CHAPTER 1

ANCIENT PLANT, MODERN THERAPY

A Brief History of Mistletoe and Modern Oncology

Dr. Steven Johnson, DO
and Dr. Nasha Winters, ND, FABNO

Special thanks to Dr. Marion Debus for advisory consultation and historic summaries included in this chapter.

"There are two principal methods of treating disease. One is combative, the other preventative."
—HENRY LINDLAHR, MD (1862–1924),
author of *Nature Cure*

"The good physician treats the disease; the great physician treats the patient who has the disease."
—SIR WILLIAM OSLER (1849–1919),
Founding Member Johns Hopkins Hospital

When patients come to us interested in mistletoe therapy, they are often entirely new to the concept. They're surprised that a plant they've known only as a holiday decoration is also a well-studied natural medicine. There's often a mix of skepticism and genuine curiosity in their questions. In the coming pages, we hope to provide

helpful insights for other patients with cancer and their loved ones who have similar questions. We also hope to provide a solid introduction for clinicians who are curious about mistletoe therapy and integrative oncology.

Let's first expand our perspective through a brief exploration of humankind's relationship with mistletoe, as well as the history and evolution of cancer treatment. Then we'll find out how mistletoe fits into the modern picture of integrative oncology and other emerging holistic paradigms. After that historical tour, we'll look at the basics of how conventional oncologists, integrative medical doctors (MDs), doctors of osteopathic medicine (DOs), naturopathic doctors (NDs), and anthroposophic practitioners use mistletoe as an *adjuvant*—a therapy that complements and enhances the effects of standard of care (SOC) therapies.

Primitive parallel lives: Mistletoe legends and the disease with no treatment

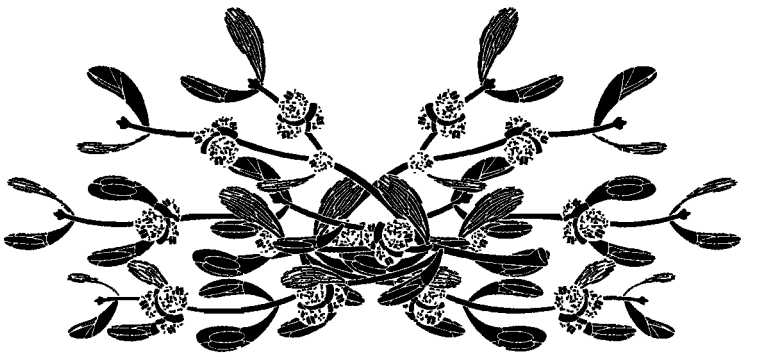
You might know mistletoe only as a curious holiday decoration—that evergreen sprig with wintery-white berries, hanging in a doorway. For some reason couples kiss under it to celebrate their love. Long before it showed up in holiday traditions, mistletoe was highly regarded in Norse and Greek mythology and in Roman epic poems. Mistletoe appeared as a wand or a key, allowing a few legendary heroes to travel safely back and forth between the land of the living and the Underworld—something not normally possible for living souls.

The ancient Druids were familiar with European mistletoe, *Viscum album*, which we use in therapeutic extracts today. In their traditions, mistletoe was considered magical because of its blooming and bearing fruit in the wintertime and for its unusual appearance: beautiful evergreen orbs growing in the winter months in an otherwise bare deciduous tree. It was highly valued when found growing in sacred oak trees. The Druids harvested mistletoe only in the winter, near solstice, and with elaborate rituals involved. For them, mistletoe was a potent promoter of fertility and longevity.[1]

In another mythic tradition, Baldur—the most beloved of the Norse gods, son of the god Odin and his wife Frigg—was killed by an arrow made of mistletoe. Baldur was later resurrected, and mistletoe was transformed into an emblem of love. This story may be the origin of today's holiday mistletoe tradition.[2]

In ancient times, such stories were a way to communicate sacred wisdom. Today, it is all too easy to dismiss them as quaint or primitive. But as we look at mistletoe's earliest uses as an herbal medicine, we begin to see some of the mistletoe benefits that contemporary researchers have now verified. Early European herbalists came to recommend mistletoe for epilepsy and as a general medicine to calm the nerves, particularly to comfort those who were incapacitated by great grief.[3] We'll see later on that many of the herbalists' observational uses have found scientific support today.

Though mistletoe had many applications in early herbal medicine, it would be centuries before it intersected with oncology. It has taken thousands of years to unlock the modern secrets of mistletoe. Our understanding of cancer has had a similar rocky evolution, fraught with mystery, fear, misunderstanding, and wonderful breakthroughs.



Humankind's early encounters with cancer

Some of the earliest known cancer cases are found in Egyptian mummies that show evidence of bone and breast cancer. There are also Egyptian medical texts by the physician Imhotep (2600 BCE), which likely describe cancerous conditions and refer to tumors as a disease

with no treatment.[4] That was the general attitude toward cancer for millennia, though Greek and Latin physicians at least developed a theory of cancer's cause and the vernacular that we find recognizable today. From the Greeks we received the term *carcinoma*—a Greek word meaning "crab," likely referring to the crab-like shape of some tumors. They also coined *oncos*, meaning swelling, from which we get the term *oncology*. The Romans first referred to the disease as *cancer*, a Latin translation of carcinoma.[5] These early Western physicians developed the theory of "balancing humors" in the body to cure disease and regarded cancer specifically as stemming from an excess of "black bile." Believe it or not, that opinion prevailed for much of written medical history, from about 400 BCE until the 1600s CE.[6,7]

Long after the early Greek and Roman physicians, but still prehistory in terms of modern oncology, we find the story of St. Peregrine Laziosi (1260–1345), who suffered from a cancerous tumor on one of his legs when he was a young man. The lesion ulcerated and became severely infected, warranting amputation. But by the time the surgeon arrived, the infection had lessened, and the tumor had miraculously shrunk.[8] The wound soon healed, the young Peregrine kept his leg, and he lived till he was 85 with no cancer recurrence. Centuries later he was canonized and is now regarded as the Patron Saint of Cancer Patients.

The St. Peregrine story would be solely the stuff of legends, except for the fact that Western medical literature continued to accumulate similar stories. Very occasionally, a cancer patient would develop a feverish infection and, if they survived the infection, their tumor had subsequently shrunk or gone into complete remission.[9,10] The physicians didn't have the scientific capacity to describe the phenomenon at the time, but it would seem they were witnessing an early clue regarding *immunotherapy*. Only in recent years would researchers begin to consider the role of warmth and fever in immune-modulation as a potential treatment for cancer. Is it possible the heightened immune activity of St. Peregrine's infection managed to breach the barriers of the tumor's microenvironment and eliminate the cancerous cells?

We'll never know for sure. But this phenomenon would be witnessed again in the future!

No one wants to reproduce such a risky experience. But the fact that such "miracles" were documented is fascinating. While conventional oncology often regards immunotherapy as new and leading-edge, the basic principles have been noted for centuries and were even practiced with intention in the 1800s and 1900s, as we'll see shortly. The roots of immunotherapy run far deeper than the recent emergence of checkpoint inhibitors.

Regardless, those lucky cancer remissions were the exception and not the rule. For centuries, in Europe and around the world, cancer was a known and named disease. It was feared, veiled in mystery, and physicians rarely recommended any effective treatments.

Mistletoe establishes itself in European herbalism

Throughout the middle ages, herbalists continued to respect mistletoe for its ancient mystical associations. They also began to keep more detailed records about its effects based on specific preparations and dosages. European herbalists continued to use mistletoe for epilepsy and other nervous system imbalances, as well as for pain management and balancing mood. The leaves, twigs and berries were harvested and dried, then tinctures were made from the dried plant material. Topical applications were used for pain as well.[11,12]

These practitioners noticed the importance of dosage. While lower mistletoe dosages were often highly effective for nervous system disorders, higher doses could actually aggravate them.[13] In the 1700s and 1800s, herbalism, like any medical practice of that time, started to apply the new scientific method throughout its treatment observations and recommendations. There was far less of a divide between conventional and herbal medicine at that time. In many regions there wouldn't have been a divide at all. Indeed, herbs comprised the primary pharmacopeia. Though the medical community didn't yet have access to the technology needed to identify the active constituents in mistletoe, the herbalists were keen observers of its effects.

Today, we now know about mistletoe's identified medicinal constituents, including *lectins* and *viscotoxins* (see chapter 2), as well as anti-inflammatory *flavonoids* and compounds that appear to interact with *GABA receptors* (nerve cell receptors involved in self-calming).[14–20] This diverse phytoactive profile explains the historic results seen when classical herbalists provided mistletoe for pain management, epilepsy, and mood balancing effects.

Renaissance to early twentieth century: Setting the stage for contemporary cancer care and research

From the mid-1500s to the early 1600s, Western medicine underwent a transformation. Da Vinci, Galileo, and Vesalius opened doors to new knowledge about health and disease as a result of their dissections and anatomy illustrations. In the 1700s, Giovanni Battista Morgagni expanded on the practice of cadaver dissection to include "determining the likely cause of death." This new understanding of anatomy and pathology made it possible for physicians to learn much more about the structures and progression of cancer.[21] This, in turn, made it possible to consider surgery as a cancer treatment option. In the mid-1700s, London surgeon John Hunter made some of the first recommendations classifying operable and inoperable tumors. He was also known for his pathology research and some of the earliest observations about tumor metastases, though no one had the language to describe that progression yet.[22]

Around the same time, medical researchers and practitioners began to revisit and question the Four Humors theory of cancer. Upon discovering the lymphatic system in the early 1600s, Gaspare Aselli hypothesized that cancer was a lymphatic disease.[23] Others postulated that cancer might be infectious, leading to unfortunate quarantining of people who had cancer from the sixteenth through the eighteenth centuries. In the late 1700s, there was one new theory of cancer that was eventually proven accurate. Physicians throughout Europe started to notice a new kind of cancer prevalent only among chimney sweeps, particularly those who began as boy apprentices

and were required to climb chimneys mostly naked—a horrifying but common practice. By the time they were young men, they developed a rare testicular cancer not seen in any other population group. Practitioners and researchers caught on: *This particular cancer was due to repeat exposure to an environmental toxin.* Somehow, the soot was causing it.[24] Though scientific validation for this assertion would not come until mouse model studies in the 1920s and '30s,[25,26] the initial conclusion still held. It even provided motivation for implementing new child labor laws, protective clothing for these workers, and other social and legal changes.[27]

From the mid 1800s through the first half of the twentieth century, the medical community laid the foundation for the modern-day practice of oncology. During that time, a wide range of treatment innovations flourished, and new laboratory technologies made significant discoveries possible. A German pathologist, Johannes Müller (1801–1858), countered the dominant theory that cancer came from degenerating lymph, and proved instead that all cancers were made up of human cells.[28] Müller's student, Rudolf Virchow (1821–1902), extended that line of inquiry even further and developed the study of cellular pathology in the 1850s.[29] Müller and Virchow opened the door to studying cancer as a cellular disease, one in which cells begin to grow out of control with a *centrifugal* (spreading outward) tendency.

Another pathologist living around the same time in England, Stephen Paget (1855–1926), introduced the "Seed and Soil" hypothesis in 1889.[30] He looked at the deceased as a pathologist, and he found that certain tumors tended to metastasize to certain organs. Particularly, he noticed that breast cancer tumors routinely metastasized to visceral organs and the bones. He believed there must be a certain "soil" where these tumors preferred to grow.

"When a plant goes to seed, its seeds are carried in all directions; but they can live and grow only if they fall on congenial soil," Paget said. "While many researchers have been studying 'the seeds,' the properties of 'the soils' may reveal valuable insights into the metastatic peculiarities of cancer cases." Paget observed that each cancer's behavior and

progression depended on *the condition of the whole person* and not solely on the aberrant cells.[31] He was thinking in a holistic way.

Paget's Seed and Soil Theory got attention in its time but wound up utterly forgotten by the mid twentieth century, replaced in the 1920s by the idea that metastasis was an entirely random process, driven only by the circulatory and lymphatic systems. Almost a hundred years after Paget shared his original hypothesis, modern medicine returned to it in the 1980s. Today researchers tend to refer to Paget's "seed cells" as *progenitor cells* or *metastatic clones* and his "soil" concept is preserved in language about the *tumor microenvironment* or *tumor niche.*[32]

In the early 1900s, Paul Ehrlich (1854–1915), a microbiologist and early immunologist working in Frankfurt and Berlin, developed the theory that the immune system may be involved in controlling cancer and eliminating cancer cells in their earliest stages.[33,34] He could not prove his intuitive theory essentially because the lab technology we have today hadn't been developed yet. Like Paget's ideas, Ehrlich's concepts were forgotten until the recent explosion of research into immunotherapy.

Surveying this time period yields many more pioneering cancer researchers who developed brilliant immunological, genetic, and metabolic theories, while lacking the technology to prove, disprove, or evolve their ideas. In addition to Paget and Ehrlich, one finds the cellular metabolism researcher Otto Warburg in Germany in the early 1900s. Warburg made the impressive discovery that tumor cells could live and thrive in the absence of oxygen. They had an *anaerobic metabolism.*[35] This theory could have inspired the next century of research, but it fell out of the limelight, even though Warburg received the Nobel Prize for his work. In recent years, innovative cancer researchers have returned to Warburg's findings, rediscovering the abnormal metabolic pathways of cancer cells. There are keys here to fighting cancer by taking advantage of its unique metabolic quirks.

In the early 1900s, one also notices geneticists like Theodor Boveri in Germany and R. C. Whitman in the U.S., developing and honing a *somatic theory* of cancer cell mutation: Perhaps cancer cells became

cancerous because of a critical mass of genetic mutations accumulated over time.[36,37] Unlike Paget's and Ehrlich's ideas, which were highly accurate but hard to prove, Somatic Mutation Theory (SMT) earned the trust of the research community and became the dominant cancer origin theory for decades. Only recently have we learned that this theory may have put the cart before the horse. It's true that cancer cells have many mutations, but it's possible that many of the mutations come about *after* they've turned cancerous.[38]

While cancer researchers were developing new theories of what caused cancer and how cancer progressed, practitioners and surgeons were forging new approaches for treatment. In Europe, Wilhelm Conrad Röntgen discovered X-rays in 1895.[39] A year later, Emil Grubbe began the first radiotherapy treatments in the United States for breast cancer.[40] Also in the U.S., William Stewart Halsted (1852–1922) introduced radical mastectomy for breast cancer—which became a feasible option with the advent of anesthesia.[41] Halsted was sure that the more radical the operation, the higher the cure rate. Even in his time, this was found to not be the case, but it would remain the dominant opinion until the 1980s.

In the first decades of the twentieth century, perhaps the most fascinating and high-risk cancer treatment innovation was pioneered by William B. Coley. As a cancer surgeon, Coley had seen the unpredictable efficacy of treating with surgery alone. Rather than ask only what had happened to the patients who did poorly, he began to wonder *what went right* for the patients whose cancers had shrunk or gone into remission. He went through medical files and found all the healthy cancer survivors. He discovered that, at some point in their cancer journeys, all of them had developed and fought off a major infection, usually accompanied with a high fever. After recovering from the infection, their cancers had shrunk or were in complete remission.

Coley took this information and began what would become highly controversial experimental treatments. He initially injected his first few cancer patients' tumors with live *Streptococcus* bacteria to induce fever. Most of his patients survived the therapy—as crude as it seems—and

Mistletoe is best known as a holiday decoration. Few know that it has a one-hundred-year history of use in cancer care.

the survivors did indeed experience tumor shrinkage or remissions.[42,43] Coley later developed a safer, heat-treated preparation from killed bacteria, going on to use this in over one thousand patients. "Coley's Toxin" can be considered one of science's earliest immunotherapies. Several contemporaries of Coley utilized thirteen different versions of these preparations. But the toxins were not well-standardized, and patient outcomes were not always tracked well. This led to Coley's toxins being abandoned by mainstream oncology.[44] Still, one hundred years later, science did return to the idea of *immunotherapy*, the concept of triggering a heightened and more efficient immune response in the battle against cancer.

Mistletoe meets cancer care: Viscum album *at the turn of the twentieth century*

In the early 1900s, the Austrian philosopher, scholar, and social reformer Rudolf Steiner (1861–1925) collaborated with his protégé, the physician Ita Wegman, MD (1876–1943), to develop the principles of anthroposophic medicine (AM). Together, they founded one of the most well-known integrative approaches to medicine in Western Europe. They also pioneered mistletoe therapy for cancer care. AM physicians were, and are, medical doctors who complete additional training in treating the whole human being. Steiner particularly emphasized the concept of "spiritual science," the idea that both spiritual awareness and science can be (and need to be) united for medical treatment to be fully effective. Both Steiner and Wegman spoke about the importance of caring for the soul and spirit of the person as well as the physical and functional aspects of the body.[45]

Our European colleagues suggest that Steiner began mentioning mistletoe as a possible cancer therapy in his lectures as early as 1904. In 1917, Dr. Wegman first administered a *Viscum album* mistletoe extract via subcutaneous injection to several of her cancer patients in Zurich and saw positive results.[46] In 1921, she founded the first anthroposophic clinic, Klinisch-Therapeutisches Institut, in Arlesheim, Switzerland, which is still a thriving AM center today. This clinic ultimately

spurred the development of many integrative hospitals in northern Europe, where conventional academic medicine, surgery, critical care, and integrative AM therapies are practiced side-by-side. Today, many physicians travel to this region from around the world to learn and train in integrative and anthroposophic medicine.

Klinik Arlesheim was founded particularly to focus on care for Dr. Wegman's patients who had cancer. Mistletoe was one of several holistic treatments she used, alongside other herbal therapies, homeopathy, anthroposophic medicines, and therapies that we might regard as soul or psychological care. These therapies include art therapy, rhythmic massage, and eurythmy (therapeutic movement).

One striking perspective in AM cancer care, then and now, was the idea that malignant cancer was the result of a decades-long process that disrupted the *rhythmic balance* in multiple body systems. This included the metabolism, nervous system, and immune system, as well as the patient's emotions and sense of spiritual purpose. The physician's role was to assist the patient in restoring a sense of rhythm and coherence within the body's regulatory systems.[47]

Most of the cancer research community was barely aware of immunotherapy and didn't yet have the language to describe the role of the immune system in preventing or inhibiting cancer growth. Yet Dr. Wegman indeed used mistletoe to encourage a heightened immune response—known today as *immune surveillance.* She and Steiner spoke of the importance of creating a "mantle of warmth" around the tumor area, and Steiner mentioned in his lectures that little result could be seen in cancer treatment unless a fever or a *warmth response* was induced.[48] Early AM physicians pioneered what they called "fever therapies" to increase whole-body systemic warmth in the patient. The warmth, whether local (focused on the tumor site) or systemic (whole body), was indicative of heightened immune activity. We'll look at the science behind these ideas in the next chapter.

Mistletoe, as a "warming therapy," came to be a core feature of AM cancer care from 1920 onward. AM physicians paired mistletoe therapy with other botanical and mineral remedies (see chapter 8) that

supported immune regulation and other aspects of health needed to recover from both cancer and conventional treatment side effects. The goal was and is to create warmth, immune balance, and systemic regulation throughout the body to support optimal conditions for remission and healing. This strategy retrains a dysregulated immune system to initiate and complete its own cycles of heightened response and resolution.[49,50] This systemic and holistic approach to cancer was ahead of its time. Recently, conventional medicine and research have rediscovered these concepts, but only after exhausting a primarily disease-centric approach.

Today's terrain: Cancer care heads to war... and returns to heal its wounds

At the dawn of the twentieth century, AM's holistic care principles did not run entirely counter to the greater world of cancer research. In both the conventional and anthroposophic realm, cancer researchers were asking what went wrong in the body to allow the cancer to take root in the first place. This cause-oriented line of inquiry was inherently more constitutional, more holistic. But conventional cancer research was quickly changing, and the biggest shift wasn't due to advances in laboratory technology and methods. It's possible that the biggest shift was philosophical and cultural. It came from a world shaken by two World Wars. In the wake, "war" became a dominant cultural metaphor. Pick any challenge in modern life, and the metaphor of "waging war" or "defeating the enemy" became the modern mindset. While war metaphors had been applied to humanity's relationship to disease before (especially with the advent of germ theory), the U.S. involvement in two World Wars seemed to cement a war mindset in much of our medical research initiatives and patient care. Disease needed to be eradicated. The idea of "cultivating health" rapidly lost ground and favor. A new massive economy developed alongside our wars on cancer and other diseases.

But cancer is unique. It's not a bacterium that we can annihilate, an infection we can kill off. Cancer cells are *our own cells.*

By adopting a war mentality toward cancer, we began to seek out potential therapies (usually chemical) that could destroy all cancer cells. We couldn't see that a war on cancer might become a war on ourselves. We disregarded the power of the body, soul, and spirit to assist in our human healing.

Sometimes the war on cancer was quite literal, as chemists who were knowledgeable in chemical warfare (and sometimes the chemicals themselves) transitioned directly from the military into early chemotherapy research labs. The first chemotherapeutic drugs were inspired by the bone marrow damages caused by mustard gas.[51] Between deeply entrenched war metaphors and the chemical revolution, cancer care in the U.S. was about to turn aggressive in its techniques and results. The idea of immunotherapy was, for a time, set aside.

Cancer treatment in the late 1940s and early 50s was defined by the work of Sidney Farber, who trialed the first chemotherapeutic agents for childhood leukemia. At the time, this cancer usually translated into a six-month life expectancy upon diagnosis. Farber was the first one to develop therapeutic courage and the will to help these children. Yet many of Farber's experimental treatments, after dramatic initial remissions, ended in fatal recurrences months later.[52,53] While chemotherapy treatments for childhood leukemia would eventually become highly effective and both life-saving and life-extending, these initial experimental treatments did not meet expectations. Despite the mixed results of early chemotherapy, most of cancer research homed in on these new synthetic solutions as oncology's shining hope.

There were occasional novel insights. From the late 1940s until the late '60s, Frank Macfarlane Burnet (1899–1985) introduced more nuanced immunological theories of cancer. His Immunosurveillance Theory pointed out how cancer might be able to hide from the immune system.[54,55] This initiated a search for *tumor-associated antigens* (TAA), the ID keys that a healthy immune system could use to identify cancerous cells and destroy them.[56]

Then, in the 1980s, the work of Mina Bissell appeared, identifying the tumor "microenvironment"—the vessels, tissues, and extracellular

matrix around the tumor—and how that space might hold clues for unmasking the cancer. If the cancer could be unmasked, perhaps the immune system could find and eliminate it. But it would be another thirty years before Bissell's work was revisited and examined for possible treatment alternatives.[57–60]

Apart from a small handful of independent thinkers, cancer treatment in the U.S. became defined by the triad that materialized in the World War era: surgery, chemotherapy, and radiation. In 1971, then-President Nixon formalized the dominant mindset by signing the National Cancer Act—publicly referred to as the War on Cancer. This would provide national funding for decades of research, though the focus remained on "fighting" cancer instead of searching for varied root causes.

Mistletoe research blossoms alongside shifts in conventional care

Founded as an *Institut* (Klinisch-Therapeutisches Institut), Dr. Wegman's Arlesheim clinic was intended as a research hospital. In 1924, Dr. Eberhard Schickler was commissioned with tracking twenty-two case studies. These cancer patients were provided what we would now consider high doses of mistletoe. Ten to twenty milligrams were injected subcutaneously near the tumor or, in some cases, as *intratumoral injections* (into the tumor). These high doses induced moderate fever. Treatments and the associated fever reaction were provided rhythmically over years-long treatment courses, with breaks in between. These cyclic fevers helped to invigorate and reeducate the immune system.[61,62]

Dr. Schickler tracked three treatment groups:

- Late-Stage Cancers: For those with inoperable conditions, mistletoe provided palliative (pain-reducing) effects and significant improvement of the "general condition." They experienced improved energy, weight stabilization, improvement of sleep and appetite, and sometimes the ability to work again.
- Adjuvant Treatment: When mistletoe was used as an adjuvant (a supportive therapy alongside conventional treatment), patients felt less fatigue and fewer side effects from radiotherapy.

Schickler noticed mistletoe's usefulness in helping conventional therapies work better, while maintaining the patient's quality of life (QOL) during treatment.

- Prophylactic Treatment: Mistletoe was also provided to patients who had a family history of cancer or constitutionally showed symptoms typical for carcinomas, for example: accelerated aging, fatigue, and constipation that were not responsive to other AM therapies. These patients became stronger and less anxious, and they came back on their own requesting follow-up injections.[63]

Schickler's preliminary case study notes were eventually joined by the research of Alexandre Leroi, who also improved mistletoe extract processing, and Georg Salzer, who oversaw and published the first randomized, controlled mistletoe trials.[64] In the 1940s and '50s lab research identified some of the most active phytochemicals in mistletoe extract, and multiple animal model studies noted the extract's ability to shrink tumor size and alter immune activity—effects that have been similarly observed in recent research.[65] The pioneering work of Schickler, Leroi, and Salzer laid the foundation for the abundance of mistletoe lab research and clinical studies since then.

Today, mistletoe is one of the most well-researched and clinically tested integrative cancer therapies in the Western world. In addition to the effects noted in human clinical findings, lab testing has identified multiple compounds in the extract, primarily the *viscotoxins* and *lectins*, which are, in varying ways, both directly cytotoxic to cancer cells, as well as immune stimulating.[66] The combination of active compounds in mistletoe extract appears to result in a general *immune surveillance* effect. Mistletoe therapy assists in breaching the tumor's microenvironment and damaging the cancer cells (see chapter 2). Simultaneously, it supports the white blood cells' ability to identify the tumor as a threat and take that information throughout the body, to educate the rest of the immune system. This leads to more efficient destruction of the cancer cells.[67]

Shifts in US research return our attention to immunotherapy

By the late 1990s, mistletoe therapy had acquired significant awareness and a research base in Europe. Meanwhile, across the Atlantic, cancer research in the U.S. had begun to come full circle, returning to questions about how a healthy immune system interacted with and eliminated cancer cells. While treatment options remained limited from the 1960s through the turn of the 21st century, we have seen recent shifts regarding cancer-cause theories. Mina Bissell's work on the tumor microenvironment would take a couple decades to gain traction. But the Two-Hit Theory of cancer appeared in the 1970s and was mainstream by the '80s and '90s. We began to view cancer as caused by a genetic susceptibility (Hit One) aggravated by an environmental risk factor (Hit Two).[68] This theory held some truth for some cancers but did little to alter dominant treatment strategies.

Meanwhile, the patients themselves began to lead the way in seeking out alternative cancer care options, often while still carrying out the recommended conventional treatment protocols. Conventional medicine and research communities began to pay attention when certain "alternative approaches" began to regularly yield positive outcomes. In 1992, the National Institutes of Health (NIH) formally established the Office of Alternative Medicine (OAM) to evaluate such practices—not only in oncology, but also in all fields of healthcare. In 1998, the OAM expanded its umbrella to become the National Center for Complementary and Alternative Medicine (NCCAM). In a more recent metamorphosis in 2014, it became the National Center for Complementary and Integrative Medicine (NCCIM). Its funding for research exploring the science and efficacy of such approaches continues to grow today.[69]

More than one-third of Americans use some form of alternative or integrative medicine in general.[70] That figure holds steady for patients who have cancer,[71] though some research suggests those numbers are much higher—possibly closer to 80 percent.[72] It's very likely that alternative medicine usage is underreported due to perceived backlash from the SOC establishment. Whatever the true number, the interest in

complementary options is common enough that conventional oncology had to take notice. A formalized definition of *integrative oncology* was published in the fall of 2017 in Oxford Academic's *JNCI Monographs*:

> Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum, and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment.[73]

This is the definition approved and used by The Society for Integrative Oncology (SIO), which was founded in 2003.[74] In part because of SIO initiatives and research, integrative offerings are quickly becoming commonplace in major cancer treatment centers. There is still a lot of work to be done, but we have come far in bridging the gap, particularly in the past twenty years!

The primarily patient-led shift has inspired researchers to ask more holistic questions. What if cancer is more systemic in nature? In the early 2000s, Dr. Thomas Seyfried of Boston College theorized that cancer was a metabolic disease, one whose course could be changed by altering the patient's metabolism, usually through dietary choices and fasting.[75] Today, cancer research is widening its lens and thinking more creatively, more systemically and holistically. The living questions are, "What if cancer is both metabolic and immunologic? What if there are multiple intertwined causes?"

Recent years have ushered in resurrected or newly emerging ideas ranging from *deutenomics* (which introduces quantum mechanics into cancer theory),[76] to TOFT (Tissue Organization Field Theory),[77] to Dr. Seyfried's expansions on his Metabolic Theory of Cancer.[78] All of these are interested in the patient's *terrain* as the focal point. They focus particularly on the mitochondria, the energy-production centers in human cells, and how mitochondrial function differs greatly in tumor cells, compared to healthy cells. These new theories explore mitochondrial

health and wellbeing as both cancer's cause and its potential remedy. For the sake of this book, we will not go into the details of each of these theories, but we do want you to be on the lookout for what the future of integrative oncology holds. Overall, this deeper questioning and sense of cancer as a systemic disease has fostered greater openness among conventional oncologists to consider the value of *systemic adjuvant therapies* like mistletoe. Contemporary researchers and practitioners alike now refer to Steven Paget's Seed and Soil hypothesis and discuss therapies that build up the body systemically, in addition to treatments that attack the cancer.

The current shift has also led to the blossoming of immunotherapy and functional medicine. In that environment of curiosity and receptivity, conventional oncologists in the U.S. are now interested in the mistletoe immunotherapy that is more commonly used in German and Swiss cancer care. After over one hundred years of research and safe use in Europe, the U.S. is beginning to research mistletoe. This therapy is finally the focus of the first clinical trial of its kind at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, now underway as of the publication of this book.[79] Meanwhile there are also hyperfocused efforts to research new cancer immunotherapy drugs across the nation.[80,81]

As the saying goes, what was old is new again. It's true that many new immunotherapy drugs, from checkpoint inhibitors to modified oncolytic viruses, often wind up mimicking the activity of herbal and nutritional therapies. But the latter have been around far longer and have fewer side effects. In the case of mistletoe, we have an herbal immunotherapy with over one hundred years of clinical use. Even if the earliest practitioners did not have the immunotherapy vernacular, their approach was certainly immunotherapeutic in nature. They used mistletoe to provoke a "warming" response in the body—to awaken the immune system. Mistletoe therapy improves autonomic self-regulation, therefore providing other metabolic and functional support as well. In the U.S., we are finally beginning to see some recognition of the science that supports this unique systemic therapy.

Currently, there are several smaller integrative oncology clinics across the country that follow integrative, functional, or anthroposophic models of care. The larger medical insurers have not, for the most part, been willing to support integrative oncology, and so they remain very modest initiatives. But Dr. Winters and her colleagues have recently founded the Metabolic Terrain Institute of Health (see chapter 12). This institute is unique; it brings together metabolic and integrative approaches to healthcare with many similarities to those European anthroposophic hospitals that integrate mistletoe and conventional care. The institute is also developing a robust algorithmic and multivariant database to collect patient data and outcomes from clinics that emphasize metabolic and integrative cancer care.[82] We envision this project as a sustainable model that will go far to ensure credibility, cooperation, and better evidence-based practices in the emerging field of integrative oncology. We look forward to this exciting development.

Mistletoe today: Basics of administration and use

To clarify, when we refer to mistletoe for cancer care, we mean European mistletoe, clinically referred to as *Viscum album* extract (VAE). In this book, we use the terms *mistletoe therapy* and *VAE therapy* interchangeably. There are numerous species of mistletoe worldwide, but *Viscum album* is best known for conveying supportive or even life-prolonging benefits in cancer care and for other chronic health conditions. As of publication of this book, over 150 studies have been conducted on anthroposophic mistletoe preparations,[83] and many patients who have cancer in Germany choose to include it as an adjuvant in their treatment plan.[84] Continental Europe is home to the largest concentration of cancer care centers that offer mistletoe therapy—used on its own or alongside conventional treatments, depending on the oncological situation. It is a rapidly growing therapeutic option in Asia and South America as well.

VAE is recognized as a homeopathic remedy in the U.S. It is listed in the homeopathic pharmacopeia as a remedy taken orally for headache—another well-studied mistletoe benefit.[85,86] This is why, when we

purchase VAE, it arrives in sterile ampules labeled as "sips." Administering mistletoe therapy for immune support during cancer care is respected as a legitimate Off-Label Drug Use (OLDU), supported by extensive European research and SOC guidelines. Indeed, even recent articles published by the U.S. National Cancer Institute recognize and respect VAE therapy.[87] Of course, practitioners must inquire within their own jurisdiction, as guidelines may vary from state to state.

Practitioners who are trained in VAE therapy for cancer care teach their patients how to open the ampules and administer the extract through *subcutaneous injections* (injected just below the surface of the skin), usually in the skin of the abdomen. After in-office training, most patients opt to complete their injection series at home. At certified infusion centers, VAE may also be administered intravenously (IV) for intensified systemic effects. There are other methods for administering VAE (see chapter 10), but subcutaneous injection and IV are the most common. Method and dosage are personalized to each patient based on the individual's state of health; the type of cancer, its stage, and how aggressive it is; and the patient's greater hopes for their treatment outcome.

The goal with all VAE therapy is to *enhance warmth* in the patient, which coincides with immune activity, autonomic regulation, and other holistic QOL benefits we'll discuss in chapters 6 and 7. With subcutaneous injections, the enhanced warmth is tangible. The injections begin at a low dosage and increase incrementally until there is a small local reaction, a reddening or darkening at the injection site, about the size of a silver dollar, and often mild to moderate itching (see appendix A). This reaction is good! It means the VAE has awakened the immune response. With IV mistletoe, we often attempt to trigger a moderate fever of no more than 100.2 degrees Fahrenheit (37.9° Celsius). More experienced providers, usually in a hospital setting, may prompt much higher fevers. This too, is a desired clinical response, though it is not always achieved. The fever typically lasts a few hours or, rarely, up to 24 hours. It is this "warming response" that indicates heightened immune activity, awakening immune cells to their larger task. We'll

look more at how VAE interacts with the immune system in the next chapter, and we'll explore more of the nuances of when and how to use subcutaneous and IV administration throughout the rest of this book, especially within the case stories shared in Parts 3 and 4.

A note on orally consumed mistletoe

There is not substantial research on orally consumed forms of mistletoe. It is possible the immune-stimulating lectins are broken down in the GI tract, limiting their immune effects. There are some promising case stories that involve providing oral mistletoe (specifically as *anthroposophic sips* produced by Helixor®) for children with brain cancers and a single case report on astrocytoma in an adult.[88–90] In such delicate situations, oral administration of anthroposophic mistletoe products might be a safe, gentle adjuvant that still conveys some benefit. But over one hundred years of successful clinical administration indicates that subcutaneous injection, IV, and similar injected applications are the most efficacious for adults.

Mistletoe as a gateway to true holistic care

We often say in our VAE trainings, "Mistletoe is not a protocol plant." There isn't a dosage chart based on height and weight and cancer type. Rather there are starting dose recommendations, followed by a process in which the practitioner and patient together determine the patient's optimal dosage based on the physical response to the injections. So VAE inherently requires individualized administration.[91] As such, for many conventional and integrative physicians, mistletoe therapy is a first encounter with truly patient-led, response-guided care. It requires active cooperation and communication between the clinician and the patient.

Personalizing mistletoe therapy begins even before the first dose. Practitioners are trained in how to pick the best mistletoe extract for the patient based on qualities of the mistletoe *host trees* (see chapter 4) and specific manufacturer nuances. European mistletoe, *Viscum album*, is cultivated on numerous types of host trees. VAE manufacturers harvest

mistletoe from more than a dozen different host tree species. They pay close attention to the time of year when they harvest and give special care to branded processing techniques. Each extract has a different lectin composition and viscotoxin concentration. Chapter 4 will describe these differences in depth, but for now it's good to be aware that host trees affect VAE composition, and this is a significant factor in personalizing the therapy for each patient.

The holistic nature of mistletoe therapy is also reflected in the plant's multitude of phytonutrients. While a handful of isolates have communicated some benefits in preliminary studies,[92] it's clear that mistletoe therapy is more effective when the whole extract is used.[93] The diverse compounds work in synergy on multiple body systems. They activate immune cells, selectively damage tumor cells, and enhance mood. Collectively they are responsible for mistletoe's best-known benefit: supporting patient QOL during conventional treatments.

Just as mistletoe works better when used as a whole extract, VAE can provide enhanced effects when paired with other natural remedies and conventional treatment options. It contains within it an orchestra of compounds that work very well in synergy with other therapies. Though it is employed as a stand-alone therapy in some parts of the world, it is a strong and adaptable adjuvant. Just as VAE therapy introduces practitioners to personalized response-guided care, it also provides an introduction to more involved *systemic thinking* when choosing additional adjuvants.

VAE shows up in diverse contexts, whether it is one natural therapy among many in complex, whole-person care or as the sole integrative adjuvant in a conventional care plan. Mistletoe can be used safely as an adjuvant therapy along with almost all other conventional and integrative treatments. Its power is in its ability to enhance the effects of other treatments and mitigate side effects during more aggressive conventional treatments.[94] That includes tempering leukopenia, thrombocytopenia, anemia, nausea, pain, fatigue, and hepatotoxicity.[95] In addition to mitigating side effects, VAE therapy also conveys QOL effects that are harder to quantify, including an increased sense of

purpose and greater spiritual clarity. We'll explore possible roots of these effects in chapter 7.

The world of anthroposophic cancer care in Europe and the U.S.

As you explore the rest of this book, keep in mind that European cancer care differs from SOC in the U.S.—especially when one looks at cancer treatment centers in Germany, where AM is more established. In AM cancer care, VAE therapy is routinely provided alone or alongside conventional treatments, but care does not stop there. In fact, soul- and spirit-care are given equal regard. In AM, the therapies that affect the *function of the physical body* include: VAE therapy, chemotherapy, radiation, personalized medicine, and immunotherapies, as well as other AM homeopathy, herbs, and nutritional changes. All these work in tandem with therapies that *cultivate soul and spirit*, such as: art therapy, music therapy, journaling (biography work), rhythmic movement (eurythmy), trauma resolution, and purpose exploration. We'll explore these concepts more in the second half of this book. The importance of soul- and spirit-care will be evident in our case stories throughout.

AM cancer care does exist in the U.S. There are about 300 AM-trained physicians in the U.S., many of whom studied in Europe and are trained in VAE therapy. These doctors often incorporate integrative and conventional medicine into their practices. Some are listed in the PAAM Provider Directory at www.AnthroposophicMedicine.org. Additionally, there is a growing number of practitioners who provide VAE therapy who are not anthroposophic doctors—though they have often trained with AM physicians on the specifics of administering VAE.

The AM community has welcomed partnerships with other practitioner communities to participate in VAE training and exchange knowledge with each other on treatment strategies. We regularly connect with practitioners with backgrounds in conventional oncology as well as Ayurveda, traditional Chinese medicine, functional medicine, homeopathy, and naturopathy. What we all have in common is a desire to cultivate health—not solely fight disease. Even if a patient can't find

an AM physician in their region, they should be able to find a naturopath or integrative physician who is trained in mistletoe administration and other aspects of integrative oncology. Clinicians who want to learn more about VAE therapy may reach out for training and mentoring through PAAM. Fortunately, the number of doctors interested in VAE therapy is growing, and the training has become more accessible and comprehensive.

Meanwhile, cancer research has expanded its scope from Somatic Mutation Theory (in which cancer is a linear progression and your genes are your destiny) to include highly layered metabolic and immunologic questions. In the Metabolic Theory, the commonality shared by all cancer cells is not defective DNA, but rather a warped *anaerobic metabolism*. Cancer cells make their energy without oxygen.[96] That cellular defect is both their strength and a weakness that we can target with strategic dietary and immune-supporting therapies. From a metabolic standpoint, cancer is a dynamic process with many points of influence. It's not your destiny at all. Early cancers come and go often, and established cancers can go dormant. Changing your inner terrain and manipulating the tumor microenvironment can starve and stunt or even regress a cancer. As the research expands, we're seeing more openness to holism and systems thinking in medical practice.

Studies around the world are making new paradigm-shifting discoveries every year: lifestyle choices affect metabolism and metabolic shift can affect cancer growth,[97,98] meditation can alter immune markers,[99] our response to stress can alter our epigenetics,[100,101] and even disturbed circadian rhythms can affect cancer risk.[102,103] The new Blue Zone studies, looking at regions with high densities of people living to one hundred years or more, have identified nine essential determinants of health. They're all lifestyle factors related to nutrition, daily rhythms, and connection to the natural world.[104] That's just the tip of the iceberg. Breakthrough findings regarding the power of integrative care and lifestyle choices are spurring U.S. cancer centers to look to their European colleagues for recommendations. What's happening

right now is another massive and beautiful shift, from a care model that's focused on fighting disease to one that addresses the disease while cultivating health. It's the difference between *pathogenesis* and *salutogenesis*—instead of asking only, "What is the cause of the disease?" we also ask, "What is required to *create health?*" Mistletoe is a powerful addition to the collection of therapies within that health-creation paradigm.

Learn more about Anthroposophic Medicine, find Anthroposophic Practitioners, and learn about upcoming mistletoe trainings for U.S. practitioners at: www.AnthroposophicMedicine.org.