CHAPTER 19

Medical Physiology

Integration Using Clinical Cases

Rushing a patient from a medevac helicopter to the emergency department. ©Comstock Images/Getty Images

Physiology is one of the pillars of the health-related professions, including nursing, occupational health, physical therapy, dentistry, and medicine. In fact, the term *pathophysiology*—the changes in function associated with disease—highlights the intertwining of physiology and medicine. You need a thorough understanding of the general principles of physiology to properly diagnose and treat diseases and disorders. We are aware that many users of this textbook may not be planning a career in the health professions. However, teachers of physiology can attest to the use of clinical examples as an effective approach to highlight and reinforce the understanding of the functions and interactions of the organ systems of the body.

This chapter uses clinical cases to allow the continued exploration of the material you learned from this book and, at the same time, review some of the general principles of physiology that were first introduced in Chapter 1. You have been introduced to the educational power of clinical cases at the end of each chapter of this book. This chapter continues this theme with more extensive cases. More importantly, this chapter illustrates the concept of *integrative physiology*. In real life, complicated clinical cases involve multiple organ systems. The art of medicine is the ability of clinicians to recall these basic principles and integrate them into a logical sequence in the

evaluation of the patient. Each case in this chapter has a section called "Physiological Integration" to highlight this fact. As you read these sections, you should consider the relationships among disease, integrative physiology, and homeostasis, the last of which has been a theme throughout this book.

Some of the conditions and physiological interactions described in this chapter are not explicitly described in the book and may be new to you. Interspersed at key points in the chapter are several places where you will be asked to "Reflect and Review." In some cases, specific answers to these questions are not provided in the case itself. We encourage you to answer these questions as the case unfolds by, if necessary, referring back to the appropriate section of the book. Furthermore, we have annotated each case with figure and table numbers to facilitate review of material covered in previous chapters. In some cases, the figures and tables from previous chapters do not specifically answer the question but provide an opportunity to review the control system in question to allow the student to propose potential answers.

We hope that the cases in this chapter will motivate you to synthesize and integrate information from throughout the book and perhaps even go beyond what you have learned. In fact, you may enjoy consulting other sources to answer some of the more challenging questions and to hone your self-directed learning skills. ■

SECTION A

Case Study of a Woman with Palpitations and Heat Intolerance

19.1 Case Presentation

A 33-year-old woman visits her family physician with complaints of a 12-month history of increasing nervousness, irritability, and ***palpitations*** (a noticeable increase in the force of her heartbeat). Furthermore, she feels very warm in a room when everyone else feels comfortable. Her skin is unusually warm and moist to the touch. She has lost 30 pounds of body weight over this period despite having a voracious appetite and increased food intake.

Reflect and Review #1

- Describe the general principles of the control of body temperature (see Figures 1.5, 1.9, 16.18 and 16.19). What may have caused her skin to feel warm and moist?

Two years ago, she was jogging about 20 miles per week. However, she had not done any running for the past year because she "didn't feel up to it" and complained of general muscle weakness. She said she often felt irritable and had mood swings. Her menstrual periods have been less frequent over the past year. Her previous medical history was normal for a person her age. She states that she has double vision when looking to the side but does not have any loss of vision when using only one eye or the other.

Reflect and Review #2

- Which hypothalamic, anterior pituitary gland, and ovarian hormones control the menstrual cycle? (See Figure 17.22 and Table 17.7.)
- What anterior pituitary gland disorder can cause a decrease in menstrual cycle frequency and loss of vision? (See Figures 17.39 and 17.40.)

19.2 Physical Examination

The patient is a 5' 7" (170 cm), 110-pound (50 kg) woman. Her systolic/diastolic blood pressure is 140/60 mmHg (normal for a young, healthy woman is about 110/70 mmHg). Her resting pulse rate is 100 beats per minute. Before she became ill, her resting heart rate was about 60–70 beats per minute. Her respiratory rate is 17 breaths per minute (normal for her was approximately 12–14 breaths per minute). Her skin is warm and moist. Her right eye is bulging out (***proptosis*** or ***exophthalmos***) (**Figure 19.1a**). Finally, when she is asked to gaze to the far right, her right eye does not move as far as does her left eye and she says she has double vision (***diplopia***).

Reflect and Review #3

- Briefly describe the control of systemic blood pressure, heart rate, and respiratory rate (see Figures 12.26, 12.54, and 13.32). What might be causing her hypertension, ***tachycardia*** (increased heart rate), and ***tachypnea*** (increased respiratory rate)?
- Describe the muscles that control eye movement (see Figure 7.35).

Upon further examination, the physician notes an enlargement of a structure in the front, lower part of her neck (**Figure 19.1b**). It is smooth (no bumps or nodules felt) and painless. When the patient swallows, this enlarged structure moves up and down. When a stethoscope is placed over this structure, the physician can hear a swishing sound (called a ***bruit*** [BREW-ee]) with each heartbeat.

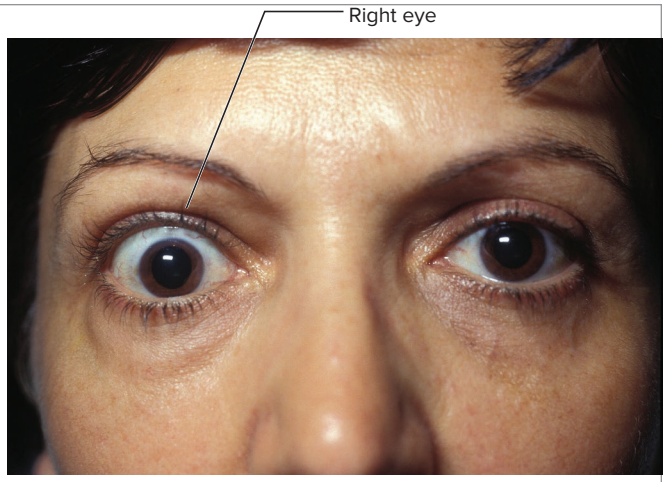
Reflect and Review #4

- What structure might be responsible for the swelling in the patient's lower neck? (See Figures 11.21a and 15.17.) What are the major functions of this structure?

Her patellar tendon (knee-jerk) reflexes are hyperactive. When she holds her hands out straight, she exhibits fine tremors (shaking).

Reflect and Review #5

- What are the neural pathways involved in the knee-jerk reflex? (See Figure 10.6.) Could the enlarged structure in her neck account for the hyperactive reflexes observed?



(a)

(b)

Figure 19.1 (a) Proptosis (right eye only) and (b) enlarged structure (circled) in the front of the lower neck. (a) ©ISM/BARRAQUER/Medical Images (b) ©Chris Pancewicz/Alamy Stock Photo

19.3 Laboratory Tests

The family physician considers the history and physical exam and decides to order some blood tests. The results are shown in Table 19.1.

Reflect and Review #6

- Describe the feedback control loops of the hormones with abnormal values (see Figure 11.23 and Figure 17.24). Which, if any, of these hormones might account for the symptoms in this patient? What might have contributed to the woman's feelings of excessive warmth?
- Why is the serum glucose sample obtained in the fasted state? (See Figure 16.9.) Does the serum glucose concentration rule out diabetes mellitus as a factor in this patient's illness?

TABLE 19.1 Laboratory Results for Patient

Blood Measurements*	Result	Normal Range
Sodium	136 mmol/L	135–146 mmol/L
Potassium	5.0 mmol/L	3.5–5.0 mmol/L
Chloride	102 mmol/L	97–110 mmol/L
pH	7.39	7.38–7.45
Calcium (total)	9.6 mg/dL	9.0–10.5 mg/dL
Parathyroid hormone	15 pg/mL	10–75 pg/mL
Glucose (fasting)	80 mg/dL	70–110 mg/dL
Prolactin	10.4 ng/mL	1.4–24.2 ng/mL
Estrogen (midcycle)	100 pg/mL	150–750 pg/mL
Total T_4†	20 µg/dL	5–11 µg/dL
Free T_4	2.8 ng/dL	0.8–1.6 ng/dL
Thyroid-stimulating hormone (TSH)	0.01 µU/mL	0.3–4.0 µU/mL

*In actuality, these measurements are performed in serum or plasma derived from blood.
†T_4, thyroxine.

19.4 Diagnosis

The most likely explanation for the findings is an increase in thyroid hormone in the patient's blood. When increased thyroid hormone causes significant symptoms, it is part of a condition called ***hyperthyroidism*** or ***thyrotoxicosis.*** The enlarged organ in the neck is likely the thyroid gland, although an enlarged thyroid gland (***goiter***) can also be found in hypothyroidism (see Figure 11.24 for an extreme example). In order to interpret the thyroid function tests shown in Table 19.1, first review the control of thyroid hormone synthesis and release (see Figures 11.22 and 11.23).

There are two circulating thyroid hormones—thyroxine (T_4) and triiodothyronine (T_3). Whereas T_4 is the main secretory product of the thyroid gland, T_3 is actually more potent and is actively produced in target tissues by the removal of one iodine molecule from T_4. Nonetheless, for practical reasons, T_4 is the form of thyroid hormone that is routinely measured in clinical situations. The release of T_4 by the thyroid gland is normally controlled by thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. Binding of TSH to its G-protein-coupled plasma membrane receptor on the follicular cells of the thyroid gland activates adenylyl cyclase and cAMP formation, which then stimulates cAMP-dependent protein kinase (see Figure 5.6). Like most anterior pituitary gland trophic hormones, an increase in TSH not only stimulates the activity of the thyroid gland but also, when sustained, stimulates its growth. As with most other pituitary gland–target hormone systems, the target-gland hormone (T_4) and its more potent metabolite (T_3) inhibit the release of the anterior pituitary gland hormone controlling it (in this case, TSH) via negative feedback (see Figure 11.23).

There are several reasons why the thyroid gland in this patient could be producing too much thyroid hormone, leading to thyrotoxicosis. TSH is not the cause since Table 19.1 shows that

this trophic hormone is actually suppressed. The most common condition to focus on here is called ***Graves' disease.*** In this condition, the thyroid gland is stimulated by antibodies that activate the receptor for TSH on the follicular cell of the thyroid (**Figure 19.2**). Therefore, these TSH receptor-stimulating antibodies mimic the action of TSH but are distinct from authentic TSH from the anterior pituitary gland. These ***thyroid-stimulating immunoglobulins*** (***TSIs***) are characteristic of an autoimmune disorder in which the patient makes antibodies that bind to one or more proteins expressed in his or her own tissues (see Table 18.10). The exact cause of an increase in TSIs in individual patients is usually not known. TSIs are produced by B lymphocytes that, in addition to residing in lymph nodes, can actually infiltrate the thyroid gland in Graves' disease. In Chapter 9 (Section 9.7), you learned about a disease called myasthenia gravis, in which autoantibodies bind to and destroy the nicotinic acetylcholine receptor in the neuromuscular junction. This is typical of antibody–antigen reactions, in which antigens are removed from the body (see Chapter 18). In Graves' disease, however, the autoantibodies are highly unusual in that they not only recognize and bind to the TSH receptor on thyroid follicular cells but this binding *stimulates* rather than destroys the receptor. Therefore, TSIs stimulate the thyroid gland to synthesize and secrete excess T_4 and T_3 independently of TSH. The increase in T_4 and T_3 would be predicted to suppress the secretion of TSH from the anterior pituitary gland by negative feedback, which is consistent with the low serum TSH concentration measured in the patient's blood. The increased serum T_4 and T_3 probably also suppressed the synthesis and release of thyrotropin-releasing hormone (TRH) from the hypothalamus via negative feedback. (Serum TRH concentrations are not determined in such situations because TRH is secreted directly into the hypothalamo–pituitary portal circulation. The actual amount of TRH from the hypothalamus that reaches the systemic circulation is too small for its measurement in a blood sample from a peripheral vein to be useful.)

The total and free (not bound to plasma proteins) T_4 concentrations in the blood of this patient are increased, confirming the diagnosis of hyperthyroidism. Measurement of free T_4 is helpful because most of the circulating thyroid hormone in the blood is bound to plasma proteins, so measuring the serum T_4 that is not bound to plasma proteins proves that there is an increase in the amount of biologically active T_4. The suppressed TSH confirms that the T_4 is increased independently of stimulation from the anterior pituitary gland. This suppression of serum TSH, as in our patient, is one of the hallmarks of Graves' disease. The measurement of serum TSH concentration is used as a screening test for many disorders of the thyroid gland. Although TSI concentrations can be measured in the serum in some patients, it is often not necessary because the diagnosis of Graves' disease is the most likely, considering that it causes the majority of cases of hyperthyroidism. It was not necessary to measure TSIs in our patient.

Although Graves' disease was by far the most likely diagnosis, the physician ordered some additional tests to rule out other

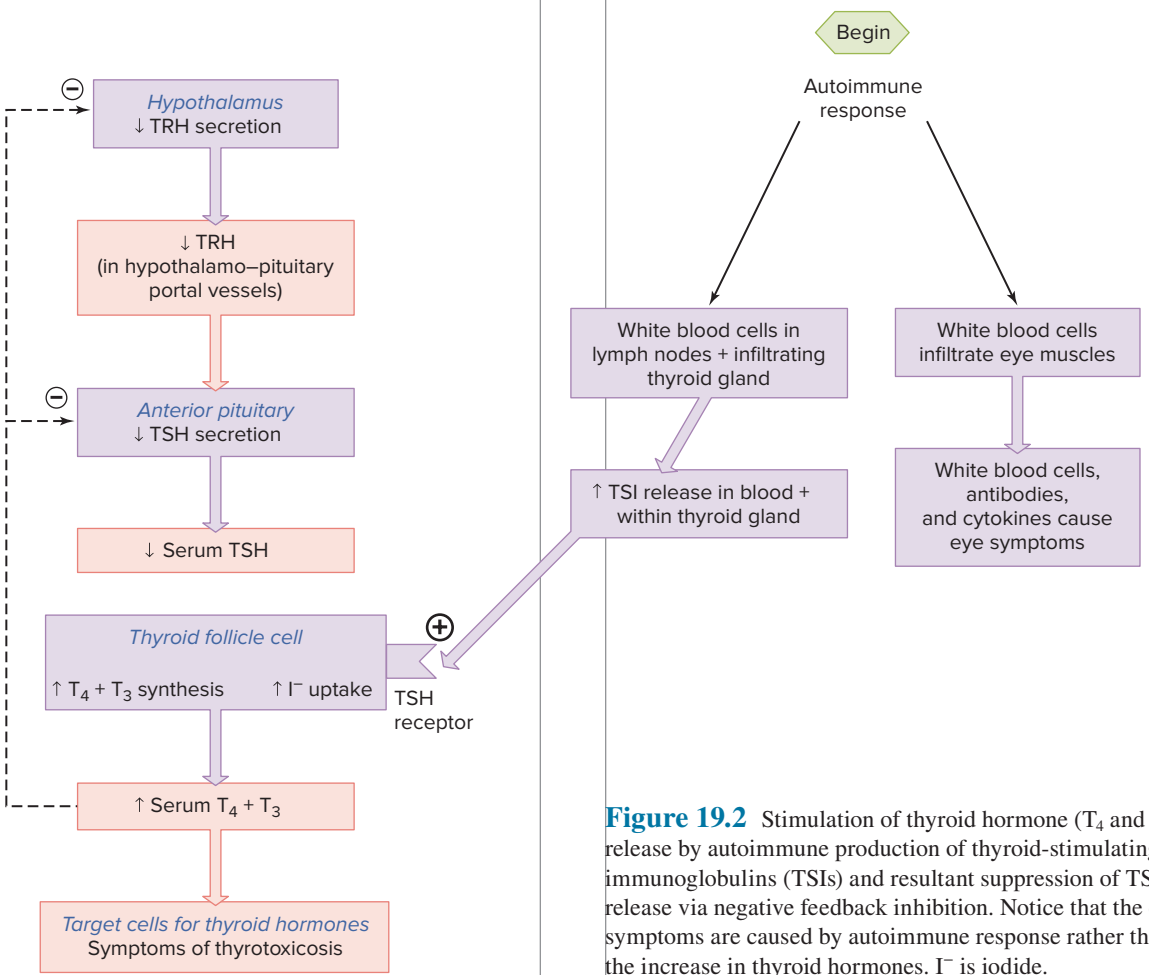


Figure 19.2 Stimulation of thyroid hormone (T_4 and T_3) release by autoimmune production of thyroid-stimulating immunoglobulins (TSIs) and resultant suppression of TSH release via negative feedback inhibition. Notice that the eye symptoms are caused by autoimmune response rather than by the increase in thyroid hormones. I^- is iodide.

possible causes of the symptoms. Serum electrolytes were measured because they are important in the generation and maintenance of membrane potentials (Figures 6.12 and 6.13) and their abnormalities can lead to weakness and palpitations. Serum calcium and parathyroid hormone were measured because weakness is a common finding in primary hyperparathyroidism (Chapter 11, Section F). A normal fasting serum glucose and pH indicated that diabetes mellitus was very unlikely to be the cause of the patient's weakness and fatigue. A normal prolactin concentration indicated that she does not have hyperprolactinemia, which can cause abnormalities in the menstrual cycle and visual disturbances (see Figures 17.39 and 17.40.

19.5 Physiological Integration

Thyroid diseases are common. Up to 10% of women will develop hyperthyroidism or hypothyroidism by the age of 60 to 65. Thyroid hormone has a wide range of effects throughout the body; therefore, an understanding of all the organ systems is extremely useful in understanding the symptoms of thyroid disease.

One of the main effects of thyroid hormone is calorigenic—it increases the basal metabolic rate (BMR). This increase in metabolic rate is caused by activation of intracellular thyroid hormone receptors (see Figure 5.4) that are expressed in cells throughout the body. This leads to increased expression of Na^+/K^+-ATPases as well as the synthesis of other cellular proteins involved in oxidative phosphorylation, oxygen consumption, and metabolic rate in many tissues (see Figures 3.45–3.47). The resultant increase in heat production by our patient explains the warmness and moistness of her skin and her heat intolerance. It also explains why, despite eating more, she is losing weight because she is burning more fuel than she is ingesting.

The nervousness, irritability, and emotional swings are likely due to effects of thyroid hormone on the central nervous system, although the exact cellular mechanism of this is not well understood. The symptoms also appear to be due to an increased sensitivity within the central nervous system to circulating catecholamines. The muscle weakness is probably due to a thyroid hormone–induced increase in muscle protein turnover, local metabolic changes, and loss of muscle mass. Despite this, there appears to be an increase in the speed of muscle contraction and relaxation, contributing to the hyperactive reflexes observed in our patient. The normal fasting blood glucose rules out diabetes mellitus as a cause of her muscle weakness.

Her thyroid gland is enlarged because TSIs are binding to and activating the TSH receptors on the thyroid follicular cells, thereby mimicking the actions of TSH to stimulate the thyroid gland to grow. The enlarged thyroid with increased metabolic activity explains why a bruit was heard over the thyroid gland. The thyroid gland has a high blood flow per gram of tissue even in healthy individuals. The increase in thyroid function in Graves' disease leads to a large increase in blood flow to the thyroid—so much so that it is audible with a stethoscope during systole in some patients.

Her increased systolic blood pressure and heart rate can be explained in several ways. First, there are direct effects of thyroid hormones on the heart, such as an increase in transcription of the myosin genes. Second, as described in Section 11.11 of Chapter 11, thyroid hormone has permissive effects to potentiate the effects of catecholamines on the cardiovascular system. Finally, the small decrease in diastolic pressure may result from arteriolar vasodilation and decreased total peripheral resistance in response to increased tissue temperature and metabolite concentrations (see Figure 12.54).

Increased thyroid hormone can directly inhibit the release of the pituitary gland gonadotropins FSH and LH, particularly in the middle of the menstrual cycle when the LH and FSH surge that stimulates ovulation occurs. This can lead to a decrease in release of gonadal steroids from the ovaries, an irregular pattern or complete loss of menstrual periods, and a lack of ovulation. This also explains the lower serum estrogen concentrations at the middle of the menstrual cycle in our patient.

The eye findings are among the most striking in many patients with Graves' disease (see Figure 19.1). The proptosis (bulging out of the eye) is due to the autoimmune component of the disease, rather than to a direct effect of thyroid hormone. Supporting this idea is that proptosis can occur before the development of hyperthyroidism, and excessive thyroid hormone therapy for hypothyroidism does not cause proptosis. The proptosis is caused by infiltration of white blood cells into the extraocular muscles behind the eye. These cells release chemicals that result in inflammation (see Figure 19.1 and Figure 7.35), causing the muscles to swell and forcing the eyeball forward. Our patient's double vision when looking to the side is primarily explained by the fact that only her right eye was affected. Sometimes, particular muscles of the eye are more affected than others, which can explain double vision even when both eyes are affected and the patient looks to the side.

19.6 Therapy

The most important component of treatment is to decrease the thyroid hormone concentrations. There are three general approaches to accomplish this. Removal of the thyroid gland is the most obvious but currently the least frequently used approach. Removing a large, hyperactive thyroid gland has surgical risk and is usually not performed unless absolutely necessary. The drugs ***methimazole*** and ***propylthiouracil*** can be used because they block the synthesis of thyroid hormone by reducing organification—that is, the oxidation and subsequent binding of iodide to tyrosine residues in the colloidal thyroglobulin molecule (see Figure 11.22). Patients can stay on low doses of methimazole for extended periods to control their thyrotoxicosis. Because of potential side effects, some patients and physicians prefer a permanent cure.

A nonsurgical treatment that usually leads to a permanent cure involves the partial destruction of the thyroid gland using a high dose of orally administered ***radioactive iodine.*** Remember that iodide (the active anion of iodine) is a critical component of thyroid hormone and the thyroid gland has a mechanism to trap iodide by secondary active transport from the blood into the follicular cell (see Figure 11.22). When sufficient tissue concentrations of radioactive iodide are trapped in the thyroid gland, the local emission of radioactive decay destroys most of the thyroid gland over time. However, the procedure does not work equally well in all people. In fact, sometimes patients have so much of their thyroid gland destroyed that they develop permanent hypothyroidism. Such people must take T_4 pills for the rest of their lives to maintain thyroid hormones in the normal range.

In the short term, while waiting for the treatments to take effect, patients benefit from treatment with beta-adrenergic receptor blockers (see Table 12.11) to reduce the effects of increased

sensitivity to circulating catecholamines. This often helps control the palpitations and increased heart rate, as well as some of the other symptoms such as nervousness and tremors. Because proptosis is not caused by the increase in T_4, its treatment can be accomplished, if necessary, with anti-inflammatory drugs, such as glucocorticoids, or surgery or radiation therapy of the eye muscles.

With adequate treatment, patients generally get better over time with most, if not all, of the symptoms resolving. Our patient was initially treated with beta-adrenergic receptor blockers, glucocorticoids, and methimazole and her symptoms slowly resolved over several months. She remains on low doses of methimazole, which has normalized her T_4 levels and kept her symptoms under control. The anti-inflammatory effects of the glucocorticoid therapy reduced the proptosis in her right eye, although the remaining proptosis may require surgery in the future.

SECTION A SUMMARY

Case Presentation

I. Her symptoms are nervousness, palpitations, feelings of warmth in a cool room, and significant weight loss despite eating a lot.

Physical Examination

I. Her systolic blood pressure is increased, and her diastolic pressure is decreased. Her resting heart rate is 100 beats per minute.
II. She has an enlarged thyroid gland (goiter) and her right eye bulges out (proptosis).
III. She has hyperactive knee-jerk reflexes and her hands are shaking.

Laboratory Tests

I. She has increased thyroid hormone and decreased thyroid-stimulating hormone in the blood.

Diagnosis

I. She is diagnosed with hyperthyroidism (excess thyroid hormone activity).
II. Hyperthyroidism is usually caused by Graves' disease—an autoimmune disease.

Physiological Integration

I. Autoimmune production of thyroid-stimulating immunoglobulins (TSIs) stimulates the thyroid gland to produce too much thyroid hormone and to enlarge. The excess thyroid hormone suppresses the release of thyroid-stimulating hormone from the anterior pituitary gland.
II. Infiltration of the muscles controlling eye movement by white blood cells leads to inflammation and proptosis.
III. Increased thyroid hormone in the blood leads to an increase in sensitivity to catecholamines, resulting in an increase in systolic blood pressure and heart rate.
IV. Increased thyroid hormone leads to increased metabolic rate in a variety of tissues. This causes heat intolerance, hyperactive reflexes, and a small decrease in diastolic pressure.

Therapy

I. Three possible therapies include radioactive iodine administration to destroy much of the thyroid gland, drugs that block the synthesis of thyroid hormone, or surgical removal of the thyroid gland.

SECTION A CLINICAL TERMS

19.1 Case Presentation

palpitations

19.2 Physical Examination

bruit
diplopia
exophthalmos
proptosis
tachycardia
tachypnea

19.4 Diagnosis

goiter
Graves' disease
hyperthyroidism
thyroid-stimulating immunoglobulins (TSIs)
thyrotoxicosis

19.6 Therapy

methimazole
propylthiouracil
radioactive iodine

SECTION B

Case Study of a Man with Chest Pain After a Long Airplane Flight

19.7 Case Presentation

A 50-year-old, obese man has just returned from vacationing in Hawaii. He took an 8 h flight during which he sat by the window and did not leave his seat. In the taxi on the way home from the airport, he starts to feel chest pain and has shortness of breath, increased respiratory rate, and nausea. Thinking he is having a heart attack (***myocardial infarction***), he asks the taxi driver to take him to the nearest hospital.

19.8 Physical Examination

An examination of the patient at the hospital emergency department indicates that he has dull, aching chest pain and is clearly upset and anxious, short of breath, and overweight. He is 68 in (173 cm) tall and weighs 300 pounds (136 kg). The emergency department nurse practitioner performs an electrocardiogram (ECG), primarily to rule out a heart attack. The ECG shows an increased heart rate (105 beats per min) but does not show changes consistent with a heart attack or with left heart failure.

Reflect and Review #7

- What are the main factors that control heart rate? (See Figure 12.26.) Might any of them explain the increased heart rate in our patient?
- How might damage to the heart be detected in an ECG? (See Figures 12.18 and 12.19 for a general discussion of ECG.)

A chest x-ray is performed in an attempt to determine the cause of the patient's chest pain and shortness of breath. The results indicate no abnormalities such as pneumonia or collapse of lung lobes (***atelectasis***).

19.9 Laboratory Tests

Based on the patient's history and symptoms, the physician obtains a sample of the patient's arterial blood in order to measure the levels of oxygen, carbon dioxide, bicarbonate, hydrogen ions (pH), and hemoglobin. The findings are shown in **Table 19.2**.

Reflect and Review #8

- What is the cause of the change in arterial pH in our patient? (See Table 14.8.)

The results of these tests reveal that the patient has hypoxic hypoxia (hypoxemia), as indicated by the low arterial P_{O_2}, and is hyperventilating, leading to respiratory alkalosis (see Figure 13.22), as indicated by the low arterial P_{CO_2} and bicarbonate, and high arterial pH. The normal hemoglobin concentration indicates that the patient is not anemic.

Reflect and Review #9

- What are some possible causes of hypoxemia? (See Table 13.11.)
- What are the two main types of alkalosis? (See Table 14.8.)
- How do we know the alkalosis in our patient was acute (of recent, short-term origin)? (See Table 14.8.)

The patient is given 100% oxygen to breathe through a mask over his mouth and nose. This results in an increase in arterial P_{O_2} to only 205 mmHg, a small increase in arterial P_{CO_2} to 32 mmHg, and a small decrease in arterial pH to 7.48. The normal response to breathing 100% oxygen in a healthy person is an increase in arterial P_{O_2} to greater than 600 mmHg, with no change in arterial P_{CO_2} or pH.

Reflect and Review #10

- Explain why increasing arterial P_{O_2} with supplemental oxygen caused the observed changes in arterial P_{CO_2} and pH (see Figures 13.35 and 13.40).

19.10 Diagnosis

Because a heart attack has been ruled out and based on the history and physical findings, the physician suspects that the patient has at least one ***pulmonary embolism.*** An ***embolism*** (plural, *emboli*) is a blockage of blood flow through a blood vessel produced by an obstruction. It is often caused by a blood clot—or ***thrombus***—in the pulmonary arteries/arterioles. These clots usually arise from larger clots in leg veins.

TABLE 19.2 Blood Gas, Bicarbonate, and Hemoglobin Results While Patient Breathes Room Air

Blood Measurement	Result	Normal Range
Arterial P_{O_2}	60 mmHg	80–100 mmHg
Arterial P_{CO_2}	30 mmHg	35–45 mmHg
Arterial pH	7.50	7.38–7.45
Bicarbonate	22 mmol/L	23–27 mmol/L
Hemoglobin	15 g/dL	12–16 g/dL

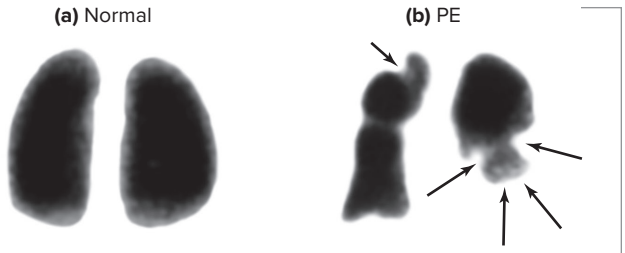


Figure 19.3 Pulmonary embolism (PE) from a deep vein thrombosis shown on a lung perfusion scan (posterior) with radiolabeled albumin. This procedure visualizes the blood flow distribution through the pulmonary vascular tree. (a) A normal perfusion scan. (b) Multiple perfusion defects are shown (arrows). From Lawrence M. Tierney, Current Medical Diagnosis and Treatment, 2006

To confirm his diagnosis, the physician orders a ***ventilation–perfusion scan,*** which is actually the combination of two different scans. In the ventilation scan, the patient inhales a small amount of radioactive gas. Special thoracic imaging devices are then used to detect the inhaled radioactive molecules and visualize which parts of the lung are adequately ventilated. Poorly ventilated areas of the lung will contain less radioactive gas. In the perfusion scan, a small amount of albumin, a naturally occurring plasma protein, tagged with a radioactive tracer, is injected into a vein. As the radioactive protein enters the pulmonary circulation, its distribution throughout the lung can be imaged. This procedure allows the physician to determine if parts of the lungs are receiving less than their normal share of blood flow because poorly perfused areas of the lungs will contain less radioactive albumin. The ventilation scan was normal, but the perfusion scan showed significant abnormalities. **Figure 19.3** shows the results of the perfusion scan, demonstrating dramatic decreases in perfusion in specific regions of the lung. These results supported the physician's diagnosis of several pulmonary emboli.

A variety of materials can occlude pulmonary arterial blood vessels, including air, fat, foreign bodies, parasite eggs, and tumor cells. The most common embolus is a thrombus that can theoretically come from any large vein but usually comes from the deep veins of the muscles in the calves (***deep vein thrombosis***). The fact that our patient sat on an 8 h flight without moving around greatly increased the chances for the formation of a deep vein thrombosis in the leg. This is because without skeletal muscle contractions, blood is not adequately pushed back from the legs toward the heart (see Figure 12.48). This allows blood to pool in the leg veins, which increases the chance for the formation of clots through a variety of mechanisms including endothelial activation leading to a release of procoagulant molecules. After the abnormal lung perfusion scan, an ultrasound examination of the legs was performed to confirm whether clots were present in the leg veins. The results showed a large clot in the femoral and popliteal veins in the right leg.

Pulmonary embolism is a common and potentially fatal result of deep vein thrombosis. In fact, pulmonary embolism and deep vein thrombosis can be considered part of one syndrome. It may cause as many as 200,000 deaths each year in the United States. Most cases are not diagnosed until after death (on postmortem examination) either because the symptoms are initially mild or because the syndrome is misdiagnosed. Most small clots that form in small veins in the calves of the lower legs remain fixed in place, associated with the lining of the vein, and do not cause symptoms. However, if a clot enlarges and migrates into larger veins such as the femoral and popliteal veins, as in our patient, large pieces of it can break off and

migrate up the vena cava, through the right atrium and right ventricle, and into the pulmonary arterial circulation, where the pieces can become lodged (see Figure 12.5 for an overview of the circulatory system). When this happens, blood flow is decreased or cut off to one or more large segments of the lung.

Reflect and Review #11

- Why will regional decreases in pulmonary blood flow lead to hypoxemia? (See Figure 13.24 and Table 13.11.)

Fortunately, these clots are too large to pass through the pulmonary circulation into the systemic circulation. When clots do form in the systemic circulation, they can occlude arteries and arterioles, thereby depriving vital organs of oxygen and nutrients and preventing the removal of toxic waste products. If this occurs in the cerebral arterial circulation, it can lead to a stroke. If this occurs in the coronary arteries, it can lead to a heart attack (see Section 12.22 of Chapter 12).

19.11 Physiological Integration

The presence of hypoxemia and hyperventilation (the cause of the acute respiratory alkalosis), the history, and symptoms suggest that the patient is suffering from an acute decrease in pulmonary blood flow to some parts of the lung. Remember that hyperventilation is defined as a decrease in the ratio of CO_2 production to alveolar ventilation (see Figure 13.22). That is, if whole-body CO_2 production stays the same and alveolar ventilation increases as in our patient, arterial P_{CO_2} will decrease resulting in an increase in arterial pH. The acute decrease in pulmonary blood flow in some regions of the lung results in a clinically significant ventilation–perfusion inequality (see Table 13.11). The hyperventilation is only partly due to the mild hypoxemia, because the arterial P_{O_2} of 60 mmHg in our patient, although low, is just at the threshold oxygen level that stimulates the peripheral chemoreceptors (see Figures 13.33 and 13.34). Other causes of hyperventilation may be anxiety and pain, which may also explain the increased heart rate observed in the patient at the emergency department.

The ventilation–perfusion inequality means that the patient is ventilating areas of the lung to which blood is not flowing, leading to increased alveolar dead space (see Figure 13.19). The blood diverted to other nearby lung regions leads to a local decrease in the ratio of ventilation to perfusion (physiological shunt). This results in more deoxygenated blood mixing with oxygenated blood from unaffected areas of the lung thereby decreasing the total oxygen content of the blood in the pulmonary vein. Remember that disruption of the delicate balance between regional ventilation and perfusion throughout the lung results in a failure to fully oxygenate the blood leaving the lung. In addition, hypoxia within the pulmonary circulation leads to vasoconstriction of the arterioles in the lungs and an increase in pulmonary artery pressure (see Figure 13.24).

We know that the hyperventilation was acute and not a long-standing problem because the arterial pH was still alkaline due to the decrease in P_{CO_2}. This indicates that the kidneys did not have time to respond to the change in pH by increasing bicarbonate excretion in the urine (see Table 14.7). When the kidney has time to compensate, the condition is called respiratory alkalosis with metabolic compensation.

Why did the pulmonary embolism cause a decrease in arterial P_{O_2} but did not increase and, in fact, decreased arterial P_{CO_2}? Remember from Chapter 13 that the relationship between partial pressure and content is sigmoidal for oxygen but relatively linear for CO_2. Because of the plateau of O_2 content as P_{O_2} increases above 60 mmHg (see Figure 13.26), increasing alveolar O_2 in hyperventilated regions of the lung does not significantly increase O_2 content of the blood leaving that region. Therefore, although hyperventilation does increase O_2 in some alveoli, it does not compensate for the significant decrease in O_2 content in some pulmonary capillaries due to ventilation–perfusion inequalities. Increasing ventilation can decrease the CO_2 content of blood due to the linearity of the relationship between P_{CO_2} and CO_2 content of the blood. The overall net effect is acute respiratory alkalosis due to decreased arterial P_{CO_2}. Interestingly, the hypoxemia can be partially overcome if the patient breathes gas that is enriched in oxygen because, although ventilation and perfusion are not well matched, there is not complete shunting of blood in the lungs. The increase in alveolar P_{O_2} can still increase oxygenation of some areas of the lung with ventilation–perfusion mismatching, at least somewhat. The arterial P_{CO_2} may have increased a little and pH decreased a little on supplemental O_2 because the improved arterial P_{O_2} decreased peripheral chemoreceptor stimulation and the degree of hyperventilation lessened (see Figure 13.34).

Our patient's initial complaint was chest pain, which made him think he was having a heart attack. He was actually fortunate to have chest pain because it caused him to go to the emergency department, which may have saved his life. Although the exact reasons for chest pain in pulmonary embolism are uncertain, one possibility is that the clots result in an acute increase in pulmonary artery pressure, which can result in pain.

Why did this man have a pulmonary embolism? Several risk factors for the development of deep vein thrombosis can result in pulmonary embolism. Prolonged sitting often causes a stagnant pooling of blood in the lower legs (see Figures 12.48 and 12.63). That is why it is highly recommended to avoid sitting for extended periods of time. Even sitting at a computer for just a few hours is discouraged. Contraction of the leg skeletal muscles compresses the leg veins. This results in intermittent emptying of the veins, decreasing the chances for clot formation. Obesity also increased the risk of deep vein thrombosis in our patient by further increasing the pooling of blood in the leg veins (due to obstruction of venous outflow and weakening of venous valves), increasing the amount of certain clotting factors in the blood, and changing platelet function.

A number of gene defects can also lead to an increased tendency to form clots, a condition called inherited ***hypercoagulability.*** The most common is resistance to activated protein C (see Figure 12.76), which can occur in up to 3% of healthy adults in the United States. In fact, our patient was tested and found to have resistance to activated protein C. Therefore, the combination of obesity, sitting for a prolonged period of time, and hypercoagulability is the likely cause of deep vein thrombosis and pulmonary embolism in our patient.

19.12 Therapy

As soon as the diagnosis of pulmonary embolism was made, our patient was immediately started on intravenous heparin and ***recombinant tissue plasminogen activator*** **(*rec-tPA*).** Heparin is an anticlotting factor that counteracts the hypercoagulability. Rec-tPA is a synthetic form of a naturally occurring molecule that helps dissolve clots. The ventilation–perfusion scan was repeated a few days later

and lung blood flow was almost normal. Supplemental oxygen was reduced over this time and then stopped when blood gases normalized.

Considering that this patient has an inherited cause of hypercoagulability, he has an increased probability to have another deep vein thrombosis and even pulmonary embolism in the near future. It is also possible that some of his family members have the same defect, for which they should be tested and adequately counseled. Our patient was sent home and continued to receive oral anticoagulants for 6 months (see description of anticlotting drugs in Section 12.26 of Chapter 12) and was actively followed by his primary care physician. He was encouraged to lose weight because obesity increases the risk of a deep vein thrombosis occurring again. Some physicians even advocate lifelong anticoagulation therapy for a patient such as ours.

SECTION B SUMMARY

Case Presentation

I. A man has chest pain and shortness of breath after an 8 h flight.

Physical Examination

I. He has an increased heart rate, but his ECG does not show evidence of a heart attack.
II. His chest x-ray is essentially normal.

Laboratory Tests

I. He is hypoxemic and has an acute respiratory alkalosis.

Diagnosis

I. His ventilation–perfusion scan shows evidence of a pulmonary embolism (blockage of pulmonary blood flow).
II. An ultrasound of his legs shows a deep vein thrombosis.
III. A clot formed in his leg veins because he sat for a long period of time. In addition, there is evidence that he has a genetic disorder of coagulation. The clot migrated to the lung, causing a pulmonary embolus.

Physiological Integration

I. Hypoxemia is caused by a dramatic disruption of the regional balance between ventilation and perfusion throughout the lung.
II. Hyperventilation due to anxiety and pain, as well as hypoxemia, caused an acute respiratory alkalosis.

Therapy

I. Treatment focuses on anticoagulation with heparin (to prevent clotting) and recombinant tissue plasminogen activator (to dissolve the clots).
II. Weight loss and long-term anticoagulation therapy are recommended.

SECTION B CLINICAL TERMS

19.7 Case Presentation

myocardial infarction

19.8 Physical Examination

atelectasis

19.10 Diagnosis

deep vein thrombosis
embolism
pulmonary embolism
thrombus
ventilation–perfusion scan

19.11 Physiological Integration

hypercoagulability

19.12 Therapy

recombinant tissue plasminogen activator (rec-tPA)

SECTION C

Case Study of a Man with Abdominal Pain, Fever, and Circulatory Failure

19.13 Case Presentation

A 21-year-old healthy college student and his friends were canoeing deep in the Alaskan wilderness when he felt the first twinge of abdominal pain. Thinking that he either ate some undercooked fish or strained a muscle while paddling, he stopped to rest for a day, but the pain steadily intensified. He began to shiver and felt extremely cold even though it was a warm day. These symptoms worsened during the 36 hours it took to paddle to the outpost camp and be airlifted to the nearest medical center.

Reflect and Review #12

- Based on your knowledge of the homeostatic control of body temperature, why might this young man feel cold despite it being a warm day? (See Figures 16.18 through 16.20.)

19.14 Physical Examination

On arrival at the hospital emergency department, the young man is confused and lapsing into and out of consciousness. His body temperature is 39.2 °C (normal range ~36.5 °C–37.5 °C), heart rate is 140 beats per min (normal range 65–85), respiration rate is 34 breaths per min (normal ~12), and blood pressure is 84/44 mmHg (normal for a young man ~120/80). He is taking deep breaths, and his lungs are clear when listened to with a stethoscope. His abdomen is rigid and extremely tender when gently pressed on, especially in the lower-right quadrant. Upon questioning, his friends state that he has not urinated in over 24 hours. Therefore, a hollow tube called a ***catheter*** is inserted through the urethra into the urinary bladder to collect his urine. An abnormally small amount of urine (10 mL) is collected from the catheter (see Figure 14.28 for a review of the control of renal excretory rate and urine output).

Reflect and Review #13

- What mechanisms link low systemic blood pressure in this patient to the low urine output? (See Figure 14.22.)
- What organs are located in the lower-right quadrant of the abdominal cavity? (See Figures 15.1 and 15.37.)

19.15 Laboratory Tests

Additional measurements are then performed, and the results are shown in **Table 19.3**.

TABLE 19.3 Initial Laboratory Results with the Patient Breathing Room Air

Blood Measurement*	Result	Normal Range
White blood cells	$25.0 \times 10^3/mm^3$	$4.3–10.8 \times 10^3/mm^3$
Arterial P_{O_2}	90 mmHg	80–100 mmHg
Arterial P_{CO_2}	28 mmHg	35–45 mmHg
Arterial pH	7.25	7.38–7.45
Arterial bicarbonate	13 mmol/L	23–27 mmol/L
Lactate	8.0 mmol/L	0.5–2.2 mmol/L
Glucose	90 mg/dL	70–110 mg/dL
Creatinine	2.2 mg/dL	0.8–1.4 mg/dL

*In actuality, these measurements are done in whole blood or serum or plasma derived from whole blood.

Reflect and Review #14

- Explain the relationship between arterial P_{CO_2} and pH values. Why is his arterial bicarbonate so low? (See Table 14.8.)
- What functions do white blood cells serve? What might be the cause of their abnormal values in this patient? (See Figure 12.2 and Table 18.1.)
- What metabolic processes produce lactate (lactic acid)? Under what circumstances would lactate production be increased above normal? (See Figures 3.42 and 3.43.)
- What effect does an increase in lactate have on alveolar ventilation? (See Figure 13.38.)
- Why did creatinine concentration in the blood increase? (See Section 14.4 of Chapter 14.)

19.16 Diagnosis

A catheter is placed into an arm vein so that an intravenous infusion of isotonic saline (NaCl dissolved in water) can be started. Antibiotics are added to the saline to fight the apparent infection. A ***computed tomography*** (***CT***) scan of the abdomen is performed, which reveals an inflamed appendix (**Figure 19.4**). The patient is admitted to the intensive care unit (ICU) for continued intravenous fluid replacement, physiological monitoring, and the insertion of additional catheters that can be used for the measurement of arterial and right atrial blood pressures.

The patient is then taken to the operating room for abdominal exploration. Surgeons remove an inflamed appendix that is found to have a small hole (***perforation***) and shows signs of ***necrosis*** (dying or dead tissue).

Reflect and Review #15

- Where is the appendix located? (See Figure 15.37.)

A bacterial infection of the membranes surrounding the abdominal organs is found. This type of infection, called ***peritonitis,*** results in ***pus*** (yellow liquid made up of white blood cells, bacteria, and

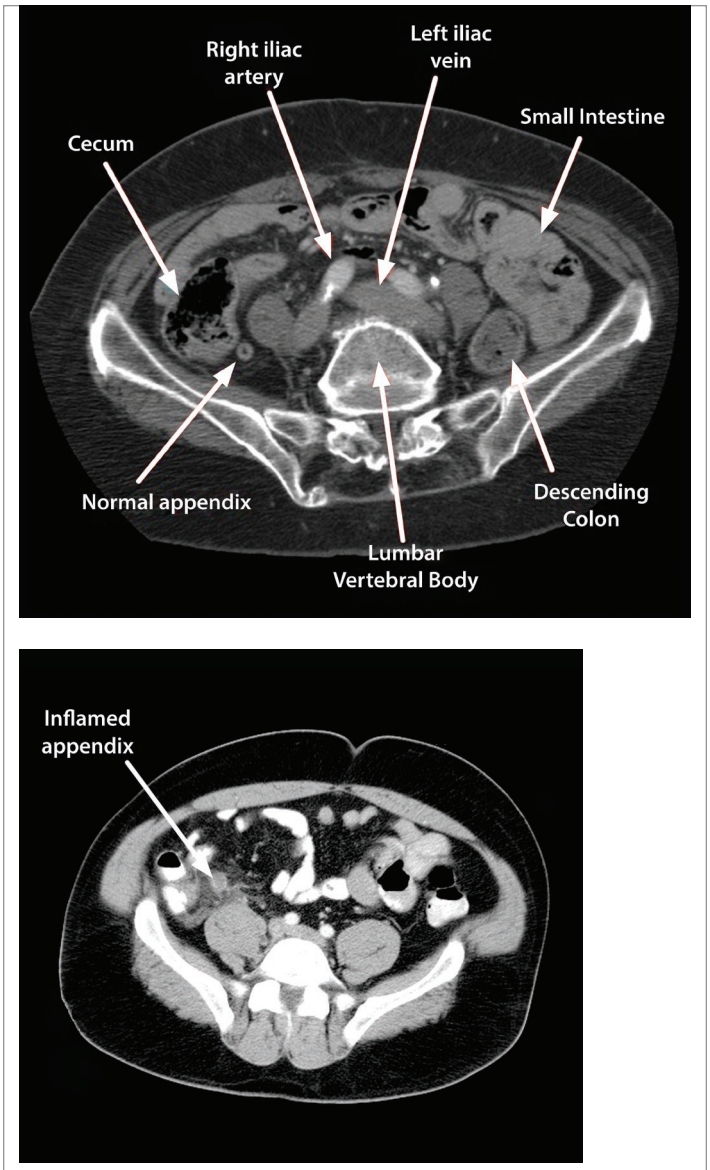


Figure 19.4 Normal abdominal CT scan (top) identifying major structures. CT scan on the bottom shows an inflamed appendix (arrow). (top) Courtesy of Dr. David Olson (bottom) ©Living Art Enterprises, LLC/Science Source

cellular debris) being produced. The pus is removed, the abdominal organs are thoroughly washed with saline and antibiotics, and the patient is returned to the ICU where arterial and central venous (right atrial) blood pressures and urine output are monitored.

Reflect and Review #16

- What is the purpose of monitoring right atrial blood pressure? (See Figure 12.49.) Suggest other variables to monitor in this patient.

In the hours after surgery, the patient is maintained on mechanical ventilation. Gurgling breath sounds and decreasing arterial oxygen partial pressure indicate the presence of fluid in his lungs. Supplemental inspired oxygen is provided to minimize the decrease in arterial oxygen by having the patient breathe a mixture of air enriched in oxygen. Widespread swelling of body tissues indicates that interstitial fluid volume is increasing, and his blood pressure and urine output remain dangerously below normal. In addition to providing continued intravenous fluids and antibiotic therapy, the

ICU staff infuses norepinephrine and vasopressin (vasoconstrictors), and methylprednisolone (a synthetic glucocorticoid given at pharmacological doses). For the next several days, the patient is critically ill while his condition is continuously monitored. Appropriate treatment adjustments are implemented as needed to attempt to normalize his blood volume, blood pressure, serum lactate, blood pH, and gas partial pressures in his blood.

This patient's condition began as acute ***appendicitis,*** but the delay in treatment allowed it to progress to the potentially lethal condition known as ***septic shock.*** Although *Escherichia coli* and other bacterial species are normally present in the lumen of the large intestine and its associated appendix, blockage of the lumen of the appendix or the blood supply to the appendix can allow those normally harmless bacteria to multiply out of control. When this happens, the appendix becomes distended and the pressure inside the appendix increases significantly due to inflammation. Eventually, these factors can lead to ulceration of the mucosa of the appendix, followed by perforation and ultimately rupture of the organ. This releases bacteria into the peritoneal cavity. The bacteria then release toxins that diffuse into the blood vessels in the abdomen, leading to a dramatic cascade of events (**Figure 19.5**). When a bacterial infection is accompanied by a ***systemic inflammatory response*** (defined by symptoms such as increases in body temperature, pulse rate, respiratory rate, and white blood cell count), the condition is referred to as ***sepsis.*** The most common sites of bacterial infections leading to sepsis are the lungs, abdomen (as in our patient), urinary tract, and sites where catheters penetrate the skin or blood vessels. If sepsis progresses to septic shock, patients also develop a significant decrease in blood pressure (a decrease in systolic pressure of more than 40 mmHg or a mean arterial pressure

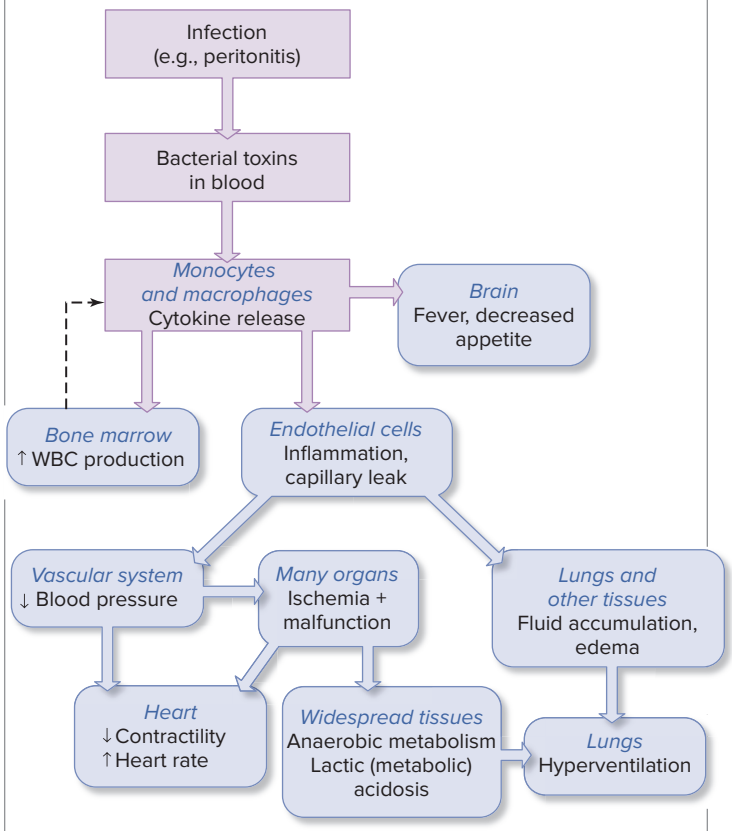


Figure 19.5 Cascade of some of the events from a serious infection to widespread organ failure in septic shock.

less than 65 mmHg) that is not reversible by intravenous infusion of large volumes of isotonic saline solution. This type of circulatory failure is an example of ***low-resistance shock,*** defined as a decrease in total peripheral resistance and blood pressure due to an excessive release of vasodilatory substances (see Section 12.16 of Chapter 12).

19.17 Physiological Integration

Bacterial infections stimulate the body to mount a rapid and widespread defense reaction (see Figures 18.16 through 18.19 and 18.22). Monocytes and macrophages (two types of white blood cells) secrete a variety of signaling molecules known generally as cytokines (see Table 18.2), which include substances such as interleukins and tumor necrosis factor. Target tissues for cytokines include (1) the brain, where they mediate the onset of fever, a decrease in appetite, fatigue, and an increase in ACTH secretion; (2) the bone marrow, where they stimulate an increase in the rate of white blood cell production; and (3) endothelial cells throughout the vasculature, where they stimulate processes leading to inflammation and increased capillary leakiness. Many species of bacteria release toxins, which greatly accelerate and exaggerate cytokine release and effects, often resulting in a maladaptive or life-threatening overreaction. The systemic inflammatory response has far-reaching effects on all body systems.

Such was the case of our patient by the time he finally reached the hospital. The set point for his body temperature was reset upward by circulating cytokines, resulting in ***fever,*** and he felt chilled and shivered in order to increase his core temperature toward the new, higher set point. The onslaught of cytokines and other inflammatory mediators (see Table 18.3 and Figure 18.2) accelerated as his white blood cell count increased and bacterial toxins were released into his circulation. Excessive amounts of those chemicals caused widespread injury to the microvascular endothelium and led to leakage of fluid out of capillaries.

When capillaries become excessively leaky, bulk flow favors the exit of fluid from the circulation (see Figure 12.44). Plasma proteins escape into the interstitial fluid, creating a significant osmotic force that draws fluid out through capillary pores. This is due to Starling forces, which are described in Chapter 12 (see Figure 12.45). This loss of fluid causes a drastic reduction in circulating blood volume, to the point at which even baroreceptor reflexes are unable to maintain arterial blood pressure (see Section 12.13 of Chapter 12). Dramatic increases in heart rate are evidence of activation of the baroreceptor reflexes via the cardiovascular control centers in the brain attempting to restore blood pressure toward normal. Even relatively large intravenous fluid infusions fail to reverse this hypotension because much of the infused fluid simply escapes into the interstitial space. Accumulation of fluid in the interstitial space leads to the tissue edema observed in our patient, and leakiness of pulmonary capillaries eventually led to fluid in his lungs (***pulmonary edema***).

Decreased systemic arterial blood pressure makes it difficult to produce adequate blood flow through the tissues. When blood flow is inadequate to meet demands for oxygen and nutrients (***ischemia***), tissues, organs, and organ systems malfunction. For example, our patient's inability to form urine resulted from low blood flow through his kidneys (see Figure 14.22). The increase in serum creatinine concentration was evidence that glomerular filtration rate was decreased (see discussion of Figure 14.12).

A more general consequence of decreased oxygen availability is that cells shift to anaerobic pathways to synthesize ATP, and significantly more lactic acid (lactate) is produced as a by-product (see Figure 3.42 and Figure 9.22). This led to the marked metabolic acidosis seen in our patient. His hyperventilation was driven by the peripheral chemoreceptors (primarily the carotid bodies), in an attempt to compensate by removing CO_2-derived acid from the plasma (see Figure 13.37). Another mechanism designed to combat acidosis is the addition of new bicarbonate to the plasma and the excretion of H^+ via the kidney (Section 14.19 of Chapter 14), but the decrease in renal blood flow and glomerular filtration rate rendered this mechanism ineffective. His pulmonary oxygen uptake and, therefore, the oxygen delivery to tissues was further compromised by the fluid buildup in his lungs. The added barrier to oxygen diffusion from lung alveoli into pulmonary capillaries (see Figure 13.28) reduced the oxygen partial pressure of his systemic arterial blood.

19.18 Therapy

Septic shock is an extremely challenging condition to treat, with mortality rates of 40% to 60%. One of the most important factors in determining patient survival is early recognition of the condition and onset of treatment. As soon as it has been determined that a patient is septic and is progressing toward septic shock, survival depends on rapid and continuous assessment of his or her physiological condition and timely therapeutic responses to changing conditions. Among the variables monitored, in addition to those listed in Table 19.3, are body temperature, heart rate, blood pressure, arterial and venous oxygen saturation, mean arterial and right atrial blood pressures, urine output, and specific biochemical blood indicators of the function of other organs, such as the liver. Using this information, clinicians can take steps to improve cardiovascular and respiratory function while at the same time battling the infection that is the root cause of the condition.

Immediate interventions in the treatment of septic shock are aimed at restoring systemic oxygen delivery, thereby relieving the widespread tissue hypoxia that is a hallmark of the condition. Mean arterial blood pressure is increased by intravenous infusion of isotonic saline and vasoconstrictors such as norepinephrine and vasopressin (see Figure 12.54). The extra circulating fluid volume increases cardiac output by increasing venous pressure and cardiac filling (see Figure 12.49), whereas norepinephrine (the neurotransmitter normally released from postsynaptic sympathetic nerve endings) increases cardiac contractility and arteriolar vasoconstriction (see Figure 12.54). Maintaining mean arterial pressure between 65 and 90 mmHg is necessary to optimize blood flow through the tissues. Right atrial pressure is monitored because it is a good index of venous return and the volume of fluid within the cardiovascular system (see Figure 12.60). The oxygen content of the blood is maintained by ventilating the lungs with supplemental oxygen to make sure that hemoglobin is saturated with oxygen (see Figure 13.26). It is also helpful to reduce the patient's demand for oxygen by paralyzing the respiratory muscles with drugs and providing mechanical ventilation, usually through a tube placed in the trachea attached to a positive-pressure pump. Otherwise, the increase in rate and depth of breathing that is typical of a patient in septic shock causes a marked increase in oxygen use by the respiratory muscles and directs blood flow away from other organs already suffering from lack of oxygen.

The infection must be treated while also restoring cardiovascular function. Antibiotics that act on a wide variety of types of bacteria are administered as soon as possible after sepsis is diagnosed. The source of the infection is then located, accumulated pus and dead tissue are removed, and the surrounding tissue is thoroughly cleaned. Ideally, samples of blood and/or pus from the site of infection can be grown in culture, and within 48 hours the specific bacterial species involved in the infection can be identified. The intravenous antibiotic therapy can then be tailored to drugs known to specifically target the invading species.

Recent clinical studies have suggested other therapeutic measures that can increase the survival rate of patients with septic shock. Pharmacological doses of glucocorticoid injections may be useful in some patients with septic shock. These hormones activate mechanisms throughout many tissues of the body that help the body cope with stress (see Table 11.2). Important among those effects are the inhibition of the inflammatory response and the enhancement of the sensitivity of vascular smooth muscle to adrenergic agents like norepinephrine. The benefit of glucocorticoid therapy in septic shock has been questioned in part because it suppresses the immune response to infection (see Chapter 11 and the legend to Figure 18.22). Current guidelines suggest that glucocorticoid therapy should be reserved only for very severe cases of septic shock as in our patient.

Over a 6-day period, the condition of our patient gradually improved. His blood pressure increased and stabilized, and the intravenous fluid and norepinephrine infusions were gradually reduced and then stopped. The edema in his lungs and tissues slowly subsided, he regained consciousness, and he was eventually able to maintain oxygen saturation in his arterial blood without mechanical ventilation. During the 2-week hospital stay, his brain, liver, and kidney function returned to normal, and he had no apparent long-term organ damage from his ordeal. He has been extremely fortunate; approximately 500,000 cases of severe septic shock occur in the United States each year, and less than half of those patients survive. His youth and relatively good initial physical condition were likely instrumental in helping him beat the odds.

SECTION C SUMMARY

Case Presentation

I. A young man has increasing abdominal pain over 3 days.

Physical Examination

I. He has a fever, increased heart and respiratory rates, and low blood pressure.
II. He has pain and rigidity localized to the lower-right quadrant of his abdomen.
III. His urine output is low.

Laboratory Tests

I. His white blood cell count is increased, suggesting an infection.
II. He has a metabolic (lactic) acidosis with a respiratory compensation (low arterial P_{CO_2}).
III. His blood creatinine concentration is increased, which indicates a decrease in glomerular filtration rate.

Diagnosis

I. A computed tomography (CT) scan shows an inflamed appendix, suggesting a diagnosis of appendicitis. The low blood pressure suggests septic shock due to peritonitis (caused by a ruptured appendix).

II. The diagnosis is confirmed in an abdominal exploration during which a perforated appendix is removed. The membranes near it are infected, proving peritonitis.

Physiological Integration

I. Toxins from the bacteria have caused the low blood pressure because of vasodilation.
II. The decreased glomerular filtration rate is due to low blood pressure and decreased renal perfusion.

Therapy

I. Therapy consists of intravenous fluids before and after surgery to support cardiac output and blood pressure and vasoconstrictor drugs to maintain blood pressure.
II. Antibiotic therapy is given to fight the peritoneal infection.

SECTION C CLINICAL TERMS

19.14 Physical Examination

catheter

19.16 Diagnosis

appendicitis
computed tomography (CT)
low-resistance shock
necrosis
perforation
peritonitis
pus
sepsis
septic shock
systemic inflammatory response

19.17 Physiological Integration

fever
ischemia
pulmonary edema

SECTION D

Case Study of a College Student with Nausea, Flushing, and Sweating

19.19 Case Presentation

A 21-year-old female Caucasian college student visits the student health clinic because of several episodes of nausea (without vomiting), flushing (redness and warmth in the face), and sweating. Although she admits to some binge drinking in the past, her recent episodes of nausea do not correlate with those events and occur without any identifiable trigger. Following the onset of her symptoms, she also notices mild tingling ("pins and needles") and rhythmic jerking beginning in the left side of her face and progressively marching down her body to include the left arm and left leg. These symptoms persist for about 3–4 minutes and then completely go away. The student health service physician assistant realizes the seriousness of the patient's history and calls for an ambulance. While waiting, the physician assistant asks the patient if she has had any recent head injuries that could account for her symptoms. The patient reports that no such injuries have occurred.

While waiting for transport to the hospital, the patient becomes nauseated, visibly flushed in the face, and sweaty. After a few seconds, twitching of the left side of her face occurs, with progressive involvement of the left arm, followed by the left leg. After a minute or so, the student loses consciousness and starts to have rhythmic ***convulsions*** (violent spasms) of both arms and legs that look like an ***epileptic seizure*** (see Figure 8.2). A seizure is a storm of uncontrolled electrical activity in the brain that in some cases can become rhythmic. In addition, her back becomes arched and stiff, and her eyes roll back into their sockets. The physician assistant applies a ***transcutaneous*** (through the skin) ***oxygen monitor,*** which is placed on the patient's finger. The patient's oxygen saturation is found to be low at 83% (normal is ≥95%) and supplemental O_2 therapy is started through a nasal cannula. The convulsions stop after about 2–3 min, but the patient does not regain consciousness and soaks her pants with urine. The ambulance finally arrives and the student is rushed to a nearby hospital emergency department.

Reflect and Review #17

- What can cause a sudden decrease in oxygen saturation? (See Figure 13.26 and Table 13.11.)
- What could be causing the flushing and sweating? (See Table 6.11 and Figures 16.18 and 16.19.)
- What controls micturition (urination)? (See Figure 14.13.)

19.20 Physical Examination

The emergency medicine physician assesses the vital signs of the patient. Her blood pressure is increased at 159/83 mmHg, her heart rate is increased at 114 beats per minute, and her body temperature is normal at 98.8 °F (37.1 °C). A thin, hollow tube called a catheter is placed in the antecubital vein in one of her arms; a blood sample is drawn for the measurement of hematocrit, white blood cell count, electrolytes, glucose, and creatinine (**Table 19.4**). A slow infusion of isotonic saline containing 150 mmol/L of sodium and 150 mmol/L of chloride (300 mOsm/L) is then started. A cursory neurological exam shows that the patient can be aroused but does not follow commands consistently and seems somewhat dazed. The pupils are similar in size and constrict symmetrically when a light is shone in either eye, which is normal. The patient does not seem to be moving the left arm and leg as much as the extremities on the right side. When the physician taps on the elbows and knees with a reflex hammer, the reflexes at the joints on the left side are

TABLE 19.4 Laboratory Tests in the Emergency Department

Blood Measurement*	Result	Normal Range
Hematocrit	47%	37%–48%
White blood cell count	$5.8 \times 10^3/mm^3$	$4.3–10.8 \times 10^3/mm^3$
Sodium	140 mmol/L	135–146 mmol/L
Potassium	4.0 mmol/L	3.5–5.0 mmol/L
Chloride	101 mmol/L	97–110 mmol/L
Calcium (total)	9.5 mg/dL	9.0–10.5 mg/dL
Glucose	130 mg/dL	70–110 mg/dL
Creatinine	0.9 mg/dL	0.8–1.4 mg/dL

*In actuality, sodium, potassium, chloride, calcium, glucose, and creatinine are measured in serum or plasma derived from whole blood.

more active, or brisker, than those of the right side. Based on this neurological exam, the physician orders an MRI scan of the head.

Reflect and Review #18

- What could cause her increase in heart rate? (See Figures 12.26, 12.30, and 12.54)
- What does hematocrit measure? (See Figure 12.1.)
- Why was blood glucose measured? (See Figure 16.12 and the description of hypoglycemia in Chapter 16.)
- Why was blood creatinine concentration measured? (See Section 14.4 of Chapter 14.)
- Why was isotonic saline infused? (See Table 4.1.)
- What is the significance of the increased reflexes in the left arm and leg? (See Figures 10.3 and 10.6.)

19.21 Laboratory Tests

Magnetic resonance imaging (***MRI***) uses a powerful magnet to create a strong magnetic field around a patient's body (**Figure 19.6**). This field acts on the spin—or resonance—of the nuclei (protons) of hydrogen atoms in the body, aligning them in the same direction. The part of the body being examined—in this case, the brain—is then subjected to a pulse of radio waves. The atoms of the brain absorb the energy of the waves and the resonance of their nuclei changes, altering their alignment with the magnetic field. The realignment of the hydrogen nuclei within the magnetic field is dependent on the type of tissue and is detected as a change in the characteristics of an electrical current passing through the radio frequency coils. Protons in different tissues like brain, adipose, and muscle behave differently, because their behavior is dependent upon the local environment such as the content of fat and water. Therefore, the different behavior of protons in different tissues can be analyzed by a computer to generate an image of the internal structures of the brain and many abnormalities and disease states.

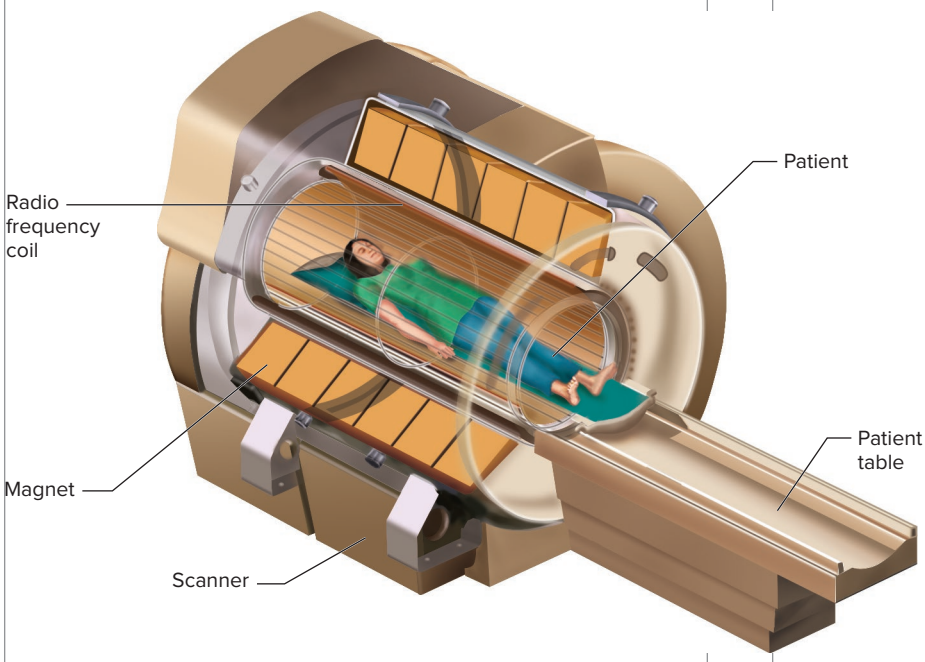


Figure 19.6 Cutaway diagram of an MRI scanner. Source: www.magnet.fsu.edu.

19.22 Diagnosis

The MRI shows a lesion in the right temporal lobe of the brain. (See Figure 6.38 and **Figure 19.7** for the location of the temporal lobe.) There are at least two possible explanations for this lesion. First, an infection may have led to the formation of an ***abscess,*** which is an inflammation characterized by a collection of neutrophils, bacteria, and fluid. Second, the lesion may be a ***neoplasm,*** which means "new growth," or tumor. Some neoplasms are malignant, that is, they are cancerous and may spread to other parts of the brain. Many CNS tumors are benign or noncancerous. Benign tumors are generally less dangerous because they usually do not grow as rapidly or spread to other organs, but they can still cause problems due to local growth. The only way to determine the tissue diagnosis is by surgical removal of the abnormal tissue via a ***craniotomy,*** in which a part of the skull is removed to give access to underlying brain tissue. This is performed on the patient and a histological diagnosis of a tumor of astrocytes (***astrocytoma***) is made (see Figure 6.6). Specifically, the pathologist examining the stained histological sections of this tumor under a microscope determines that the patient has a ***glioblastoma multiforme.*** These tumors get their name because they arise from glial cells (in this case, astrocytes) that are not fully differentiated; such cells are known as blast cells. The tumors are "multiforme" because they can attain varied appearances depending on their age, location, and the extent of surrounding damage to the brain. Unfortunately, glioblastoma multiforme is a cancerous form of tumor.

Reflect and Review #19

- What is the significance of the anatomical location of this lesion? (See Figure 7.13.)

19.23 Physiological Integration

Glioblastoma multiforme is a fast-growing and potentially lethal form of brain cancer. Of the approximately 13,000 new cases of brain tumors in the United States each year, about 65% are of glial origin and are known collectively as gliomas. These tumors arise from astrocytes and invade normal brain tissue. As they grow, these tumors can infiltrate, compress, and destroy the healthy brain tissue surrounding the tumor. In addition, these invading tumor cells can irritate the brain, causing seizures. In fact, like our patient, approximately 20%–30% of patients with brain neoplasms experience epileptic-like seizures (see Figure 8.2). During seizures, there is often a large increase in sympathetic nerve activity that was, at least in part, the cause of the nausea, facial flushing, sweatiness, and increase in blood pressure and heart rate that occurred in our patient. The decrease in oxygen saturation was due to a rigid and prolonged contraction of the respiratory muscles during the seizure leading to hypoventilation (see Table 13.11). The patient urinated after the seizure because, when the increased sympathetic activity from the seizure subsided, the remaining parasympathetic tone resulted in micturition (see Figure 14.13).

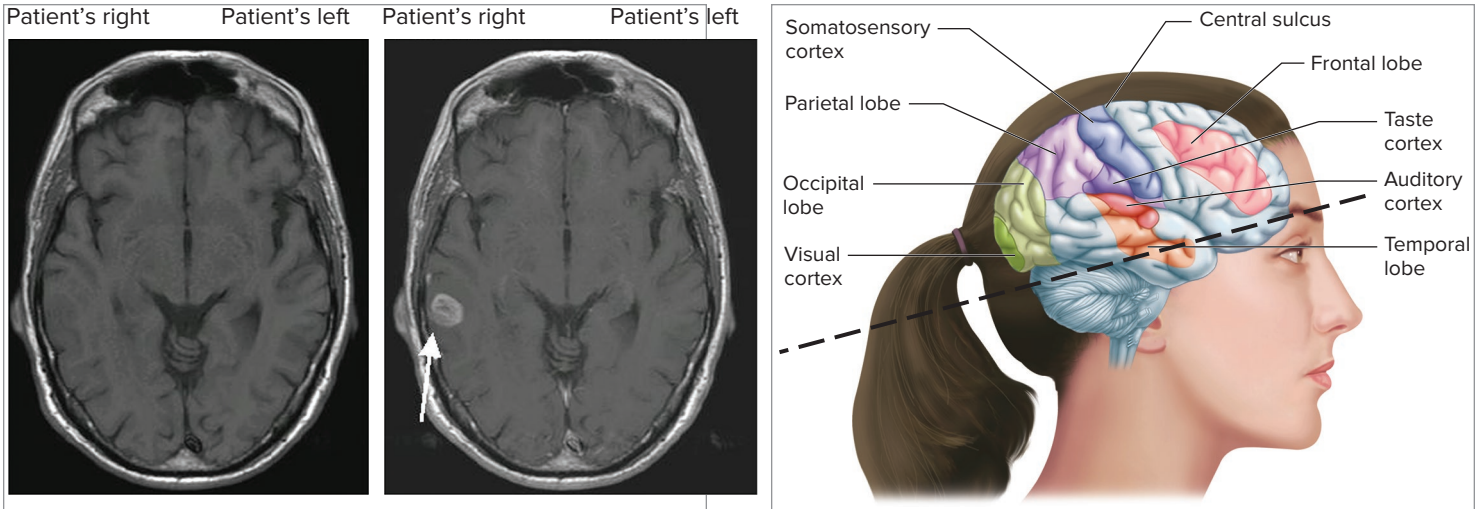


Figure 19.7 In these images, the settings on the MRI scanner are first set so that the brain tissue looks homogeneously gray, the fat surrounding the brain is lighter, and the water within the cerebral ventricles is dark (left scan). By convention, the MRI images are reversed so that the right side of the brain appears on the left side of the image. The front of the brain is shown at the top of the MRI image. A contrast agent containing the element gadolinium is then infused intravenously into the patient and a repeat scan is taken (right scan). Gadolinium has paramagnetic properties, which are magnetic properties that only arise in the presence of an externally applied magnetic field. When infused intravenously, the contrast agent can enter the brain in regions where the blood–brain barrier (see Figure 6.6) is absent or damaged, as is sometimes the case in sites of brain injury or disease. Once inside the brain, the association of gadolinium with water and fat changes the local environment and causes an area of higher intensity. This MRI scan demonstrates an area of signal abnormality in the right temporal lobe of the brain that measures about 2 cm in diameter (white arrow). The dashed line on the right image shows the plane of the MRI image. Courtesy of Dr. Douglas Woo/Medical College of Wisconsin

Until the brain MRI was done, the physicians did not know the cause of the seizures. A variety of metabolic disturbances can cause seizures. Abnormalities in blood electrolytes such as Na^+, K^+, and Ca^{2+} can interfere with normal neuronal resting membrane and action potentials (see Figures 6.12, 6.13, and 6.19). This could not explain the patient's seizures since her blood electrolytes were normal (see Table 19.4). The patient was given an intravenous infusion of isotonic saline because its osmolarity is very similar to that of plasma. This fluid infusion helps to maintain blood volume and also ensures that the intravenous line stays open in case drugs need to be infused. Renal failure can also cause metabolic and fluid-balance abnormalities leading to abnormal brain activity. Because the concentration of creatinine in the blood is a good estimate for glomerular filtration rate in the kidney, we know that this patient had normal renal function (see Table 19.4). Severe hypoglycemia can decrease the amount of glucose available for brain metabolism, which can cause seizures. This did not occur in our patient (see Table 19.4). In fact, she had a small increase in blood glucose concentration that was probably due to an increase in the blood concentrations of stress hormones such as cortisol and epinephrine (see Section D of Chapter 11, Figure 16.12, and Tables 16.3 and 16.4).

Another problem with intracranial lesions is that they may interfere with the drainage of cerebrospinal fluid from the lateral and third ventricles. If this were to happen, it could result in an increase in pressure within the cerebral ventricles. This leads to an enlargement of the ventricles that results in compression of the brain within the cranium. This is called ***hydrocephalus*** (from the Greek words for "water" and "head"; see Figure 6.47). It can cause many functional abnormalities including the convulsions that occurred in our patient. The MRI scan of our patient, however, did not show signs of hydrocephalus such as increases in the size of the cerebral ventricles.

A revealing aspect of this patient's condition was that most of the neurological symptoms were localized to one side of her body—in this case, the left. This included tingling, rhythmic jerking, and loss of motion. Just as sensory afferent information crosses from one side of the body to the other side of the brain (see Figure 7.20), motor control by descending pathways from the cerebral cortex to skeletal muscles also crosses from one side of the body to the other (see Figure 10.11). Therefore, the lesion on the right side of the temporal lobe caused seizures primarily on the right side of the brain leading to increased rhythmic motor activity on the left side of the body. Furthermore, the increase in reflexes on the left side was due to a loss of descending inhibition of spinal reflexes from the right side of the cortex to the motor neurons on the left side of the spinal cord (see Figures 10.3 and 10.6). Without the restraint provided by these descending pathways, the spinal reflexes were free from inhibition and were brisker than normal.

19.24 Therapy

This patient underwent brain surgery to have the tumor removed, followed by radiation therapy and a number of courses of chemotherapy. Chemotherapy is usually administered by an oncologist and typically involves administration of drugs that are toxic to fast-growing tumors. However, these drugs also have toxicity to normal tissue in which growth continues throughout life, such as blood cell–producing tissue and the epithelium of the small intestine. In radiation therapy, a beam of radiation is directed onto the tumor site to kill the tumor cells. In addition to these

treatments, the patient was given an antiepileptic drug to prevent more seizures. One such drug is ***phenytoin*** (***Dilantin***), which acts by blocking voltage-gated Na^+ channels (see Figure 6.18), particularly in neurons that are very active and firing with a high frequency. The patient was also treated with high doses of potent synthetic glucocorticoids because of their anti-inflammatory and anti-edema properties; these hormones, therefore, were given to reduce the swelling in the region of the patient's brain that was affected by the tumor.

After removal of the tumor and a small part of the surrounding right temporal lobe, our patient's right auditory cortex was damaged (see Figure 7.13) and she had trouble recognizing familiar musical melodies. Discrimination of melody (as opposed to rhythm) is a function that has been localized by researchers to the right temporal lobe of the human brain. Our patient remained stable for 16 months after her diagnosis but subsequently had a recurrence of the tumor that could not be surgically removed because of its position and size. She underwent further rounds of chemotherapy and radiation therapy. Sadly, however, only about 25% of patients survive more than 2 years from the time of diagnosis of glioblastoma multiforme. ■

SECTION D SUMMARY

Case Presentation

I. A 21-year-old woman has several episodes of nausea, flushing, and sweating.
II. She also has tingling and jerking on the left side of her face, which progresses to the left arm and leg. This is followed by a loss of consciousness and convulsions.

Physical Examination

I. She has a decrease in motion on her left side.
II. She has an increase in her reflexes in the left arm and leg.

Laboratory Tests

I. Her blood tests are essentially normal except for a small increase in blood glucose.
II. An MRI of the brain is administered with gadolinium contrast injected intravenously.

Diagnosis

I. The MRI of the brain reveals a bright 2-cm-diameter lesion in the right temporal lobe.
II. A craniotomy is performed to obtain a tissue sample of the lesion, which the pathologist identifies as a glioblastoma multiforme, a malignant brain tumor arising from astrocytes.

Physiological Integration

I. The tumor in the right temporal lobe causes seizures on the left side of the body because descending motor pathways cross from one side of the brain to the other side of the body.
II. Increased reflexes on the left side are due to a loss of descending inhibition from the right side of the brain to the spinal motor nerves on the left.

Therapy

I. After as much of the tumor as possible is removed, the patient is treated with radiation and chemotherapy.
II. In addition, antiepileptic medicine and glucocorticoid therapy to decrease swelling and edema are administered.

SECTION D CLINICAL TERMS

19.19 Case Presentation

convulsions
epileptic seizure
transcutaneous oxygen monitor

19.21 Laboratory Tests

magnetic resonance imaging (MRI)

19.22 Diagnosis

abscess
astrocytoma
craniotomy
glioblastoma multiforme
neoplasm

19.23 Physiological Integration

hydrocephalus

19.24 Therapy

phenytoin (Dilantin)

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