough examination and screening tests for their aging pet with an increased risk for cancer. It is up to us to educate our clients.

Cancer often invades a pet's body insidiously, with only a few (if any) warning signs. When the diagnosis of cancer strikes a beloved pet, fear and anxiety fill the exam room. Unfortunately, these gripping emotions often fall on unwilling, deaf ears or they are dismissed impatiently by the attending doctor who is rushing from one exam room to the next in a busy practice. Much is left unsaid.

This book serves to reconstruct the initial steps when the veterinarian is working up or presenting the diagnosis of cancer. It can help that a first oncology consultation be a life-supporting and client-saving opportunity. This work can also help you understand how to keep your clients affectionately bonded to your practice, despite their pet's passing at your facility. Carers need to know that you care about what happens to their pets, and that you care about them.

In the past, an exam room scenario resembled an old Norman Rockwell painting or one of those beloved scenarios from a James Herriot book. Picture the wise Dr. Smith discussing Fido's cancer problem with Jane (the stay-at-home wife, one child in a stroller and another concerned child in hand). Jane explains Fido's problem to husband Joe at dinnertime, and Joe calls Dr. Smith to verify the gravity of the situation. The two men make the decision to put old Fido down. Times have certainly changed!

Today, the exam room scenario is often a single adult millennial, perhaps a man and his cat, consulting with a woman veterinarian. She explains a disease process and offers high-tech diagnostics and therapeutic procedures as options. Carers search the Internet and develop the confidence to assert themselves with their doctors, because they want to prolong their pet's life. This generates the need for further consultation, to answer a list of questions. Carers may not know how to inform their doctor that they are highly attached and willing to fulfill their sick pet's needs, to preserve the human–animal bond, even during the hospice setting while their pet declines at home.

Many pet carers have the willingness and ability to pursue diagnosis, staging, and therapy for their geriatric dog or cat, and will pursue referrals for specialty consultation and treatment. Others cannot afford costly diagnostics and treatment, or are philosophically against cancer therapy for their geriatric pet. However, many of these would fully want palliative care, hospice, and home euthanasia, if they knew about it.

Carers openly and proudly regard their geriatric pet as a family member who has loved them unconditionally for a long time. An older pet is often regarded as a "partner" or "best friend" or "family member" who helped their carers during difficult times. The human–animal bond is especially strong if the pet is a guide dog or involved in pet-assisted therapy, service work, agility, or show work. Many relationships with pets have outlived friendships, marriages, and helped ease the loss of family members.

It is up to the veterinarian to ask the client pointed questions to find out about the unique human–animal bond that they share with their geriatric pet with cancer. There is no doubt that veterinarians would be appreciated more by their clients if cancer could be detected earlier and treated with more forethought, expertise, and kindness.

The goal of this book is to provide readers with a useful decision-making tool. Like other resources, it spotlights the warning signs, and the most common forms of cancer in geriatric pets, and current treatment options. However, this text goes much farther. It unlocks the mystique about cancer, reveals pitfalls and adverse events that can be avoided, and arms readers with the ability to think through the variables and complexities of geriatric oncology. It gives examples of good communication skills in planning therapy based on the family's concerns, philosophy, and budget restrictions. This book introduces electrochemotherapy (electroporation) and yttrium-90 brachytherapy as novel options and provides the rationale for combinatorial palliative cancer care using various modalities such as metronomic chemotherapy, radiation therapy, immunotherapy, immunonutrition, and palliative end of life support to enhance and maintain a good quality of life. The book stresses the importance of quality of death, offering a protocol for peaceful passage. It also describes ways to provide emotional and grief support to the family during end of life care and after life. It offers colleagues another way to think about euthanasia as being truly a privilege to help our beloved patients peacefully transition, without feeling diminished. Last and very importantly, self-care strategies are presented to lift ourselves up to regain and sustain resilience so that we may continue our special calling for a fulfilled and loving career.

Veterinarians across the United States contact me daily to fill in the gaps left between the lines in their textbooks. This book tells what is often left unsaid in the exam room, and fills in the gaps left between the lines in textbooks about treating cancer. It is the only book dedicated to caring for geriatric oncology patients.

Part One

Chapter 1
Molecular Biology of Cancer and Aging

The roots of the problems of cancer and aging involve the molecular changes of aging priming aging (cellular senescence). These changes prime aging cells to be more susceptible to the effects of environmental carcinogens. These changes are only partly understood and may or may not be reversible.

Lodovico Balducci, MD

What Is Cancer? How Does It Start?

Hippocrates coined the name for malignant cancer from the Greek word for crab (*karkinos*), because tumors resembled the claws of a crab. Cancer is an insidious, nefarious, complex, obstinate, and disruptive disease. Cancer is an intricate set of biological aberrations that originate in the nucleus of cells that transform and progress with diverse heterogeneity, which is not completely understood. Cancer results in the uncontrolled and reckless growth of destructive cells that overwhelm the body as they accumulate. Cancer's immortal cells replicate relentlessly. They can use existing vessels or recruit cells to form new blood vessels via angiogenesis for nourishment. Cancer cells slip into the lymphatic and vascular systems and invade vital structures via metastasis to ultimately kill its host with its fatal agenda.

This chapter will attempt to describe the intricacies of cancer's malignant processes. Terms are defined and readers will be subjected to only a small taste of the alphabet soup milieu that drives the intracellular and extracellular microenvironment. As you read, keep in mind that this is an attempt to illustrate the essentials of a complex disruptive process and forgive or congratulate me if the text has oversimplified or exemplified cancer!

Normal cellular division creates a constant flow of injured genes. These defective genes are regularly corrected by innate repair mechanisms present in normal cellular function. Certain genetic point mutations become multifarious if they are not repaired. Genetic damage occurs in cells that lack coordinating signals necessary for self-repair. If genetically damaged cells escape innate detection and destruction and are allowed to live and replicate, cancer gets a foothold and then proceeds with its mechanistic drivers to grow and metastasize and disrupt vital functions.

Each of the trillions of cells that compose a body contains over one hundred thousand genes, arranged in chromosomes. The DNA that composes normal genes is called a "proto-oncogene." A proto-oncogene encodes all genetic information and regulates cell replication so that cells can replenish themselves normally in the bone marrow, intestine, skin, connective tissue, and organs when needed. Genes also regulate normal wound healing, hair growth, puberty, and gestation (Abeloff et al. 2004).

Canine and Feline Geriatric Oncology: Honoring the Human–Animal Bond, Second Edition. Alice Villalobos with Laurie Kaplan.

About one in every million cell divisions undergoes a point mutation resulting in defective, aberrant, or altered genes that clone and initiate tumorigenesis. These genetic mutations can be seen by the immune system as copy errors and they are normally corrected by immunosurveillance. If the mutations are involved in the mechanism that controls repair, replication, proliferation, tumor suppression, or telomere (the terminal portion of genes, encoding programmed cell death) control, the defective genes are converted into oncogenes and their descendant cells take on a renegade behavior.

Cancer evolves on a cellular and sub-cellular level through three basic stages: initiation, promotion, and progression. *Initiation* involves exposure to carcinogens such as sun, tobacco smoke, alcohol, herbicides (2,4-D weed killer), insecticides, asbestos, free radicals, viruses, infections and so forth. This initial exposure may result in permanent damage "hits" to DNA. Initially this damage may not be a direct cause of cancer; however, continued exposure causes more gene "hits" and increases the risk of tumorigenesis. Tumor initiation and promotion is also seen in chemically induced tumors in experimental animals.

Promotion events are poorly understood. The *promoter* (an abnormal DNA base sequence in genes) stimulates cell division and results in the accumulation of cells that cause the formation of tumors. Aging, poor diet, obesity, toxins, smoke, and chemicals injure the stability of genes and are also considered potential promoters.

Progression to malignancy occurs when the tight controls that normally govern cell cycle progression are suppressed or break down. This results in the uncontrolled growth of abnormal immortal cells (cells that do not respond to normal cell death signals). Progression also involves the ability of cancer cells to initiate the formation of new capillaries (angiogenesis) to nurture growth. The most malignant cancer cells invade surrounding tissue, work their way into vessels and lymphatics and metastasize to distant parts of the body.

These events involve proteins that function by giving and receiving signals on the surface of the cell and along complex and intricate intracellular pathways in the process of cell-to-cell communication. Understanding the complexity and specifics of cell signaling and the alphabet soup that names the proteins and receptors can be overwhelming to the busy practitioner. There are basic families and systems of signaling that share certain pathways that aid and abet neoplastic changes. These basic mechanisms are fascinating and some have clinical relevance. Targeting aspects of these basic signaling mechanisms holds the key to promising therapeutics that will interfere with clonal evolution, progression, and relapse in cancer patients. Scientists attempt to manipulate the proteins that govern the intricate cell signals in ways to prevent, protect, and reverse cancer, especially in the senescent (Ihle 2004).

Tumor Suppressor Genes, Apoptosis, and Genomics

Tumor suppressor genes (*p53*) are responsible for repair of the hordes of copy errors and genetic damage that occurs during normal cell replication. When tumor suppressor genes malfunction, the risk of cancer rises. Tumorigenesis may also arise due to the loss of programmed cell death (apoptosis) signaling pathways. All normal cells have a certain life span dictated by telomere shortening after every division and suicide signaling. Suicide mechanisms to self-terminate can malfunction due to mutations of the signaling systems for apoptosis, causing cells to persist and become immortal. Scientists have identified the programmed death ligand 1 (PD-L1) gene, which promotes cancer by protecting cancer cells from T-cell mediated destruction. A ligand is a molecule on the cell surface that binds to another (usually larger) molecule. Researchers are very enthusiastic about using PD-L1

as a treatment target. Targeting PD-L1 and other tumor specific ligands is expected to provide great benefit in controlling aggressive and advanced cancer in patients in the future, with fewer adverse events.

Cell immortality is dangerous to the host. Armed with immortality and lack of suppression by tumor suppressor (*p53*) genes, these aberrant cells become malignant. They replicate and accumulate into clones of neoplastic cells. The clones undergo successive genetic changes that select for growth factors and chaotic replication. Malignant clones acquire the ability to create their own capillary blood supply (angiogenesis). These new capillaries provide nourishment and oxygen for new cell growth, thus allowing more abnormal cells to accumulate and create larger tumors. Tumors send their most vigorous, athletic scout cells into lymphatic vessels and capillaries. These resilient scout cells are able to slip under the radar of the immune system using checkpoint inhibitors that protect them from being detected and recognized for destruction by the immune system. The cells travel and metastasize into immortal tumor clonogens (cell clones or tumor stem cells that are more resistant to treatment). Clonogens may appear anywhere in the body (Khanna 2004; Morrison 2002).

Because renegade cancer cells have minimal cell death, do not curb their telomeres, and bypass senescence, they continue to divide and replicate tumultuously without repairing. Cancer cells grow wildly without control since they lack the ability to terminate themselves through apoptosis. In frenzy, they push, crowd, and dissolve their way into the society of normal tissue cells causing mayhem. *The battle against cancer is often won or lost at this microscopic preclinical stage.*

Most scientists realize that the real and decisive battle against cancer is truly fought at this molecular and immune system level, long before the tumor has expanded and accumulated enough cells to be detected. At this early, preclinical stage, a healthy, militant immune surveillance system could identify and eliminate every renegade cancer cell. Unfortunately, aging is associated with a weakened immunosurveillance system, leaving our geriatric patients at greater risk for cancer. New technology may enhance the immune system to detect and destroy malignant cancer cells.

Cancer genomics helps researchers identify the biological drivers of particular cancers. By blocking the effects of these drivers, targeted therapy may be able to inhibit cancer progression. Many human cancers have a correlation between the presence of certain genomic aberrations and the clinical outcome of the tumor and/or the tumor's response to therapy. Therefore, many chromosome aberrations are of prognostic value and the information generated via machine data collaboration may be used by clinicians to determine the most appropriate therapy. It is inevitable that veterinary oncology will benefit enormously from data derived from genomics and that this era will see a huge shift in the ways in which companion animal cancer patients are evaluated and subsequently treated (Breen 2009).

Cancer and Aging

Cancer is a disease, but aging is not. Aging is the phenotype of the normal phenomenon of cellular senescence. Carcinogenesis is a nefarious multistep process that takes time. Aging animals provide that time as their life span increases. Cancer's multistep process, enhanced by a longer exposure to carcinogens, emerges as a major syndrome associated with aging. Basic molecular and genomic research proposes many reasons for the increased incidence of cancer in older animals. Aging is associated with a decline in antitumor defenses. Older animals have less resistance, less immune competence, less DNA repair, more damaged tumor suppressor genes (*p53*), reduced numbers and function of mitochondria, and defects in biological responses. Aging is associated with diminished functional reserve of multiple organ systems, sarcopenia (muscle loss) and an increase prevalence of

chronic diseases, which may cause frailty and stress, causing the geriatric body to be more susceptible to cancer.

Certain proteins or cytokines such as interleukin-6 (IL-6), D-dimer, and C-reactive protein (CRP) are found to be elevated in the aging process. D-dimer is a product of fibrin lysis and CRP is an acute phase protein produced in the liver. These cytokines increase with inflammation and age-related conditions such as osteoarthritis. Cancer creates an immune challenge, which drives the activation and release of a cascade of cytokines including tumor necrosis factor (TNF-α, cachexin), which is responsible for creating the hypermetabolic state of cachexia. TNF-α, IL-6, D-dimer, and CRP also increase with cytokine signaling induced by inflammation, infection, cancer, thromboembolism, and acute illness.

These factors are likely to be responsible for the higher incidence and mortality rate from cancer in older and geriatric companion animals. Cancer cells proliferate with anarchy and defiance of the normal constraints that keep cell growth and division in check. Cancer instigates cytokine dysregulation and a domino effect as it disrupts the aging body.

Research hopes to provide new molecular and genomic detection and prevention methods to target and tackle the intricate cytokines and signaling steps of cancer as it evolves. The goal would be to "target" cancer out of existence at the precancerous stage, before it embarks on its fatal course. One day, we may be able to provide dogs and cats with immunoprophylaxis using preventative cancer vaccines, and chemoprophylaxis using tumor specific agents (Modiano 2016).

One Medicine and Cancer Awareness

Human and animal cancers and diseases often share a similar pathogenetic process. Companion animals are often good comparative models for human cancer. This concept fueled the "One Medicine" philosophy, which was strong in the late 1960s to 1970s. The One Medicine concept has reemerged in the last decade with universal vigor and it is universally supported by the CancerMoonShot2020 campaign. Client education regarding prevention and awareness of risk factors can help companion animals live longer and avoid some cancers. Educating pet owners about carcinogenesis, and the preliminary stages and early warning signs of cancer may help save millions of beloved pets. A well-informed clinician, using improved diagnostics in a timely fashion, can help clients with geriatric pets identify and treat cancer in its earliest stages, which may offset its devastation.

The most obvious tumors in elderly dogs and cats appear on the body surface, in the skin, in the subcutis layer below the skin, or fixed to the body wall. Cutaneous cancers may appear as tumors, ulcers, non-healing sores or petechiae (pinpoint blood blisters). They may appear as plaques or crusts on the ears, eyelids, and nose and in the non-pigmented skin of sun-exposed senior cats and dogs. The contemporary veterinarian will not suggest, "Let's wait and see if it grows." It is justifiable to examine every mass on a geriatric pet (other than obvious warts) with fine needle aspiration (FNA) cytology to determine whether the mass is truly a lipoma, inflammation, a mast cell tumor, or a malignant tumor. Read the section on cytology.

Epigenetics, Environmental Influences, Toxins, and Risk Factors

Epigenetics is the study of how genes are switched on and off. The multistep process of cancer development over time explains why we see more cancer in aging animals. One Medicine researchers view animals as sentinels that parallel human diseases and cancers that result from environmental