

Chapter 2

The Symptoms and Signs of Dying

Whenever a doctor diagnoses a fatal disease, the typical patient immediately asks two questions: How long will I live and will I suffer? Chapter 5 addresses the first question; this chapter, the second.

Professionals who provide any part of end-of-life care must understand something of the physical symptoms that dying patients experience. These patients often fear the symptoms of dying more than death itself. Their highest priority is symptom relief. I believe that relief is critical: Patients must be physically comfortable before their minds can focus on other aspects of care, including the psychological, social, and spiritual aspects this book describes. All professionals who attend the dying, therefore, must commit to a compassionate, effective plan to address physical symptoms.

An open discussion is a key first step in providing symptom relief. That discussion should include four elements. First, it should state explicitly the clinicians' commitment to relieve symptoms to the maximum extent possible. Making this commitment should include a sense of urgency about addressing symptoms when they arise [1]. Some clinicians, in fact, rightfully consider pain in dying "a medical emergency." Second, the discussion should mention access to expertise for treating persistent symptoms. That expertise already exists widely in numerous textbooks and journal articles. It also exists in many hospitals and healthcare systems through special palliative care teams. Third, the discussion should explain that conscientious care can significantly relieve many symptoms of dying, especially pain [2]. Common side effects of symptom relief treatments such as opioid-induced nausea and constipation can also be managed successfully. However, some symptoms such as poor appetite may yield only partly to treatment. And, fourth, the discussion should assure patients and family members that the attending professionals will never ignore patients' symptoms or neglect their care.

The attending professionals, especially the biomedically trained clinicians, must be able to respond to the concerns of patients and families as particular symptoms arise. Good care begins with good explanations. This chapter can help with its descriptions of the prevalences, presentations, and pathologies of common

end-of-life symptoms. The chapter also briefly describes treatments for the symptoms, but limitations of space and focus prevent any extensive discussions of those treatments. Readers can find detailed discussions of them in other sources.

The symptoms of dying, of course, vary somewhat among the many diseases that can cause death. The most common fatal diseases in North America these days are (in order of descending incidence) cardiovascular diseases (including congestive heart failure and strokes), cancer, chronic obstructive lung disease (such as chronic bronchitis or emphysema), dementias, and degenerative nervous system diseases [3, 4]. Yet likely due to the public's long focus on cancer and the resulting generous funding for it most research on end-of-life symptoms concerns cancer. Relatively little research concerns other fatal diseases [5]. This chapter, therefore, follows the professional literature's lead by concentrating on cancer. I believe, though, many points about cancer apply to other fatal diseases, too. In fact, as the chapter explains later, some experts believe dying from most fatal diseases follows one "final common pathway" of symptoms [6].

The chapter starts by describing frequent symptoms in dying including pain, dyspnea (shortness of breath), fatigue, confusion (delirium), cachexia (loss of weight), anorexia (loss of appetite), and depression. The chapter then discusses three phases of symptoms as death becomes imminent. The chapter concludes by describing the various physiologic signs people use to determine for themselves a patient's time of death. A woman with brain cancer illustrates many of the chapter's points.

The Case

Mrs. W. an elderly Euro-American woman, lives with her husband, Mr. W. in a retirement center. She suffers increasing weakness in her legs over several weeks. Her mobility declines from standing and walking independently to just lying in bed. Her ability to speak also declines to the point she rarely speaks at all.

One day a bilateral paralysis suddenly strikes Mrs. W. from the neck down, and she cannot respond. Mr. W. calls an ambulance, which transports her to the nearest hospital. A work-up there reveals a large brain cancer. Treatment with maximal steroids and irradiation shrinks the tumor, reducing its encroachment on nearby normal brain tissue. The oncologist informs Mr. W. that no further treatment exists, and the tumor will eventually grow back, worsening her symptoms again. At the oncologist's suggestion Mr. W. authorizes Mrs. W.'s transfer back to the retirement center for long-term care.

Mrs. W.'s symptoms and signs distress the family over the next weeks. She regains some ability to respond but only intermittently. She fluctuates unpredictably between responsive good days and unresponsive bad days. Mr. W. feels whipsawed. Even when Mrs. W. does respond, she is confused and does not recognize family and close friends. She often complains of a headache, and groans and grimaces. Her family interprets these signs to mean Mrs. W. is suffering pain despite her intensive

opioid regimen. The retirement center's primary care doctor adjusts the opioid doses with some improvement in Mrs. W.'s alertness and apparent comfort.

Mrs. W. also does not eat well and has lost considerable weight since hospital admission. The local nutritionist introduces high-calorie, high-protein foods into Mrs. W.'s diet. Her intake improves slightly. The primary care doctor explains to Mr. W. that weight loss may be inevitable with Mrs. W.'s cancer. Mr. W. also worries that his wife fatigues easily and occasionally appears short of breath. The doctor says he cannot help the fatigue much, but he does prescribe supplemental oxygen for the shortness of breath. All the while, Mr. W. wonders whether the doctor has told him "the whole story" about Mrs. W.'s condition.

Pain

Pain is the unpleasant sensory and emotional experience associated with tissue damage [7]. All pain travels along peripheral nerves to one central spinal cord tract, the spinothalamic tract, and then on to the brain. But different pain sensations travel along different fibers within those nerves. "Fast" fibers carry the transient, well-localized pains that serve a protective function. Pain from noxious pressures or extreme temperatures on the skin travels along these fast fibers. When activated, these fibers initiate an automatic reflex that instantly withdraws the affected body part from the noxious stimulus. "Slow" fibers, in contrast, carry the long-term, diffuse pains that often arise deep in the body and appear to serve no biological function. Those pains occur with many internal diseases and after surgeries.

Pain characteristics, of course, vary by site of origin [8]. Pain from bones, muscles, or joints ("somatic pains") localizes to the general area of injury and presents as dull, throbbing, or achy. Bone fractures or tissue wounds have those pains. In contrast, pain from internal organs such as heart or bowels ("visceral pains") localizes poorly and presents as cramping, squeezing, or gnawing. Heart attacks ("myocardial infarctions") or bowel obstructions have those pains. Finally, pain from nerves ("neuropathic pains") localizes either well or poorly and presents as shooting, burning, tingling, stabbing, or electrical shock-like. Tumor invasion into nerves or post-amputation "phantom" limbs have those pains [9].

Patients and their families fear pain more than any other symptom in dying [1]. Although palliative care specialists believe current treatments can alleviate pain for most dying patients, many still suffer with it regardless of their particular fatal diseases. Various studies report high prevalences of end-of-life pain with cancer (35–96 %); acquired immunodeficiency syndrome, or AIDS (63–80 %); various serious heart diseases (41–77 %); COPD (34–77 %); end-stage kidney failure (47–50 %) [7]; and end-stage liver failure, or cirrhosis (30–40 %) [10].

Why does pain still plague dying patients? Several possibilities exist. First, patients may not report their pain. Although the decreased quality of life associated with pain should prompt patients to report it, counterbalancing considerations may act as obstacles to doing so. One study asked cancer patients to rate eight attitudes

Table 2.1 Cancer patients' ratings of possible obstacles to reporting pain

Possible obstacle	Mean ratings*	
	Patients with controlled pain	Patients with uncontrolled pain
Fear of opioid addiction	1.7	2.6
Fear that increasing pain means disease is progressing	1.8	2.5
Fear of medication side effects	1.8	2.2
Fear of injections	1.8	2.1
Belief that taking opioids early in a cancer's course will make them ineffective later	1.2	2.2
Belief that treating pain distracts clinicians from fighting the cancer	0.9	1.7
Belief that "good" patients do not complain of pain	0.9	1.4
Belief that pain is inevitable	0.9	1.4
Average score for all items	1.4	2.0

Adapted from Ward et al. [11], with permission

*The rating scale ranges from 0 ("do not agree at all") to 5 ("agree very much"). 2.5 is the neutral point between the disagree and agree ratings

that might act as obstacles to reporting pain (Table 2.1) [11]. The researchers contrasted the ratings of patients with and without uncontrolled pain. Patients with controlled pain tended to doubt that *any* of the eight attitudes creates obstacles to reporting pain. Yet patients with uncontrolled pain tended to believe more (or doubt less) that *all* of these attitudes create such obstacles. Specifically, compared to patients with controlled pain, patients with uncontrolled pain tended to see as reporting obstacles the fear of opioid addiction, the fear that increasing pain means the disease is progressing, the belief that taking opioids early in a cancer's course will make them ineffective later, and the belief that treating pain distracts clinicians from fighting the cancer. Furthermore, women more than men tended to believe medication side effects create obstacles to reporting pain, the elderly and the poor more than the young and the well-to-do tended to believe "good" patients do not complain about pain, and the poorly educated more than the better educated tended to believe pain is inevitable in dying.

Second, many clinicians may lack the knowledge to provide sufficient pain relief. Professional medical organizations have responded by sponsoring educational initiatives to increase that knowledge and to encourage its use. These initiatives stress the World Health Organization's stepped approach [12] to analgesia: Nonopioids such as acetaminophen (e.g., Tylenol) or nonsteroidal anti-inflammatories (e.g., aspirin, Motrin, and Aleve) are the Step I drugs; the weak opioids such as tramadol (e.g., Ultram) or codeine are the Step II drugs; and the strong opioids such as morphine or meperidine (e.g., Demerol) are the Step III drugs. Many somatic and visceral pains respond adequately to analgesics alone when used in a stepped fashion. Yet many neuropathic pains require supplemental "coanalgesics," drugs

used together with analgesics to increase their pain relief effect. Coanalgesics include antidepressants such as nortriptyline (e.g., Pamelor), desipramine (e.g., Norpramin), duloxetine (e.g., Cymbalta) or venlafaxine (e.g., Effexor), and anticonvulsants such as gabapentin (e.g., Neurontin) or pregabalin (e.g., Lyrica).

Third, because opioids occasionally depress respiration, some doctors hesitate to dose them adequately for fear of causing severe respiratory depression and death. (I firmly believe this fear arises mostly from doctors' concerns over the life-threatening harm to patients rather than over medical-legal liability for themselves.) Palliative care specialists counter that dosing opioids carefully but adequately often relieves pain completely, and, if respiratory depression occurs, special antagonist drugs can reverse the opioids' effects. Doctors must simply be prepared to use those drugs quickly if necessary. Palliative care specialists conclude that all patients deserve optimum pain relief, and doctors have the duty to provide it [1].

The old ethical doctrine of double effect justifies that duty best. Whenever an act will have simultaneous, inseparable good and bad effects, this doctrine permits the act if the total expected good effects outweigh the total expected bad effects and the actor intends only the good effects. The doctrine, therefore, permits escalating opioid doses sensibly as needed to relieve a patient's pain despite the simultaneous, inseparable risk of respiratory depression. The doctor's single-minded intention to provide adequate pain relief is the key ethically permissive feature. But, in case questions might arise afterward, the doctor should always document that intention in the medical record.

Fourth, although inpatient and outpatient palliative care services are increasingly available, doctors sometimes hesitate to use them [13]. One reason is that many doctors misunderstand palliative care as applying only to end-of-life, hospice-like situations. In fact, palliative care applies to *any* illness—fatal or not—requiring a “focus on quality of life and the alleviation of symptoms” [8]. Furthermore, doctors may underuse hospice even for dying patients, and the palliative care that goes with it. The requirements for hospice may be partly to blame [3]. To reimburse for hospice care, Medicare requires a doctor's prediction that the patient has less than six months to live. As Chap. 5 points out, many prolonged, fatal diseases including most cancers defy precise prediction of remaining life span up to only a few days before death. Doctors balk at making such uncertain predictions due to concerns about misinforming patients and family members. Medicare also requires adequate direct caregiving. While relatives or close friends may voluntarily provide that care for some dying patients say, at home, many others have no one to give it. And, while Medicare does not officially require it, one other condition often precedes hospice referral: Patient, family, and attending doctors must all agree the patient is dying and should receive no further aggressive care for disease control, only care for comfort. Achieving that agreement can be difficult, sometimes delaying or even preventing hospice referral.

How can clinicians help overcome the obstacles to getting dying patients the pain relief they need? Clinicians can certainly educate themselves about pain relief, legal and moral factors related to it, and hospice use. Clinicians should also actively educate patients and families about pain relief. The education need not take much

extra time: It can often take place at the bedside as clinicians conduct their usual patient care. And they can encourage patients to report their pain and can emphasize, repeatedly if necessary, that conscientious efforts usually achieve adequate relief [2, 14].

Clinicians often need to address explicitly people's fears about opioids. Defining addiction, tolerance, and physical dependence is important in doing so [1]. "Addiction" refers to the persistent misuse of drugs—legal or not—despite significant damage to one's physical health, personal relationships, or work performance. "Tolerance" refers to increasing dosing requirements over time to achieve the same drug effects. And "physical dependence" refers to having certain symptoms and signs when a medication is withdrawn too quickly.

Having defined these terms for patients or family members, clinicians should then explain that pain relief with opioids as needed is safe and beneficial: Addiction occurs never; tolerance, rarely; and physical dependence, only occasionally. Such pain relief does not damage patients' physical health, personal relationships, or work performance but promotes instead overall fulfillment during remaining life. The absence of pain facilitates participating in relationships and functioning in other ways. Furthermore, patients in pain request only the opioid doses they need, no more. Almost no one encounters tolerance. The typical opioid regimen for adequate pain relief reaches a dosing plateau and goes no higher. But even in the rare case of true tolerance the ever-increasing doses have little significance: The opioid regimen is usually short term, limited by the patient's death. Furthermore, physical dependence presents only an occasional problem because opioids are always tapered gradually when decreased, and almost never stopped before death. (If withdrawal symptoms do arise during a taper, clinicians can temporarily increase the doses to eliminate symptoms and then taper again more slowly than before.) Above all, clinicians must stress to patients and family members that adequate pain relief is an essential part of end-of-life care. All patients deserve that relief.

Ethnic Similarities and Differences in Pain Experiences

Recent studies suggest American ethnic groups share certain pain characteristics but differ on others [15, 16]. All groups share roughly the same pain threshold (the lowest pain intensity a person detects), the same pain tolerance (the maximum pain a person will voluntarily endure), and the same willingness to use mainstream medical methods for relief. But the groups differ in heat/cold pain tolerance, which decreases steadily from Euro-Americans (EAs) to Hispanic Americans (HAs) to African Americans (AAs) [15]. The groups also differ in what prompts them to seek pain relief. EAs tend to act on high pain intensity and interference with activities; HAs, on frustration and worry; and AAs, on frustration and high numbers of pain sites. Moreover, the groups differ in their use of nonmainstream methods for relief [16]. Unlike EAs, HAs and AAs tend to use conscious rest, social support, and prayer or other spiritual techniques.

Clinicians who attend dying Americans might keep these differences in mind when assessing pain and planning pain relief measures. EAs, for example, might bear more pain than others without complaining. EAs may need frequent, explicit encouragement to report their pain. Clinicians might also need to ask patients of *all* ethnic groups for suggestions about how to use their cultural or spiritual practices to achieve holistic pain relief.

The Case

Systemic steroids, oral opioids, and maximal radiation to the tumor provide considerable relief from Mrs. W.'s dull, visceral-like headaches during the first weeks of treatment. Visits from friends, trips outside in a wheelchair, and gentle physical therapy in her room help distract her from the residual pain.

But the doctor knows Mrs. W.'s headaches will worsen again as her tumor regrows. He also knows that, as an EA, Mrs. W. may underreport her pain. He makes a mental note to ask her periodically about it. He emphasizes to the W.s that treatment now aims primarily to relieve pain, and he urges Mrs. W. to report it so he can treat it. The doctor explains what addiction, tolerance, and physical dependence are and why they pose no problem for her. He insists the opioids will help her function better, not worse. And he warns her about possible side effects including nausea, decreased appetite, and constipation. He assures the W.s he can treat those symptoms if they arise.

Three Other Common Symptoms: Dyspnea, Fatigue, and Confusion

Dying patients may fear pain most but often suffer other symptoms, too. Three symptoms—dyspnea (shortness of breath), fatigue, and confusion [2, 6]—occur especially commonly before death from such varied fatal diseases as atherosclerotic heart disease, congestive heart failure, cancer, COPD, AIDS, and kidney failure. The documented end-of-life prevalences of these symptoms range widely from 10 to 95 % for dyspnea; from 32 to 90 % for fatigue; and from 6 to 93 % for confusion. All three symptoms increase in prevalence as death nears [17].

Dyspnea (shortness of breath) is a feeling of difficult, but not necessarily rapid, breathing. It has many known causes including disturbances in the chest wall's bellows that expand and contract the lungs, in the lungs' inner membranes where oxygen diffuses into the blood, and in the receptors that monitor the blood's oxygen and carbon dioxide concentrations [18]. Multiple causes often operate at once. Curiously, up to 25 % of dying patients have dyspnea without detectable abnormalities in chest anatomy, lung function tests, or arterial oxygen or carbon dioxide concentrations [17]. Some authors attribute those dyspneas to cultural or psychiatric factors.

Whenever dyspnea arises or worsens, a doctor should perform a thorough examination to determine cause and treatment. However, a few simple measures can provide some immediate relief. Those measures include elevating the head of the bed, directing a fan gently across the patient's face, and providing supplemental low-flow oxygen by short nasal tubes [19]. Some dyspneas, of course, require more sophisticated treatments such as special breathing techniques, low-dose opioids, thoracentesis (a procedure that removes obstructing air or fluid from the space around the lungs), and tracheal intubation with mechanical respiration.

Fatigue is an extreme tiredness, exhaustion, weariness, or lethargy that impairs activity [7]. Excessive physical activity, insufficient rest, dehydration, and even poor diet can cause temporary fatigue in healthy people. That fatigue protects the body from overexertion and responds to rest. The persistent fatigue in dying patients, however, appears to serve no protective function and does not respond to rest. The pathology of that fatigue remains unknown: It can exist independent of infections, anemias, and other plausible causes. Some authors speculate that advanced cancer or its chemotherapy causes fatigue by disrupting the body's immune and inflammatory systems, but little research has tested the idea. The lack of a tested, credible clinical explanation for this end-of-life fatigue prevents effective assessment and treatment of it.

Confusion is a broadly dysfunctional mental state causing disturbed comprehension and bewilderment. The two most important end-of-life confusions are delirium and dementia. They afflict approximately 28 and 11 %, respectively, of dying patients. While these confusions share some presenting features such as short-term memory deficits and mood lability, effective treatment and prognostication depend on distinguishing the two [7, 20].

Delirium, also called "acute confusional state" or "terminal restlessness," is a sudden impairment of consciousness with cognitive, affective, and physical manifestations. Risk factors include advanced age, male gender, prior illicit drug or alcohol abuse, underlying dementia, malnutrition, brain tumor, kidney failure, and poor pain control. Delirium causes primarily inattention, that is, poor concentration. Problems with perception and reasoning may also occur. Other common features are fluctuating consciousness [9] (typically more awareness in the morning and less at night), delusions (the inability to distinguish reality from imagination), hallucinations (disordered visual, auditory, or olfactory sensations), and speech which may be louder, faster, or slower than normal. Delirium often causes either baseline drowsiness, hyperalertness, or a mixture of the two [21].

Many conditions can trigger delirium: acute illnesses such as hip fracture, infection, and kidney failure; dehydration, low blood pressure, or abnormally high or low body temperatures; abnormal concentrations of sodium, calcium, glucose, or other substances in the blood; psychoactive drugs including opioids, antidepressants, and corticosteroids; sensory impairments; constipation or stool impactions; liver or kidney failure; and physical restraints [9]. Multiple triggers often work together simultaneously [22].

Treatment can reverse many of these triggers and the resulting delirium. When an opioid causes the delirium, for example, either reducing the dose or changing the

opioid can improve the delirium. Maximal improvement may require 3–4 days. Approximately 50 % of deliriums occurring a month or more before the end of life resolve within a week. Unfortunately, 88 % of deliriums occurring in the last two weeks of life do not resolve before death [22].

A patient's delirium, of course, often distresses patient, family, and caregivers. When it does, education helps [21]. Clinicians might use the preceding explanation as a guide. They should give a brief description of delirium in plain language and identify any triggers that might be reversed in the case. Clinicians might also instruct others in simple interventions that may help calm the patient: providing adequate but not glaring light, displaying pictures of family members at the bedside, eliminating extraneous noise, speaking in soothing tones, reading aloud to the patient, caressing parts of the patient's body, or holding his or her hand. If the delirium defies treatment, clinicians might explain that despite appearances to others the delirium (say, hallucinations depicting long-dead relatives) may actually be easing the patient's transition from life to death. After all, delirium may be the brain's last coping mechanism [20].

Many people confuse delirium and dementia. The importance in distinguishing the two lies in the different treatment approaches and prognoses. In contrast to delirium, dementia is a slowly and steadily progressive deterioration of memory with at least one simultaneous other cognitive problem. Both problems together must be severe enough to impair social or vocational function [7, 23]. Risk factors for dementia include advanced age, female gender, low educational attainment, and dementia in the family. Memory deficits are the usual presenting complaint and predominant feature of dementia, but the associated cognitive problems range from being unable to remember words, perform previously learned tasks, or recognize familiar objects to getting lost in familiar surroundings, losing impulse control, or having problems with planning and judgment [24]. Treatment for dementia involves frequent reorienting and other supportive care. Table 2.2 contrasts delirium and dementia.

The Case

Although Mrs. W. has no obvious dyspnea, she does have persistent fatigue in her first several weeks back on the retirement center's nursing ward. She tires quickly with simple activities such as eating a meal or sitting up briefly in bed. She may sleep for a whole day after a visit from well-wishers.

She also has new confusion. She cannot recognize close family and friends and often becomes disoriented to time and place. She sometimes sees visions of her long-dead parents, waves her hands aimlessly above her head, or makes stitching motions in the air. Her strange visions and motions improve in the morning and worsen in the evening. She cannot concentrate on conversations, however brief. And, when she talks, her speech is unusually loud and slow. Naturally, her confusion distresses the family.

Table 2.2 Distinguishing delirium and dementia

Characteristic	Delirium	Dementia
Onset	Sudden (over hours to days)	Gradual (over months to years)
Identifiable triggers	Frequent	Infrequent
Predominant deficit	Inattention/poor concentration	Memory lapses
Consciousness	May be clouded but fluctuates.	Alert until late stages
Speech patterns	Often loud and unusually fast or slow	Difficulty in finding words, articulating thoughts
Hallucinations (disordered visual, auditory, tactile, or olfactory sensations)	Common	Uncommon
Delusions (the inability to distinguish reality from imagination)	Common	Uncommon
Course in a day’s time	Fluctuates. Typically better in the morning, worse at night.	Stable
Duration	Most resolve in days to weeks. Average duration is one week.	Worsens steadily over years.

Adapted from Bookbinder and McHugh [7, Table 6, p. 312], with permission

The doctor believes Mrs. W. has a delirium. Her underlying risk factors include advanced age and the brain tumor. The doctor tries to identify specific, treatable triggers. He can prove or disprove some with blood and urine tests. But he can only suspect others: her psychoactive drugs such as the opioids and steroids, her confinement to bed much of the time with resulting dehydration and constipation, and her low sensory stimulation in an unfamiliar, single-occupancy ward room.

The urine and blood tests return normal. The doctor tells the family he can still treat other possible triggers. He reassures the family that most deliriums respond to such multifaceted “shotgun” treatment plans even when no one specific cause is identified. The doctor lowers the opioid doses but makes sure Mrs. W. stays comfortable. He hydrates her with oral and intravenous fluids and increases her time out of bed. He starts a laxative. The doctor also encourages the family to orient her frequently to time and place during their visits, to place family pictures around her room, and to use a lot of therapeutic touch with her.

His treatment plan works. Mrs. W.’s delirium subsides over the next few days. She regains her ability to recognize visitors and to carry on a coherent conversation. Her speech returns to normal. The strange visions and motions stop. The family is relieved.

Cachexia (Loss of Weight) and Anorexia (Loss of Appetite)

A medical school classmate of mine once naively asked a world-renowned oncology professor what ultimately kills cancer patients. The question stumped the professor. Today some oncologists believe cachexia—the severe, progressive weight loss occurring with long-term anorexia (loss of appetite)—does so [25]. But cachexia and anorexia accompany not only fatal cancers (especially those of the internal solid organs such as the lungs, stomach, and ovaries), but also other fatal diseases (such as advanced tuberculosis, AIDS, and heart or liver failure).

Two theories suggest mechanisms for cachexia [26]. One theory says that certain diseases prompt one kind of white blood cells (macrophages) to secrete special proteins (cytokines) that cause widespread inflammation and destruction of body fats and proteins [27]. The other theory says those diseases excite nerves that stimulate secretion of natural steroids or chemical transmitters (specifically, serotonin) in the brain. One or both then stimulate the breakdown of fats and proteins by some still unknown processes. These two theorized mechanisms, if valid, may operate simultaneously.

How does cachexia differ from the other common kind of weight loss, starvation? The distinction is critical for end-of-life care (Table 2.3) [27, 28]. Starvation—prolonged food deprivation in a healthy person—prompts no abnormal inflammatory response and shifts the body into survival mode to conserve fat and protein. Starvation generally maintains blood concentrations of albumin (a major body protein) and cholesterol. Starvation also increases body sensitivity to insulin and uses energy sources efficiently. All these metabolic changes reverse with careful refeeding. Furthermore, body weight during starvation does not predict survival. Voluntary dieting, of course, is the most common example of starvation.

Cachexia, in contrast, occurs in chronically ill people and may prompt the abnormal inflammatory response the one theory suggests. Cachexia persistently and indiscriminately destroys body fats and proteins. Blood concentrations of albumin and cholesterol decrease early and remain low. Cachexia also decreases body

Table 2.3 Distinguishing starvation and cachexia

Characteristic	Starvation	Cachexia
Overall body condition	Healthy	Sick
Pathologically increased inflammation present?	No	Yes
Total body fat and protein	Conserved	Destroyed
Blood albumin	Low only late	Low from early on
Blood cholesterol	May remain normal	Low from early on
Energy use	Efficient	Inefficient
Insulin sensitivity	High	Low
Does refeeding reverse the condition?	Yes	No
Does body weight predict mortality?	No	Yes

Adapted from Thomas [28], with permission

sensitivity to insulin and uses energy sources inefficiently. These metabolic changes do not reverse with refeeding. Furthermore, body weight in cachexia *does* predict survival: Reduction to below 66 % of ideal body weight signals imminent death [26].

The anorexia that accompanies cachexia understandably worries family and caregivers because food has such important emotional and social meanings [26, 29]. Human instincts about food are primitive, deep seated, and powerful. We associate food with love, nurturance, and care. Providing and consuming food during meals provide a supportive, communal experience; emotional comfort; and culturally significant pleasures. Understandably, then, when a dying patient stops eating, loved ones fret. They may mistakenly label the patient as “starving to death” and cannot bear that prospect. Such a fate seems to them uncomfortable and inhumane. Intending to help the patient live, they try to force him or her to eat.

Recent research on starvation and cachexia strongly refutes the common assumption that they are uncomfortable [30]. Healthy people who voluntarily starve themselves in fasts may experience little discomfort after the first day. I myself have fasted a day or two at a time on many occasions and have had little discomfort. I do not feel hunger, in fact, until I resume eating. Studies on dehydration and cachexia in dying cancer patients have shown similar results. One study showed that, as fluid intake increases after dehydration, so does thirst [31]. And another showed that despite requesting and receiving little or no food or fluids 63 % of the terminal study patients never felt hunger, another 34 % felt hunger only briefly, and 62 % never felt thirst. Furthermore, patients’ symptoms with thirst usually required only ice chips by mouth or lubrication on the lips for relief [32]. Cachexia may even cause a mild euphoria in dying. One doctor describes this euphoria in his 85-year-old mother as she died [33]. Suffering from chronic depression, progressive debilitation, and an acute pneumonia, his mother decided to die by not eating. The doctor-son supported her wish. Once his mother stopped eating, she smiled for the first time in months. Friends visited, and she chatted animatedly with them. But she weakened steadily after some days and became ever more sleepy. She finally did not wake up at all and died on the sixth day. She never complained of hunger or thirst.

Such evidence, systematic and anecdotal, argues strongly that limited nutrition and hydration for the dying do *not* have the ill effects many people think [30, 34]. The actual effects may be beneficial: maintaining comfort; preventing nausea, vomiting, and other troublesome problems; and producing some euphoria [9]. Monitoring patients carefully, of course, is important to ensure the good effects outweigh any bad effects. Cachexia may be one way nature eases terminal patients’ transition into death.

With that idea in mind, I have changed my practice in recent years. I no longer aggressively urge dying patients to eat or drink. Instead, I offer them food and water and allow them to take what they want. I support whatever choices they make. With the approval of patients (if conscious), family members, and other attending professionals, I sometimes stop all nutrition and hydration for patients who obviously have only a few hours to live.

The Case

Mrs. W. loses considerable weight during her hospitalization. When she returns to the retirement center, she has little appetite and eats only a few bites off each meal tray. Mr. W. worries that “starvation” will keep her from recovering. He asks the doctor to prescribe “appetite pills” or feeding tubes to increase Mrs. W.’s intake. The doctor responds by explaining how starvation and cachexia differ and why Mrs. W. is probably not suffering from her anorexia. He knows Mrs. W.’s cancer may eventually cause additional weight loss, but he urges patience for the time being. The doctor also tries several simple ways to boost Mrs. W.’s intake. He decreases her opioid doses, asks the dietician to put Mrs. W.’s favorite foods on every menu, and urges Mr. W. to sit with Mrs. W. during meals to provide companionship. The doctor stresses not “force feeding” her. He also asks the nurses to give her ice chips by mouth and lubrication for the lips.

Mrs. W.’s appetite improves over the next few weeks. She remains comfortable despite the lower opioid doses. She especially enjoys the ice cream on her trays and eats better when Mr. W. joins her for meals. Her weight stabilizes but at a lower level than when she was healthy.

Depression

Psychiatric disorders affect many people, including 15 % of the general public and 12–30 % of primary care patients. These disorders are predictably even more common among patients with fatal diseases. One survey of patients with newly diagnosed cancers, for example, found psychiatric diagnoses in 47 %, including adjustment disorders in 32 % and depression in 6 % [35]. The prevalence of depression increased with the duration of the cancers.

These data raise a vexing question for professionals who attend the dying patient: Is a patient’s sadness “pathologic” depression or “normal” grief? [36] Depression and grief, of course, share the characteristic of sadness. Sadness is certainly not surprising in end-of-life situations. The many losses involved—losses of health, physical abilities, roles, relationships, and anticipated futures—invariably create sad feelings. The unwelcome and sometimes unpredictable losses may frighten the patient or erode his or her sense of wholeness, continuity, and control. Depression and grief share other features, too, including sleep problems, anorexia, fatigue, and poor concentration [37].

But the different treatment strategies involved—formal psychotherapy and medications for depression, and brief formal psychotherapy or informal support groups for grief—require clinicians to distinguish the two disorders. A prominent cancer psychiatrist, Susan D. Block, MD, draws useful contrasts between the two disorders (Table 2.4) [38]. The depressed dying patient, unlike the merely grieving one, has constant sadness; feels hopeless, helpless, worthless, or guilt-ridden [37];

Table 2.4 Distinguishing “pathologic” depression from “normal” grief in dying patients

Characteristic	Pathologic depression	Normal grief
Constancy of sad feelings?	Yes	No, episodic only
Feelings of hopelessness, helplessness, worthlessness, or guilt?	Yes	No
Capacity to experience pleasure in the present?	No	Yes
Capacity to imagine a positive future?	No	Yes
Preferred involvement in death	Sometimes active (i.e., suicidal)	Always passive
Suggested management	Formal psychotherapy and/or medications	Sometimes formal psychotherapy or support groups

Adapted from Block [38], with permission

and has lost the capacity to experience pleasure in the present or to imagine a positive future. Furthermore, the depressed patient, but not the merely grieving one, may consider active steps such as suicide to cause his or her death.

Dr. Block urges attending professionals to respond actively and positively to depression, grief, and other psychiatric disorders in dying patients. She decries fatalistic attitudes revealed in such comments as “If I were dying, I’d be depressed, too.” or “The patient’s depression doesn’t matter. The patient will die soon anyways.” Dr. Block believes health professionals should take instead an active, optimistic approach to soothing the psychological and spiritual traumas of dying, even late on. Keeping up frequent contact with the patient and the family, maintaining a reassuring presence, and providing explicit emotional support help. Empathetic listening, though emotionally difficult at times, can ease patients’ despair and provide important professional satisfactions. Attending professionals need only patience and courage to do it. And promising to continue contact with patient and family through the patient’s death can calm any fears of abandonment.

Dr. Block also emphasizes the need for attending professionals to follow up any patient statements about suicide. She suggests responding promptly with questions such as “Would you like to talk about that?” or “What causes you to think about suicide now?” If patients do not answer directly, professionals might probe specifically for the worries that many Oregon patients who have requested physician-assisted suicide express: progressive, serious debility; inability to care for themselves; loss of control over their deaths; and burdensome medical bills and physical care for their families. Chapter 11 elaborates on these worries in its section on physician-assisted suicide.

Finally, Dr. Block encourages attending professionals to nurture the inner strengths and supportive external relationships of *all* their dying patients whether depressed, grieving, or not. She suggests four ways to do so. First, professionals can encourage dying patients to conduct life reviews and to tell especially significant

memories to others. Patients can thereby remember important accomplishments, fill important gaps in their life histories for others, and leave a legacy of values and life lessons. Second, professionals can suggest patients allow family members the privilege of contributing to their care. Taking part in that care at such a meaningful time can strengthen bonds of intimacy perhaps for the last time. Third, professionals can urge dying patients to “get their affairs in order” by making testamentary wills, funeral arrangements, and plans for body disposition. Tying up life’s “loose ends” in this way renews patients’ sense of control over their lives and gives the satisfaction of having prepared their worldly affairs properly for survivors. And fourth, professionals can encourage patients to explore with clergy or others the big transcendent questions patients may have about life and death. Dying patients surely wonder about these questions and can use the impetus of dying to grow through them.

The Case

When healthy, Mrs. W. enjoyed playing sports, entertaining, and keeping house. But the neurologic complications from her brain tumor now make those activities impossible. She wants to go home, but her nursing care necessitates her staying permanently in a spare single room on a skilled nursing ward. She looks sad, never laughs, eats little, sleeps a lot, and mentions fatigue. She never actually complains or expresses suicidal wishes. Her doctor wonders whether she is depressed, quietly grieving her lost prior lifestyle, or simply recovering as the tumor shrinks with treatment. He chooses to monitor her mood closely.

One day Mrs. W. suddenly perks up without specific psychiatric treatment. She eats better, begins watching sports events on television, converses (though sparingly), smiles, and laughs. She enjoys visitors again and invites them to “come back soon.” Both responses indicate a renewed capacity to experience pleasure and to imagine a positive future. The doctor concludes Mrs. W. has not been depressed but has either been grieving her new physical limitations or improving mentally after the tumor treatments. He can make no definite determination. Regardless, Mrs. W.’s upbeat mood continues for some weeks.

Symptoms and Signs at the Very End of Life

Some palliative care experts believe many long-term eventually fatal diseases follow a final common pathway of symptoms and signs [6, 14]. As conceived, that pathway lasts days to months and exhibits many of the symptoms and signs this chapter discusses. Cancers and some major-organ-failure diseases such as end-stage congestive heart failure, COPD, and cirrhosis may take this pathway, but the existing research documents it most strongly for cancers (Table 2.5) [39–41].

Table 2.5 Prevalence of symptoms in end-stage cancer patients in palliative care

Symptoms	1–2 months before death (%)	1 week before death (%)	1–2 days before death (%)
Pain	54	30–99	51
General malaise/debilitation or “unhealthy” feeling	58	82	—*
Dyspnea/shortness of breath	17–70	46–47	22
Anorexia/poor appetite	8	80	—
Nausea/vomiting	12–62	13–71	14
Dry mouth	—	70	87
Death rattle	—	56	56–92

Adapted from Morita [39], with permission

* The dash means no data available.

Different diseases, of course, will present variations on the general pattern depending on particular pathologies, body locations, timelines, and treatments [41]. While not all palliative care experts accept the concept of a final common pathway, I believe it provides a clinically useful framework for anticipating many patients’ end-of-life experiences.

I imagine the pathway divided into three phases—the early decline, the later decline, and the very end—based on the typical progression of symptoms and signs. Readers should realize, however, that patients may not progress neatly from phase to phase in order. Pinpointing even approximate transition times between phases may be difficult [6]. Symptoms and signs wax and wane, patients may simultaneously show characteristics of more than one phase, and different clinicians may interpret patients’ clinical pictures differently. Furthermore, predicting a patient’s remaining life span much before death is often impossible [5, 42]. The phases, therefore, represent a general pattern of decline, not a rigid one.

The Early Decline

Increasing pain and dramatically deteriorating function characterize this phase [5,44]. It may last a few months for cancer but only a few weeks for other prolonged, fatal diseases. Individualized, intensive analgesia based on World Health Organization guidelines usually provides adequate pain relief [14]. Yet the patient’s steadily increasing debilitation requires ever more help with the basic Katz Activities of Daily Living (i.e., bathing, dressing, grooming, eating, toileting, walking, and transferring). Increasingly frequent serious complications from the disease require increasingly frequent hospitalizations. Unfortunately, the American healthcare system, fragmented among specialist caregivers and between in- and outpatient settings, manages this phase poorly [14]. Family members must often take time off work to give the care that the patient needs but that the health system

does not provide or the family cannot pay for. Family members may suffer financially with lost workdays and unreimbursed, out-of-pocket care expenses [10]. Their savings may dwindle [45].

A particularly curious phenomenon, called “taking to bed,” [46] deserves mention here. Apparently healthy, elderly nursing home residents may fall and then complain of vague body pains or show a small weight loss (about 5 lb). They go to bed and quickly lose their appetites, functional independence, and mobility. The mortality can be high. One study reported the outcomes of such elders a year later: Only 36 % had regained the ability to walk, 6 % remained bed bound, and 58 % had died. Somewhat surprisingly, the lack of localizing medical findings predicted death best.

Taking to bed may occur as often as 1.3 times per 100 resident-months in a typical nursing home population. The exact mechanism for the sudden, unexpected decline is unknown. Some experts speculate it is progressive apathy and loss of the will to live stemming from accumulated physical and personal losses over a lifetime. Yet these elders demonstrate few features of classic depression and do not improve with antidepressants.

The Later Decline

Some describe this phase as “agonal,” a word derived from the Greek noun, *agonia*, meaning a struggle or an anguish. Lasting a few days to a few weeks, the later-decline phase encompasses a progressive shutdown of whole organ systems. That process, some people believe, is nature’s or God’s way of helping the body disengage from life.

The patient often suffers multiple increasing symptoms at once, typically 6-10 symptoms altogether including pain, fatigue, confusion, dyspnea, dry mouth, and anorexia (Table 2.6) [2, 4, 6, 39, 40, 47]. Pain that diminished with prior intensive treatment may increase again [10, 42]. Some 40–65 % of cancer patients end up with pain “most of the time” in their last days or weeks [43, 48]. The gynecology, head-and-neck, and prostate cancers produce the most pain late on [40]. This resurgence of pain often prompts last-minute referrals to hospice for expert palliation [13].

Such chronic, unremitting pain demoralizes the terminal patient and distresses the family. For that reason palliative care specialists believe it should be treated as

Table 2.6 Levels of consciousness for terminal cancer patients at various times before death

Level of consciousness	1 week before death (%)	1 day before death (%)	6 h before death (%)
Awake	56	26	8
Drowsy	44	62	42
Comatose	0	12	50

Adapted from Morita et al. [42], with permission

an emergency. Clinicians should use adequate opioid doses, titrating them methodically upward to achieve maximal relief [9]. The ideal achievement is complete relief. Despite the highly reported prevalences of terminal pain, palliative care specialists insist skilled analgesia can relieve pain completely for 98 % of patients [2, 40]. The side effects should be minimal. Any sedation caused by the opioids usually subsides within several days after doses stabilize. And excessive sedation or respiratory depression is rare and reverses immediately with opioid antagonist medications [9]. Still, clinicians should anticipate family concerns about addiction and tolerance and address them with explicit reassurance at the time of treatment. Even if pain relief requires high opioid doses, [42] compassion dictates giving those doses for the short time until the patient's death.

For the rare cases when no other regimen achieves sufficient pain relief, induced sedation to unconsciousness is a last resort. This technique uses medication to cause the patient to sleep through the pain of his or her last days [29, 49, 50]. Such a drastic step, of course, requires careful informed consent beforehand.

Confusion presenting as hallucinations also may occur in this phase [21]. The hallucinations may be visual, auditory, or tactile. They may involve out-of-body experiences or encounters with dead relatives or significant religious or cultural symbols such as Jesus or angels [51]. A man in one of my studies described being "dead" in a prior coma and standing "on the other side of a mountain (from Jesus). I kept asking Him to take me. I was ready (to die)" [52]. Hallucinations may comfort or distress patients but usually distress family members. Clinicians should reassure them about the common occurrence of such hallucinations near death [22].

The Very End

Waning consciousness characterizes this final phase of dying, which may last just hours (Table 2.6). Patients move progressively from being awake (arousable, able to converse and to follow commands), to being drowsy (arousable with difficulty, unable to converse or to follow commands) to being comatose (unarousable) [42]. If the patient has already become drowsy or comatose and survivors have not yet said their final goodbyes, the attending professionals should urge survivors to do so. The patient, though drowsy or unresponsive, may still be able to hear.

The imminently dying patient often shows other physical signs, too (Table 2.7) [42]. The "death rattle" is a noise caused by vibrating patches of saliva or mucus when the weak and drowsy terminal patient can no longer clear those secretions from the mouth or upper airways [9, 37]. Like hallucinations the death rattle often distresses observers at the bedside [53]. Clinicians can minimize the distressing sound by restricting the patient's fluids and giving drying medications [9, 54]. Clinicians should avoid deep suctioning, which appears to irritate patients. Other physical signs of imminent death include lower jaw movements with respiration, a blue color (cyanosis) on the arms and legs, and the absence of a radial artery pulse at the wrist [42]. The dying patient may sometimes show Cheyne–Stokes breathing,

Table 2.7 Duration from onset to death for various clinical signs in terminal cancer patients

Sign	Duration from onset to death (in hours)	
	Mean	Median
“Death rattles” with respiration	57	23
Lower jaw movements with respiration	8	3
Blue color (cyanosis) of the arms and legs	5	1
Absence of a pulse at the outer wrist (i.e., over the radial artery)	3	1

Adapted from Morita et al. [42], with permission

a pattern characterized by frequent respiratory pauses for up to 20–30 s. Urine production decreases, and the patient may become incontinent of urine and feces [9]. The dying patient may also spontaneously grimace, groan, and rub or scratch specific body areas. Medically untrained observers may interpret these actions as signs of distress [55]. Attending clinicians should explain such actions are common in dying [9]. They may indicate restlessness but probably not conscious distress. Nonetheless, clinicians should pledge continuing efforts to keep the patient as comfortable as possible [9]. In this last phase of dying, clinicians’ demonstrated competence, attentiveness, respectfulness, and compassion toward the patient attest best to high-quality end-of-life care.

The Case

As I originally draft this chapter, Mrs. W. is still alive three months after the diagnosis of her brain tumor. Her Karnofsky Performance Score (KPS) varies day-to-day between K40 (moderate disability, needs special assistance) and K30 (severe disability, needs institutional care) (see Table 5.2 for the full KPS scale [56]). Because her KPS falls below K50, Mrs. W. probably does not have long to live, maybe only months [40].

Nonetheless, she does not yet show signs of entering the terminal phases of her illness. Treatment with steroids and radiation has improved her alertness and function. Unlike during her hospitalization she now can sit up for a while each day in a wheelchair. She also follows simple commands. Mr. W. performs daily range-of-motion exercises with her in the room and takes her for wheelchair rides outside. Mrs. W. feeds herself. Her appetite and weight have stabilized. Mrs. W. denies any significant pain on her current opioid doses, but she fatigues easily and sleeps a lot. She wakes up for visitors, enjoys their company, and holds brief conversations with them. The W.s’ children visit frequently to support both their parents.

Mr. W. provides constant companionship for Mrs. W. except when he returns to their independent living apartment to sleep or do household chores. He believes Mrs. W. will make a miraculous recovery. The primary doctor warns him gently not

to get his hopes up: Mrs. W.'s improvement in function and symptoms is only temporary. The doctor urges Mr. W. to savor his interactions with her now. The primary doctor continues to see Mrs. W. several times weekly, monitoring her for signs that she is deteriorating again and becoming terminal.

Epilogue to Mrs. W's Case

Mrs. W.'s improvement holds for about 8 weeks. She then deteriorates again as she enters the early-decline phase of her illness. She can no longer sit in the wheelchair and remains all day in bed. She complains of constant, severe headaches. The doctor recommends hospice care for pain relief, and Mr. W. agrees. Hospice's titration of the opioid doses improves the headaches somewhat but never completely eliminates them. More symptoms appear as Mrs. W. enters the later-decline phase. She loses her appetite, becomes lethargic, and complains of shortness of breath. Her circumstances confuse her. She no longer understands why she is not living in the W.s' apartment. She sees visual hallucinations of family members who died long ago. And she criticizes Mr. W. uncharacteristically often.

Mrs. W. finally becomes drowsy and loses consciousness completely as she enters the last phase of her illness, "the very end." She moans and grimaces periodically. Family members at the bedside hear death rattles and notice a blue color creeping up her legs. The doctor assures the family that despite these understandably distressing observations she is not consciously suffering. Mrs. W. dies peacefully only hours later with Mr. W. and a daughter at the bedside.

Which Signs Define the Time of Death?

The last important signs in dying indicate the time the patient dies. That time has significant implications for survivors because it determines in part their memories of the death, their visitation and funeral plans, their entitlements (such as Social Security and perhaps life insurance benefits), and their possible liability for healthcare charges. That time also has significant implications for attending professionals because it affects their immediate duties and workloads, and for other patients because it may affect their access to healthcare resources (possibly including transplantable organs).

Official medical, legal, and financial procedures take that time to be whatever the attending doctor determines. He or she typically uses the clinical examination to make the determination by cessation of either effective cardiorespiratory function or total brain function. The absence of spontaneous chest wall motions, of prominent pulses (such as at the carotid arteries in the neck), and of heart and respiratory sounds through a stethoscope imply cessation of effective cardiorespiratory function. The absence of adequate respirations, of spontaneous responses or movements

(such as to painful stimuli), and of brainstem reflexes imply cessation of total brain function. Hypothermia (excessively cold body temperature) and deep sedation from drugs—two conditions that can mimic cessation of total brain function—must be absent. A standardized protocol, called “the apnea test,” proves inadequate respirations. All required deficits for cessation of total brain function must persist for six hours to three days, depending on the cause of brain injury. Tests for brain circulation or brain waves are never required, merely confirmatory, for determining death.

Despite these well-established medical and legal procedures, disagreements over the time of death can arise because the medically untrained may determine that time for themselves according to various other physiologic signs. Colleagues and I once asked an ethnically diverse group of elders how they recognize a person’s time of death [52]. The elders mentioned several different signs; no one sign predominated. Some elders mentioned the traditional signs of cardiorespiratory death: cessation of heartbeat and visible respirations. But some mentioned other signs such as turning cool; being unable to recognize others, speak, or move; making gurgling or gasping sounds; and turning the eyes back into the head. One difference occurred by ethnic group: Some Mexican Americans and Euro-Americans, but no African Americans, recognized time of death by cooling of the body [52].

Such differences may create a difficult problem at the end of life: A moribund patient may be simultaneously alive to some people and dead to others. For example, an observer who recognizes time of death by cooling of the body may consider the patient alive at the same time another observer who recognizes time of death by cessation of respirations considers the patient dead. Such differences may complicate postmortem procedures including organ harvesting, autopsies, and transfers to the morgue or funeral home. I think that, whenever a patient meets standard medical criteria for death, clinicians should ask family members, “Do you agree or not that the body is already dead?” Only when (within reason) everyone agrees the body is dead, should clinicians stop all treatments and initiate post-mortem procedures.

Summary Points

1. Pain, dyspnea (shortness of breath), fatigue, confusion, cachexia (weight loss), and anorexia (loss of appetite) occur in many prolonged, fatal illnesses.
2. Patients often do not report their symptoms, especially pain. Clinicians must ask about them, repeatedly if necessary.
3. Nearly all the pains of fatal illnesses respond well to treatment until perhaps very late. Other common symptoms do not respond consistently so well.
4. The general public may rely on physiologic signs other than cessation of heartbeat and breathing to determine for themselves when a patient dies.

To Learn More ...

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