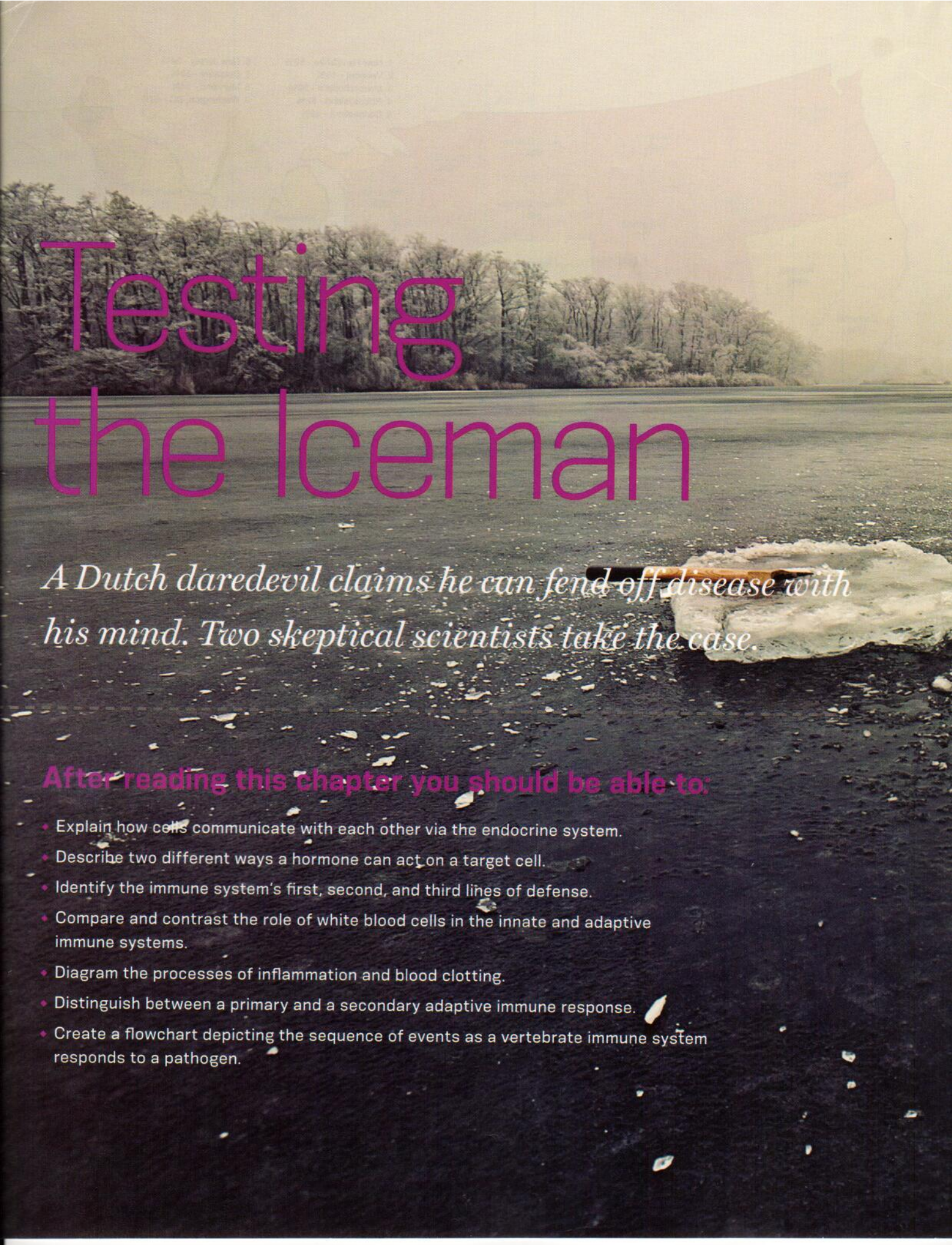
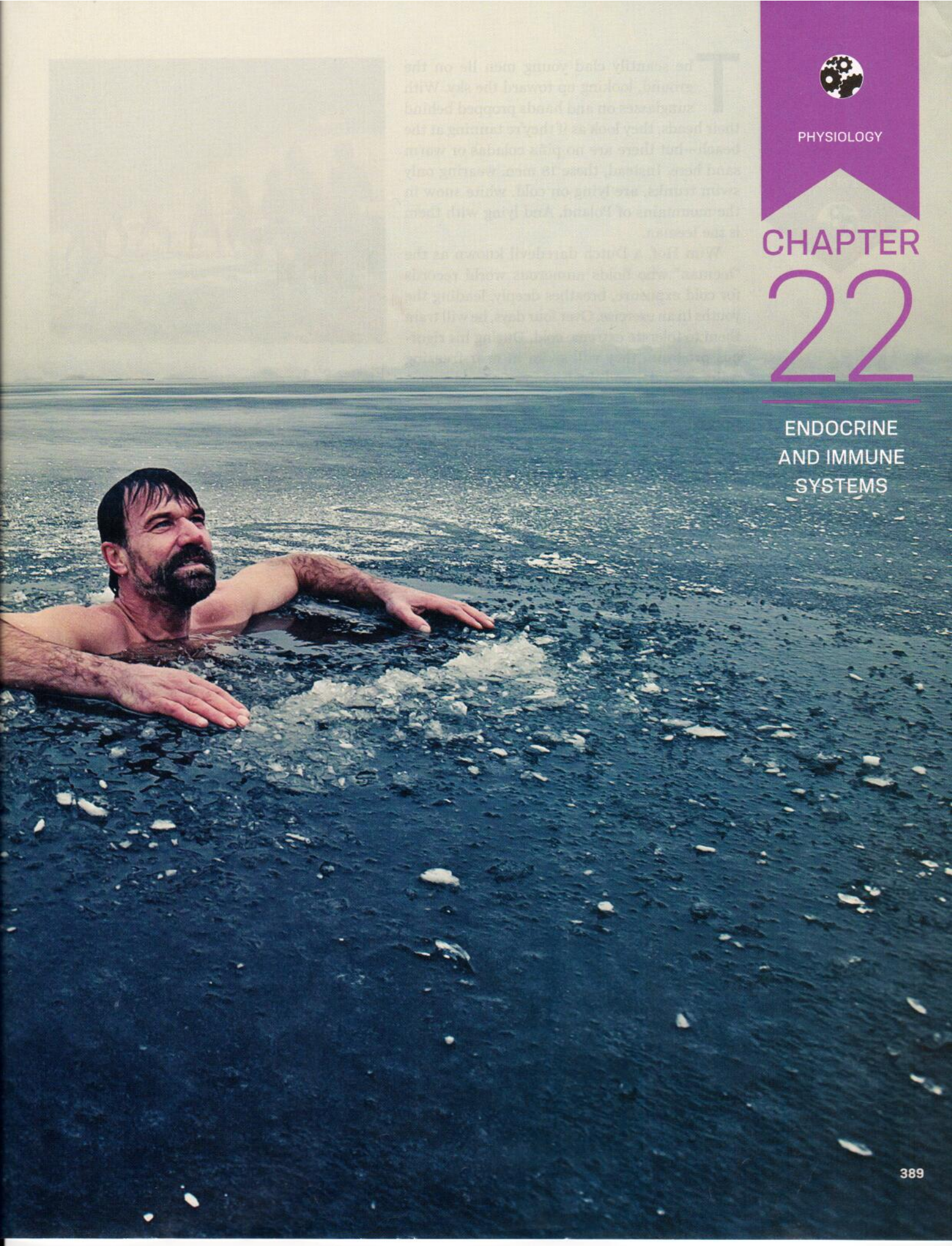


# Testing the Iceman

*A Dutch daredevil claims he can fend off disease with his mind. Two skeptical scientists take the case.*

## After reading this chapter you should be able to:

- Explain how cells communicate with each other via the endocrine system.
- Describe two different ways a hormone can act on a target cell.
- Identify the immune system's first, second, and third lines of defense.
- Compare and contrast the role of white blood cells in the innate and adaptive immune systems.
- Diagram the processes of inflammation and blood clotting.
- Distinguish between a primary and a secondary adaptive immune response.
- Create a flowchart depicting the sequence of events as a vertebrate immune system responds to a pathogen.



PHYSIOLOGY

# CHAPTER 22

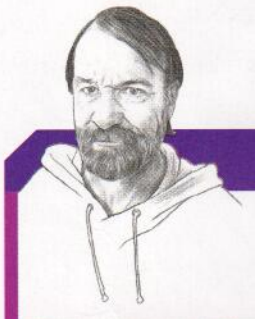
# ENDOCRINE AND IMMUNE SYSTEMS

The scantily clad young men lie on the ground, looking up toward the sky. With sunglasses on and hands propped behind their heads, they look as if they're tanning at the beach—but there are no piña coladas or warm sand here. Instead, these 18 men, wearing only swim trunks, are lying on cold, white snow in the mountains of Poland. And lying with them is the Iceman.

Wim Hof, a Dutch daredevil known as the "Iceman" who holds numerous world records for cold exposure, breathes deeply, leading the youths in an exercise. Over four days, he will train them to tolerate extreme cold. During his rigorous program, they will swim in near-freezing water every day and climb a snow-covered mountains in just shorts (**Figure 22.1**). Hof claims that exposure to the cold, combined with meditation and breathing exercises, will enable the men to fend off illness and disease.

Matthijs Kox stands to the side of the Iceman's trainees, taking notes. Kox, a researcher in intensive-care medicine at Radboud University Medical Center in the Netherlands, first met Hof in 2010, when the Iceman was visiting another laboratory at the university. A team in the physiology department was measuring Hof's ability to regulate his core temperature while standing in an ice bath (**Figure 22.2**). The scientists were surprised to find that rather than decreasing as expected, Hof's core temperature actually increased, and his metabolism climbed. While standing in the ice bath talking to his examiners, Hof mentioned that he could also consciously modulate his autonomic nervous system and immune system.

It was an unbelievable claim. The autonomic nervous system operates body functions that humans cannot voluntarily control, such as heartbeat and blood pressure. The **immune system**—a remarkable defense system that protects us against most infectious agents—has also long been known to be involuntary.



**WIM HOF**

Wim Hof, better known as the "Iceman," is a Dutch celebrity who holds numerous world records for withstanding extreme cold.

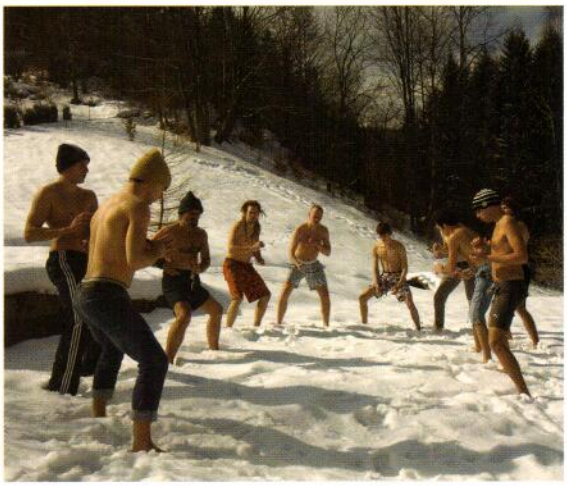


Figure 22.1

**"Iceman" Wim Hof trains volunteers under extreme conditions**

Figure 22.2

**Hof's vital signs are monitored while he is immersed in ice**

But Hof had a history of doing the unbelievable. He had claimed the Guinness World Record for longest ice bath by staying immersed in ice for 1 hour, 52 minutes, and 42 seconds. He had climbed part of Mount Everest wearing nothing but shorts. He had run a marathon through the snow at −20°C (−4°F), again wearing only shorts.

Hof's testers in the physiology unit told him that a Radboud University professor named Peter Pickkers had a way to measure a person's immune response. So Hof hoofed it to Pickkers's office, shook his hand, and said, "I can modulate my immune system. I heard you can measure it. Will you measure mine?"

# Hormonal Changes

Pickkers was skeptical of Hof's claim, which had the whiff of pseudoscience. But Hof was an interesting character, so Pickkers went online and watched videos of his feats. "There were remarkable things I did not know of—things that, if you had asked me beforehand, I would have said, 'That's not possible. It's not possible to run half a marathon barefoot in the snow,'" says Pickkers. "But he did that."

Pickkers raised the idea of testing Hof to Kox, who was one of Pickkers's PhD students at the time, studying how the brain and immune system interact. Pickkers and Kox discussed the possibility at length, and they decided to give Hof a chance to prove his claim. But they were going to do it while adhering strictly to the principles of the scientific process. "You can imagine some people wondered what we were doing with this guy," says Kox. "So we really focused on doing this in a very sound, precise manner, with no doubt about the scientific integrity of the project."

Hof claimed that the regimen for consciously controlling his immune system required three components: cold exposure, meditation, and breathing exercises. So, the team tested Hof's blood before and after an 80-minute full-body ice bath while Hof performed breathing and meditation exercises. Each time the scientists took blood, they went back to the lab and exposed the blood cells to molecules of endotoxin, a substance found in the cell walls of bacteria that activates an immune response in the human body. After the regimen of ice, breathing, and meditation, Hof's cells had a far more subdued immune system response, showing very low levels of proteins associated with activation of the immune system, compared to similar cells before the regimen. The cause of that subdued immune response was unclear, but the researchers suspected stress hormones played a role.

**Hormones** are signaling molecules that tell other cells what to do under specific situations or at certain times in the life cycle of the individual. Hormones are produced by specialized secretory cells of the **endocrine system** (**Figure 22.3**).

These secretory cells are often organized into discrete organs called **endocrine glands**. Major endocrine glands are located throughout the human body. Unlike other glands, such as tear ducts, endocrine glands do not have ducts or tubes that deliver secretions from the gland directly to the site of action. Instead, endocrine glands release hormones into body fluids such as blood, which carries these chemical messengers throughout the body (**Figure 22.4**). In a

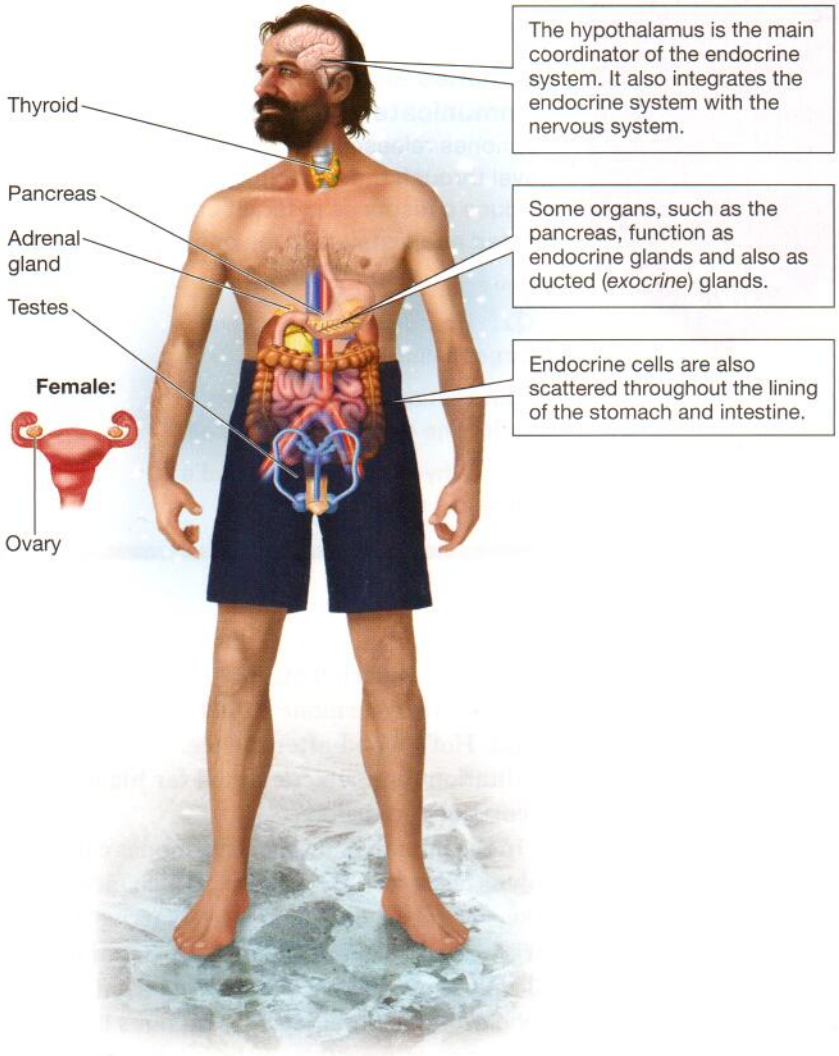



Figure 22.3

**The endocrine system is composed of hormone-secreting cells**

The endocrine system consists of cells organized into ductless glands, plus scattered endocrine cells embedded in other tissues or organs. These cells all release hormones directly into the circulatory system.

**Q1:** What organ coordinates the endocrine system?

**Q2:** How does an endocrine gland differ from an exocrine gland?

**Q3:** How do male and female endocrine systems differ?

Figure 22.4

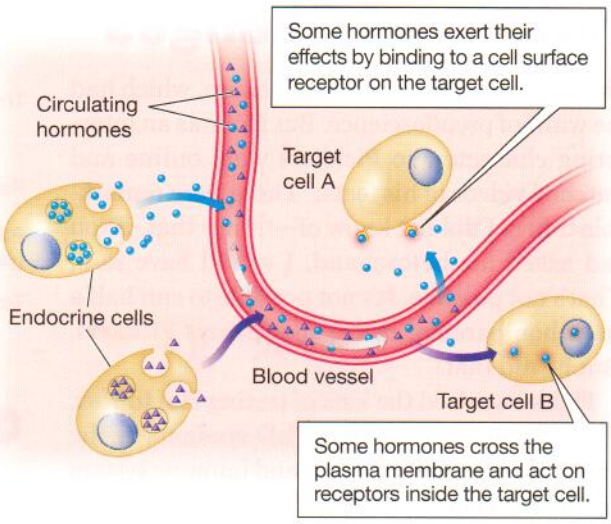
**Hormones enable cells to communicate with one another**

Hormones released by endocrine cells travel through the circulatory system to produce a response in target cells often located at a distance in the body.

**Q1:** How do hormones travel to target cells?

**Q2:** Distinguish between an endocrine cell and a target cell.

**Q3:** Why is a hormone called a signaling molecule?




subsequent experiment, Kox measured the levels of a stress hormone called cortisol in Hof's blood. Hof's blood after the ice, breathing, and meditation regimen contained far higher levels of cortisol than before.

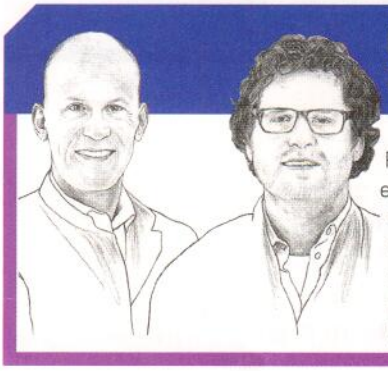
In the human body, most hormones can travel only as fast as the blood moves, which means they take several seconds or more to arrive at their target cells. Hormones coordinate functions that take place over timescales ranging from seconds (such as immediately increasing one's heartbeat in reaction to fear) to months (such as preparing a uterus to contract during the birthing process; see Figure 19.11).

Typically, hormones become greatly diluted after they are released into the circulatory system. They must therefore be able to exercise their effects at very low concentrations, as vitamins do. Hormones are effective in small amounts because they bind to their targets with great specificity. Cortisol, for example, binds to a very specific receptor present on the surface of almost every cell in the body.

Cortisol, adrenaline (also called epinephrine), and noradrenaline (norepinephrine) are three hormones produced by the **adrenal glands**, a pair of endocrine glands that sit atop the kidneys. The release of these hormones launches a number of rapid physiological responses, including boosting blood glucose levels.

When a single hormone molecule binds to its receptor, it sets in motion a chain of events that may ultimately activate thousands of protein molecules in the target cell (**Figure 22.5**). When cortisol binds its receptor, it initiates a pathway that results in the regulation of genes involved in development, metabolism, and immune response. This signal amplification—from a single hormone molecule to the activation of many proteins and genes—means that just a few hormone molecules can have a substantial impact on a target cell. Through its effects on many cells, a hormone can exert a profound influence on the body as a whole.

Some hormone-secreting cells are not organized into distinct glands like the adrenal glands, but are instead embedded as single cells or clusters of cells within other specialized tissues and organs. For example, the main role of the kidneys is to filter blood, yet some cells in the kidneys produce hormones that stimulate red blood cell production. Altogether, the endocrine glands and the endocrine cells embedded in other organs, such as the kidneys, make up the endocrine system.



**PETER PICKKERS AND MATTHIJS KOX**

Peter Pickkers (left) is a professor of experimental intensive-care medicine who studies the innate immune system. Matthijs Kox (right) is a researcher in intensive-care medicine. Both work at Radboud University Medical Center in the Netherlands.

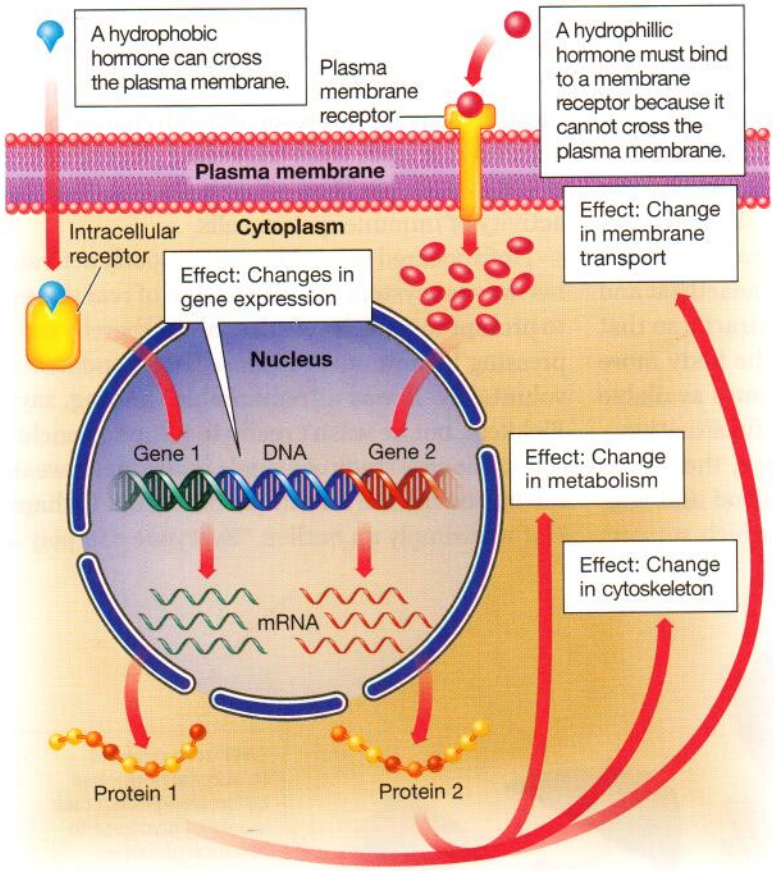



Figure 22.5

**Hormonal signals are amplified within the cell**

Hormones are effective at low concentrations because of their specificity and because tiny amounts of a hormone can generate a large internal signal within a target cell.

**Q1:** **Describe the two ways that a hormone outside a cell can exert its effect on a cell.**

**Q2:** **Within the cell, how does a hormone bring about a change in cell activity?**

**Q3:** **It takes very little of the hormone cortisol to have large effects throughout the body. Explain why.**

# Brain-Body Connection

Testing Hof's cells alone wasn't enough for Kox and Pickkers. They wanted to measure his entire body's immune response, and wanted to know if the breathing and meditation techniques made any difference. After the ice bath, they asked Hof to perform his meditation and breathing techniques while they injected him directly with the endotoxin. In previous experiments, healthy volunteers injected with endotoxin experienced fever, headaches, and shivering, accompanied by high levels of signaling proteins, called **cytokines**, that immune system cells use to communicate when an invader is present.

At various times before and after the injection, Kox measured Hof's blood levels for hormones and cytokines. Kox then compared Hof's results to those of a control group of 112 healthy volunteers who had previously taken the same test. To the scientists' surprise, as soon as Hof began practicing his breathing techniques, his adrenaline levels skyrocketed. And unlike the other volunteers, Hof reported almost no flu-like symptoms. Topping it off, the number of cytokines in his blood—indicative of an immune response—was less than half that of the control group. Hof appeared to have suppressed his immune system—voluntarily.

How was that possible? Kox considered the possibilities. First, a tiny region at the base of the vertebrate brain, the **hypothalamus**, coordinates the endocrine system and integrates it with the nervous system (refer back to Figure 22.3). The hypothalamus contains neurons, which interact with the brain, and endocrine cells, which produce hormones. It is a literal brain-body connection.

One well-known part of that connection involves the adrenal glands. In response to stress messages from the brain, the adrenal glands release adrenaline into the blood. If a man sees a rattlesnake in front of him, for example, he is likely to jump back or at least freeze in place, his heart racing. This quick response is due to the connection between the nervous system and the

adrenal glands (**Figure 22.6**): The nervous system processes visual information (*Snake!*) and transmits an alarm signal to the adrenal glands within a fraction of a second. The adrenal glands kick in right away, pouring adrenaline and noradrenaline into the blood. Adrenaline stimulates glycogen breakdown in liver and skeletal muscle cells, causing glucose to be released into the bloodstream. It also speeds up the heartbeat and the force with which the heart contracts, so that glucose is delivered throughout the body more rapidly. In this way, glucose becomes available to fuel a rapid response to a stressful situation.

Within just a few seconds, then, these hormones increase the pumping of blood and trigger the release of glucose, all of which support the next move: fight or flight. In the case of an encounter with a snake, that may mean either arming oneself with a stout stick or running away. It turns out, however, that adrenaline plays another role aside from triggering glucose delivery: Research has shown that it also subdues the activity of immune system cells.

Hof appeared to be able to consciously activate his nervous system (in the absence of real stress) to prompt the release of adrenaline, thereby suppressing his immune response to the endotoxin voluntarily. It was a "remarkable" finding, says Pickkers, but he wasn't ready to jump to conclusions. The case study of a single individual is weak scientific evidence for any phenomenon. Perhaps Hof was simply an outlier: "Everyone can play a

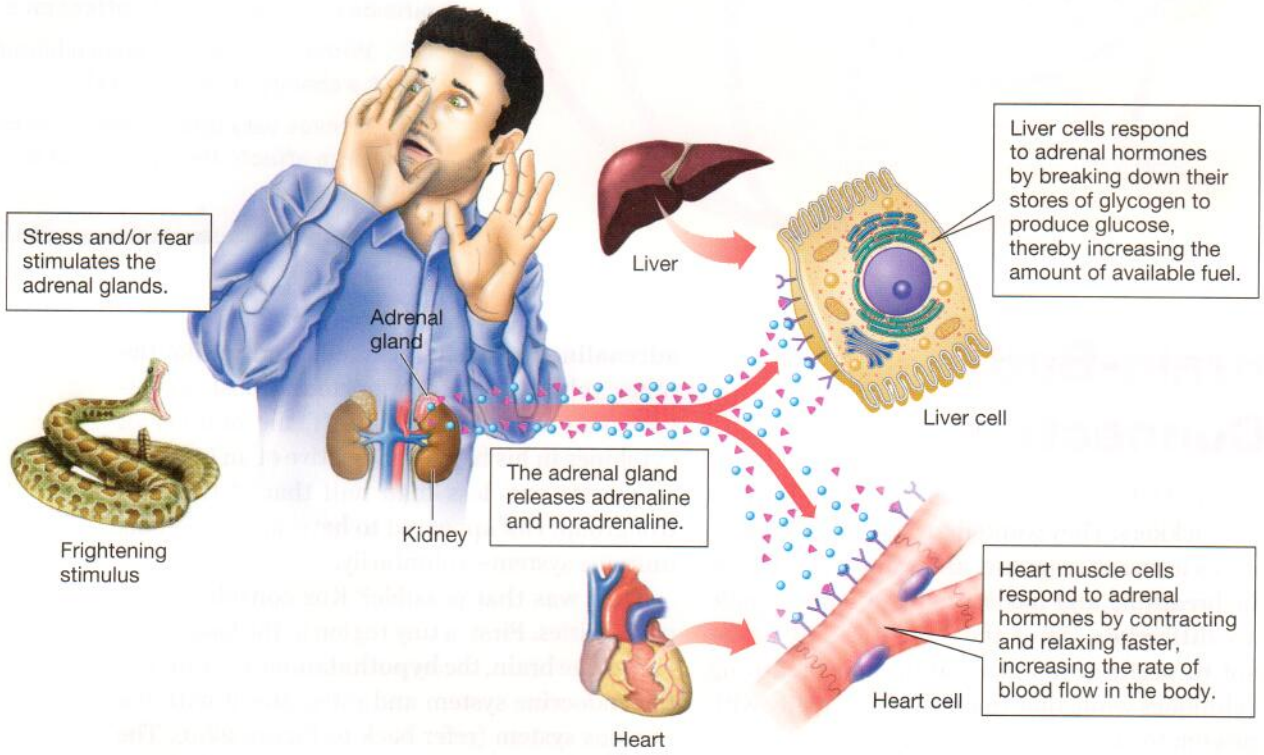



Figure 22.6

**Adrenal hormones produce a rapid response to stress or fear**

The adrenal glands produce adrenaline (epinephrine) and noradrenaline (norepinephrine), which trigger the rapid release and delivery of stored energy.

**Q1:** **Describe an event (other than the one illustrated in the figure) that might cause the release of adrenaline.**

**Q2:** **What organs does adrenaline affect?**

**Q3:** **What do you think would happen if your adrenal glands were constantly releasing adrenaline?**

little baseball, but there is only one Derek Jeter," says Pickkers. It could have been that Hof had a unique genetic mutation or another factor that enabled him to control his autonomic nervous and immune systems.

But Hof claimed that he was not an outlier, that he could teach his technique to anyone. "I'm sure everybody is able do this," Hof told Pickkers. Pickkers challenged him to prove it. For scientific validation, Hof needed to teach his method to a group of healthy volunteers so that Pickkers could then compare that group's immune responses to those of an untrained control group of volunteers. In this controlled way, Hof might produce stronger scientific evidence for his claim.

## Innate Defenders

If Hof was right—if it was possible to voluntarily control the immune system—the discovery would do more than change our understanding of the immune system; it would offer hope to people with autoimmune diseases, individuals in whom the immune system is overactive.

When healthy, the immune system protects animals from most infectious agents, called **pathogens**. Human pathogens include viruses, bacteria, and protists, as well as some fungi and multicellular animals such as parasitic worms. A well-known example is human immunodeficiency virus or HIV, the virus responsible for AIDS (see "What Makes HIV so Deadly?").

Pathogens infect animals only if they can find a way into the body. An animal's first line of defense against pathogens is **external defenses**, which reduce the likelihood that a harmful organism or virus will gain access to internal tissues. Linings that separate the "outside" from the "inside" of the body—the skin and the linings of the lungs, for example—act as a physical barrier to keep out most pathogens. Other external defenses include chemical agents (such as enzymes) and chemical environments (such as acidic conditions) that keep the invaders from attaching to or growing on body surfaces (**Figure 22.7**).

Although external defenses do a good job of keeping out most pathogens, the body is still vulnerable. Wounds, in the form of cuts, abrasions, and punctures, are common, and many pathogens will take advantage of breaks in the skin to gain entry to their hosts.

### What Makes HIV So Deadly?

In the early 1980s, doctors in the United States began to notice that gay men were dying of a variety of rare diseases, including a skin cancer called Kaposi's sarcoma, an unusual kind of pneumonia, and other infections that most people ordinarily shake off. By the mid-1980s it was clear that patients with the syndrome—named acquired immunodeficiency syndrome, or AIDS—had broken immune systems, the result of infection by a virus called the human immunodeficiency virus, or HIV.

In North America and Europe, the number of new cases rapidly increased, claiming the lives of tens of thousands of people each year. Initially, most new cases were limited to gay men, intravenous drug users, and people who had received blood transfusions. The common denominator was contact with the blood or body fluids of others: Couples during sex, drug users when sharing used needles, and surgical and hemophilia patients who received blood transfusions contaminated with HIV.

In time, safe-sex education and clean-needle programs reduced the rates of infections among gay men and blood transfusion patients, but the virus spread to other populations. Globally, 39 million people have died of AIDS, leaving over 17 million orphaned children. In just one year, 2013, 1.5 million people died of AIDS and 2.3 million more became infected.

Inside the bloodstream, individual HIV enters immune system cells and reproduces inside them, eventually killing so many immune cells that the body's defenses are crippled. In the short term, remaining immune system cells track down HIV-infected cells and destroy them. Because they do such a good job of killing HIV-infected cells in the blood, most people with HIV have about a decade of normal health before they become ill, even without any treatment.

Over time, however, the HIV viruses in the body evolve. As HIV evolves, the immune system cells no longer recognize and kill the virus. The population of HIV viruses increases and begins destroying immune system cells faster than they can multiply. The body no longer has the immune system cells it needs to fight off infections by bacteria, yeasts, and other viruses. Once the immune system collapses, a person is vulnerable to almost any infection.

So far, there is no effective vaccine or cure for HIV. But a variety of new drugs enable people with AIDS to live years longer with fewer symptoms. "HIV cocktails," as the standard mixture of therapeutic drugs are called, prevent the viral genetic material from replicating or prevent the virus from merging with plasma membranes and entering cells. But the drugs can cost hundreds or thousands of dollars a month. Because treatment is so costly, only one in five AIDS patients in Africa and Asia receives effective treatment. For now, the best way to slow the spread of the disease remains safe-sex education, the free availability of condoms, and clean-needle programs.

Once inside, pathogens confront a second line of defense—the cells and defensive proteins of the **innate immune system**. To mount an internal defense that kills, disables, or isolates invading pathogens, the body first must recognize that

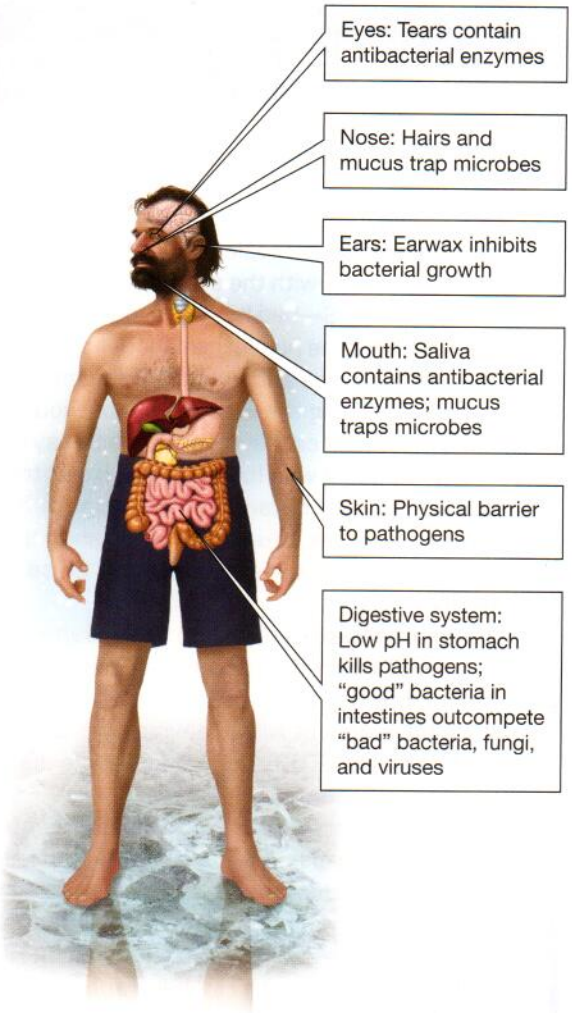



Figure 22.7

**The immune system's first line of defense is preventing the entry of pathogens**

Our skin and the linings of our respiratory and digestive systems form physical and chemical barriers against pathogens.

**Q1: What is the main physical barrier that animals use to keep out pathogens?**

**Q2: Give an example of a chemical defense within the digestive system.**

**Q3: Explain why rubbing your eyes and nose during flu and cold season is not recommended.**

an invader is present. Although a person is not consciously aware of it, a healthy body can distinguish foreign invaders (nonself) from its own cells (self). If the internal defenders fail to tell self from nonself, they mistakenly attack the body's own cells, leading to autoimmune diseases such as rheumatoid arthritis (in which immune cells attack the lining of the membranes that surround joints) or type 1 diabetes (in which immune cells attack the pancreas, which makes insulin).

If there were a way, as Hof claims, to subdue the immune system at will, people with these diseases would have another avenue, aside from expensive drug therapies, by which to control their rebellious immune systems.

## Team Effort

Despite Hof's personal achievement, Pickkers and Kox didn't really think he would be able to teach others to voluntarily control their innate immune systems. "We thought it would be a negative result," says Pickkers. If nothing else, Hof had been performing his technique for 30 years, so even if he could teach it, Pickkers doubted he could teach a novice enough to influence his or her own immune system in just a few days. Hof disagreed, arguing that a short training regimen would be sufficient to impart the ability. Kox didn't think that most of the volunteers would even make it through the training.

It was no easy study for the participants. Over four days, 18 healthy, young male volunteers were taken into the mountains of Poland and exposed to the cold in various ways: standing in the snow barefoot for 30 minutes, lying in the snow bare-chested for 20 minutes, swimming in ice-cold water each day for several minutes, hiking up a snowy mountain in nothing but shorts and shoes. Hof also taught them his meditation and breathing techniques, including deep inhalations and exhalations.

Contrary to Kox's expectation, all 18 participants completed the training, and 12 of them were then randomly selected to come back to the lab for the final part of the experiment: Exposure to the endotoxin, to test whether they could consciously regulate their immune response. Their results would then be compared to those of 12 healthy controls who had also been exposed to the endotoxin but had not received Hof's training. Now the scientists would finally find out whether Hof could teach someone to control the activity of the innate immune system.

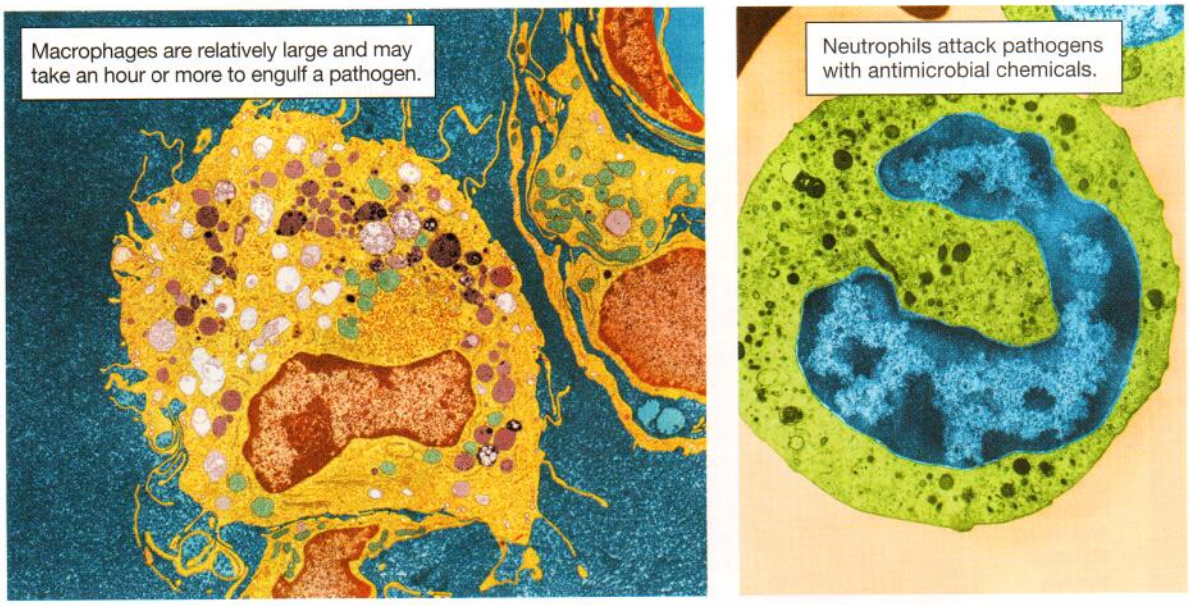



Figure 22.8

**Phagocytes destroy pathogens by engulfing them**

Phagocytes are a kind of white blood cell, a family of defense cells found in body fluids including blood, where they intercept invading pathogens. Two different kinds of phagocytes—a macrophage and a neutrophil—are seen in these colorized transmission electron micrographs (TEMs).

**Q1:** **Place these terms in order from most to least inclusive: neutrophil, white blood cell, phagocyte, innate immune system.**

**Q2:** **Compare and contrast macrophages and neutrophils.**

**Q3:** **Why would it be a problem if your innate immune system identified the insulin-producing cells in your pancreas as "nonself?"**

The innate immune system reacts to cells or molecules that do not belong in the body by activating defense cells and proteins to eliminate the unwelcome guests. A suite of pathogen-recognizing cells called **phagocytes**, a type of white blood cell, mark and destroy foreign invaders by engulfing and digesting them (**Figure 22.8**).

This immune response is said to be innate (inherent) because the necessary components are constantly at the ready for deployment against an invading pathogen. The innate response can be local, occurring at the point of entry, or global, involving the whole body. Like the external defense system, innate immunity is indiscriminate as to which foreign invaders it repels, so it is considered a **nonspecific response**. The innate immune system is an ancient defense mechanism found in both invertebrates and vertebrates.

In addition to defending against invaders, the innate immune system plays two other critical roles. First, it responds to tissue damage from a pathogen invasion or wound by mounting an immediate and coordinated sequence of events known as **inflammation** (**Figure 22.9**). Cytokines are a clear marker of inflammation, and thus a good way to measure the action of the immune system. The second role of the innate immune system is clotting blood to close a wound. Sealing an open wound reduces blood loss and restores the integrity of external defense barriers (**Figure 22.10**).

To test the innate immune response of the 24 study participants (the 12 trained volunteers and the 12 untrained controls), the scientists injected

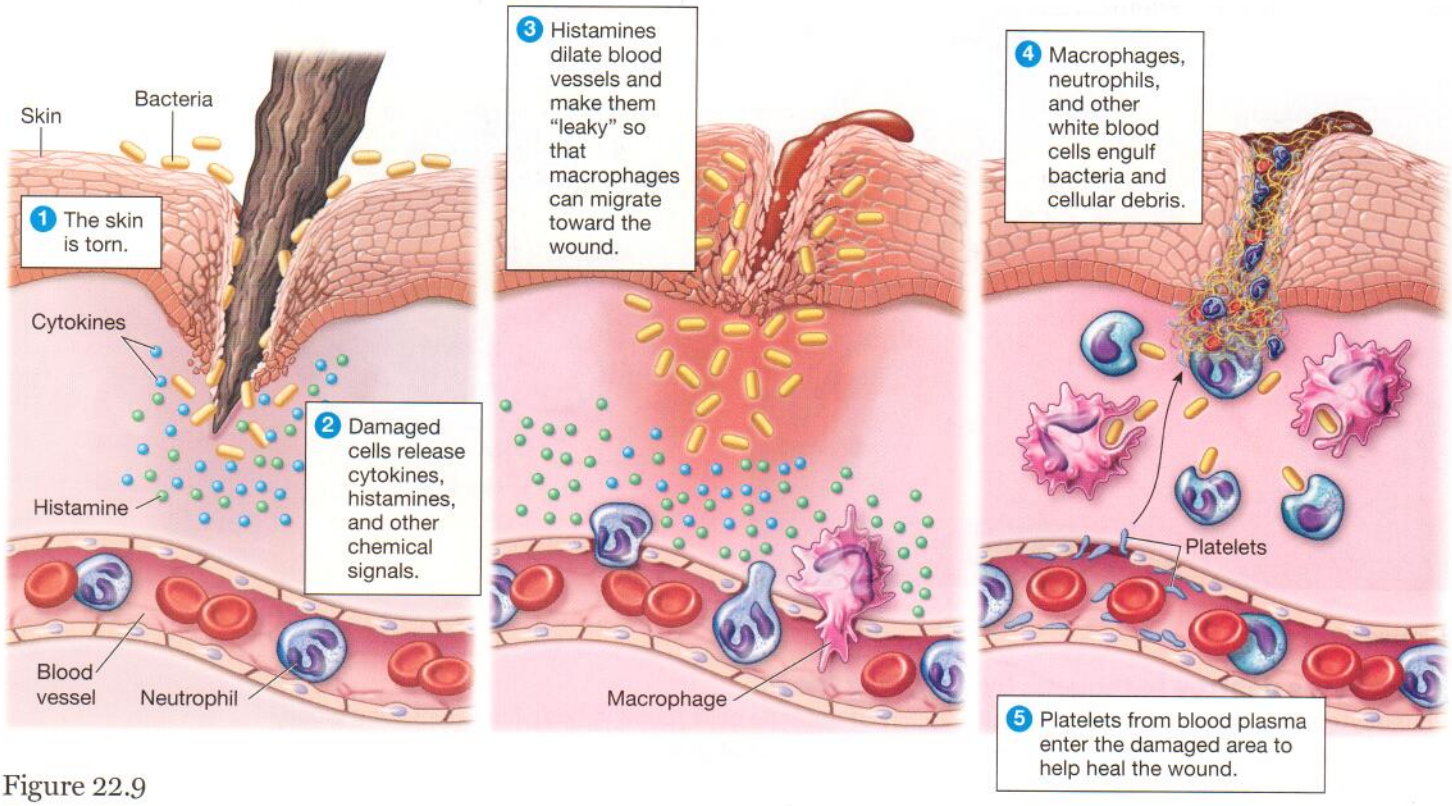



Figure 22.9

## The inflammatory response acts against invading pathogens

Inflammation occurs when the innate immune system swings into action after cellular damage is detected, cleaning up damaged tissues and preventing the spread of pathogens. Inflammation can occur anywhere inside the body. Here we see an inflammatory response following a puncture wound to the skin.

**Q1:** What is the role of white blood cells in inflammation?

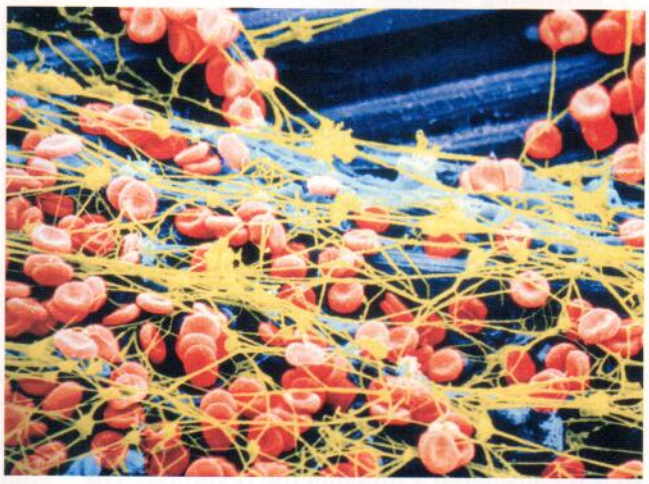
**Q2:** What would happen if histamines were not produced during inflammation?

**Q3:** Why is inflammation called a "nonspecific" immune response?

Figure 22.10

## Blood clots help prevent pathogens that may be present in a wound from spreading

Sticky cell fragments, or **platelets** (shown here in light blue), and clotting proteins (yellow) form a gel-like mesh that traps blood cells, creating a blood clot that seals broken skin. Clotting can begin as quickly as 15 seconds after tissue damage occurs. Growth of new tissue eventually repairs the wound more permanently.



**Q1:** Why is blood clotting an important immune response?

**Q2:** How are the inflammatory response and blood clotting similar?

**Q3:** Some people have a genetic disorder in which their blood cannot clot. Why would this be a problem?

each participant with endotoxin and monitored them for six hours. Hof visited his trainees during the experiment, coaching them through his breathing techniques.

The results were clear: After being injected, and while performing the breathing techniques, the trainees showed higher adrenaline levels than the controls—higher even than the adrenaline produced by a person's first bungee jump. "They produced more adrenaline just lying in bed than somebody standing in front of an abyss going to jump in fear for the first time," says Hof. "That means direct control of your hormone system, and your hormones have a direct relationship to the immune system."

In addition, the trainees had fewer flu-like symptoms and lower fevers, and their cytokines—the signaling proteins of the immune system and markers of inflammation—were at less than half the level of the control group. "We were very surprised," says Kox. "It was impressive that these guys could do all this cold exposure training, but I still thought the chances were slim they'd be able to modulate their immune systems. But the results were so convincing."

## Adapting to the Enemy

Kox and Pickkers's study did not address the human immune system's third line of defense. In contrast to the nonspecific responses of external defenses and the innate immune system, the more complex **adaptive immune system** is tailored against specific invaders.

Adaptive immunity goes beyond simply recognizing something as nonself. Instead, specialized defense cells are trained to recognize only one strain of pathogen and to activate a **specific response**. The adaptive immune system is based in the lymphatic system and relies on two main weapon systems: *Antibody-mediated immunity* and *cell-mediated immunity* (**Figure 22.11**).

**Antibody-mediated immunity** uses powerful Y-shaped proteins called **antibodies** to recognize and attack invaders. Antibodies recognize nonself markers—**antigens**—on the pathogen and mark the pathogen for destruction. **B cells**, specialized lymphocytes created and matured in the bone marrow, produce thousands of antibodies per second aimed specifically at the pathogen that has been recognized.

**Cell-mediated immunity** recognizes cells that have been infected by a pathogen such as a virus, as well as cancer cells. **T cells**, lymphocytes created in the bone marrow and matured in the thymus, recognize markers on the surface of a cell that has been infected. The T cell then kills the infected cell so that it cannot spread the disease to other cells.

Compared to innate immunity, adaptive immunity is slow to mobilize. However, it is the most sophisticated and effective of animal defense systems because of the amazing selectivity with which the adaptive immune system attacks a particular invader.

Adaptive immunity occurs in two stages. The very first time a person is exposed to a particular pathogen, the **primary immune response** is activated. This response takes time—more than two weeks, sometimes—to reach full steam. Because of that slow start, and because pathogens multiply so rapidly, people infected with an aggressive pathogen for the first time can sometimes lose the race, becoming ill and dying. Therefore, any pathogen that is new to humans is particularly dangerous, and the nonspecific response of innate immunity may be more beneficial. However, the combined action of innate immunity and the primary response of adaptive immunity prevails against most pathogens.

A distinctive feature of the adaptive immune system is **immune memory**, the capacity of this defense system to remember a first encounter with a specific pathogen and to mobilize a speedy and targeted response to future infection by the same strain. This "memory" is what enables us to become immune to attacks by the same strain after we suffer the disease a first time. Once you've had measles, for example, you never get sick from the measles virus again, because the adaptive immune system recognizes the virus and quickly eradicates it the next time. Keep in mind that this means you are not born with immune memory. Each individual must build one over time by being exposed to various pathogens.

Because of immune memory, the adaptive immune system produces a faster, more dramatic response to pathogens when it encounters them a second time. The second encounter, when the adaptive immune system is poised and ready to respond, is the **secondary immune response**.

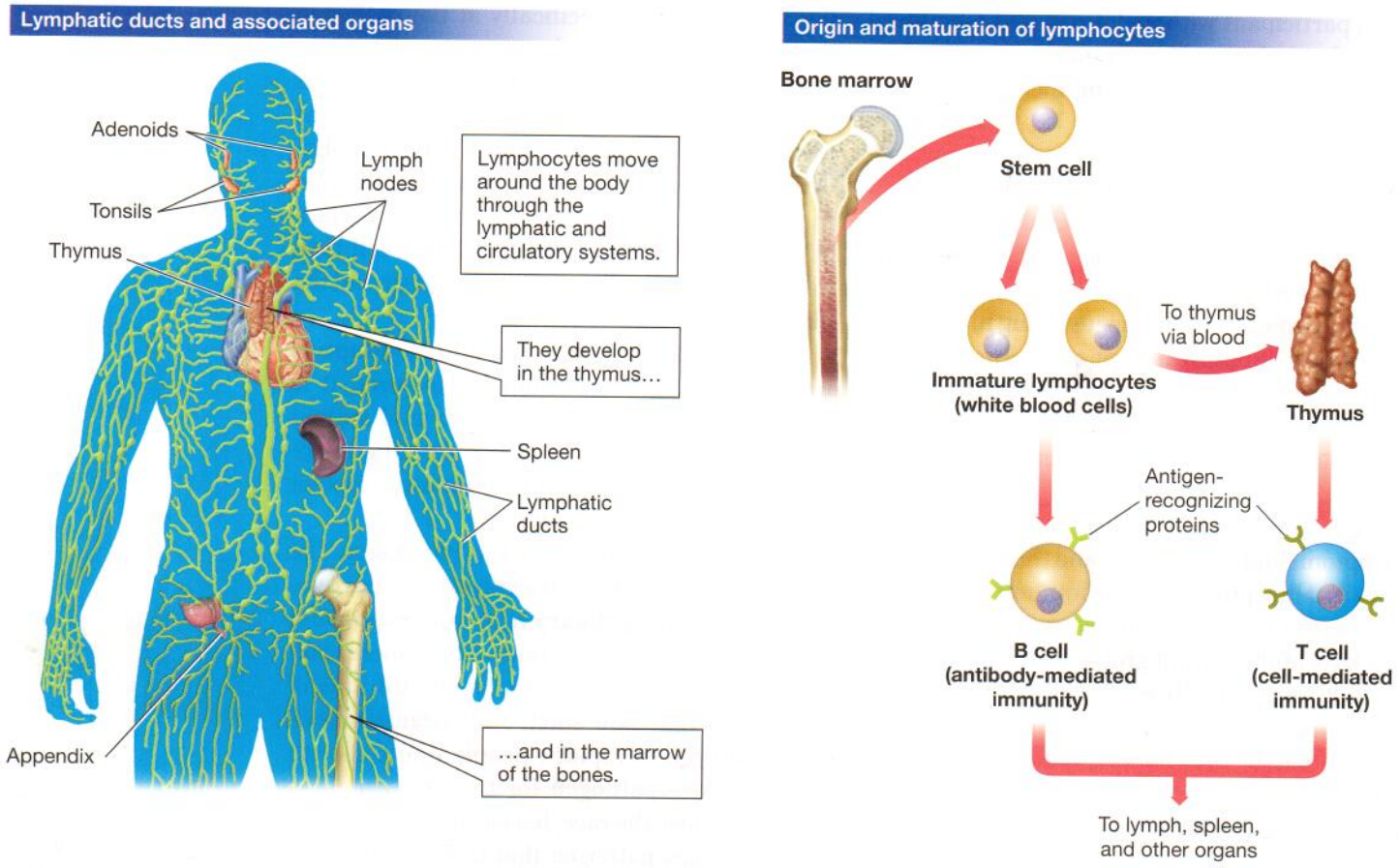



Figure 22.11

**Adaptive immunity resides in the lymphatic system**

(Left) The **lymphatic system** consists of lymphatic ducts, lymph nodes, and associated organs. (Right) **Lymphocytes** originate from stem cells in bone marrow. B cells mature in the bone marrow; T cells mature in the thymus. Lymphocytes circulate in the lymphatic and circulatory systems and accumulate in lymph nodes and other organs, such as the spleen, appendix, and tonsils.

**Q1:** Why are B and T cells so named?

**Q2:** In what way is this immune system "adaptive"?

**Q3:** Why is the adaptive immune response considered the third layer of the immune system?

We acquire immunity in two ways: either actively or passively. We acquire **active immunity** to a particular pathogen when our own bodies produce antibodies against that pathogen; they are not received from an outside source. This happens naturally when we're exposed to certain pathogens, such as the measles virus. We can also acquire active immunity to certain diseases through vaccination.

We acquire **passive immunity** by receiving antibodies that were not made by our own bodies. A human fetus acquires antibodies from exchanges between its blood and its mother's blood. This antibody sharing continues after birth: Mother's milk is rich in antibodies because the mother's immune system has encountered many antigens and made many antibodies in her lifetime. Thanks to that antibody-rich milk, a nursing baby receives passive immunity to a broad range of pathogens. Passive immunity produces no memory cells, so it wears off as the received antibodies degrade, usually within a few weeks or months. There is no evidence, yet, that Wim Hof is able to control his adaptive immune response.

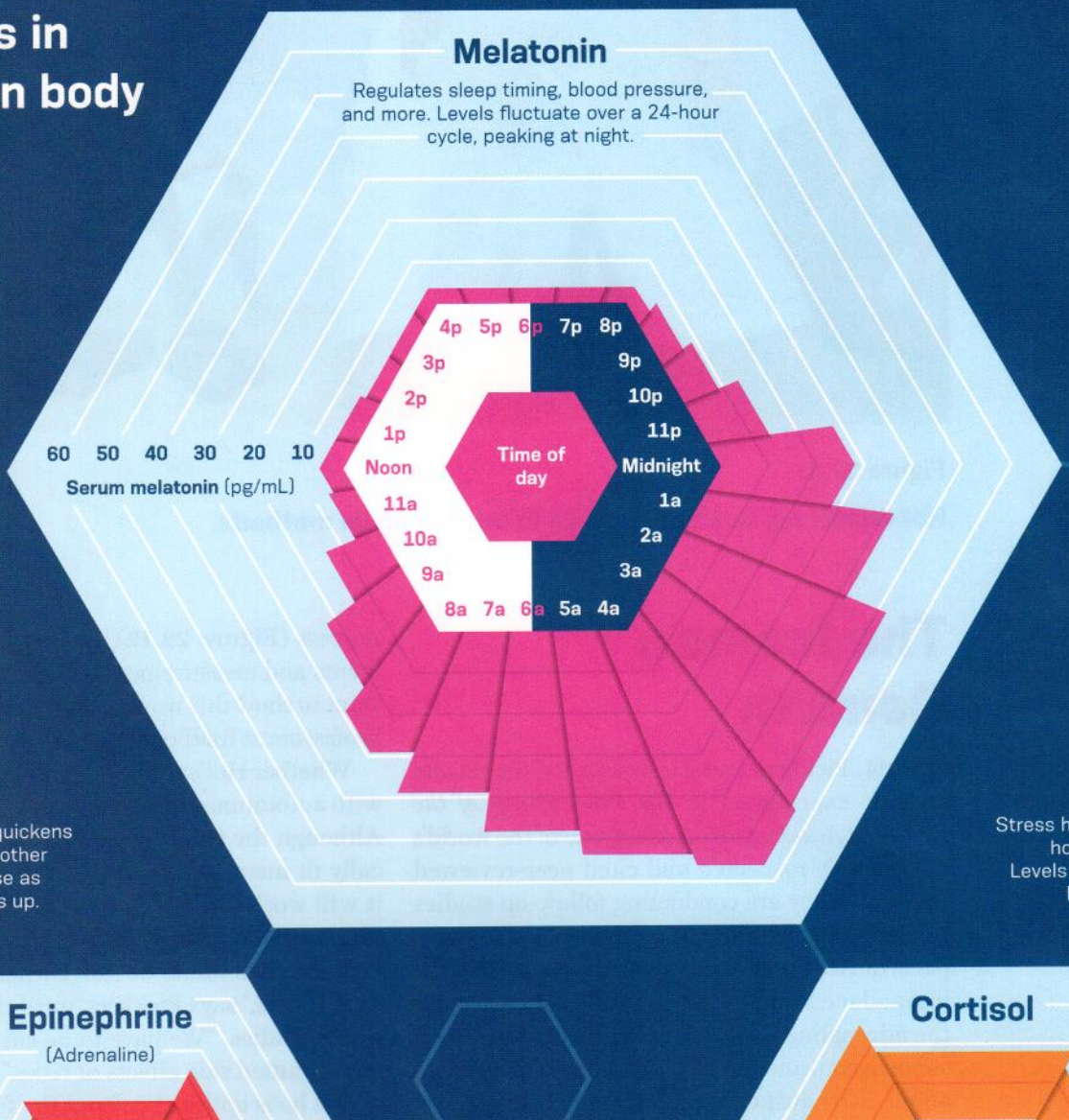
# Driven by Hormones

Hormones regulate not only the classical "fight or flight" response, but also the sleep and wake cycles of all people. These signaling molecules in the blood also become elevated or depressed during periods of stress (cramming for a test, anyone?) and exercise. What are your levels of melatonin, epinephrine, and cortisol right now?

## Hormones in the human body

### Melatonin

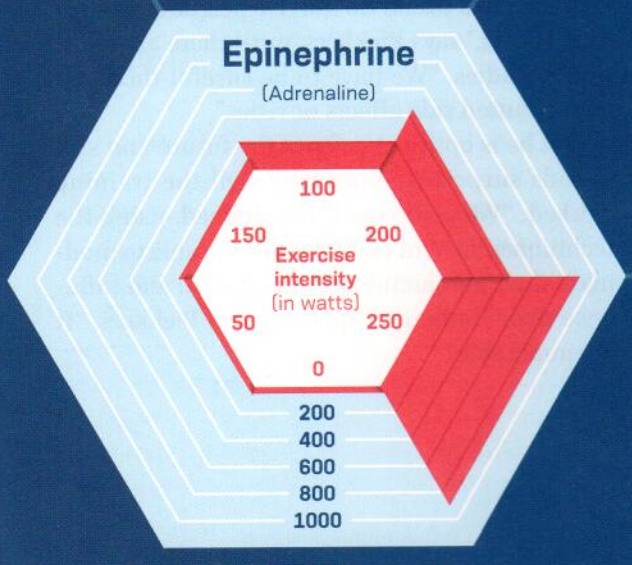
Regulates sleep timing, blood pressure, and more. Levels fluctuate over a 24-hour cycle, peaking at night.




Stress hormone that quickens the heartbeat, among other effects. Levels increase as exercise intensity goes up.

### Epinephrine

(Adrenaline)




Stress hormone that regulates homeostasis in the body. Levels drop during prolonged high-intensity exercise.

### Cortisol

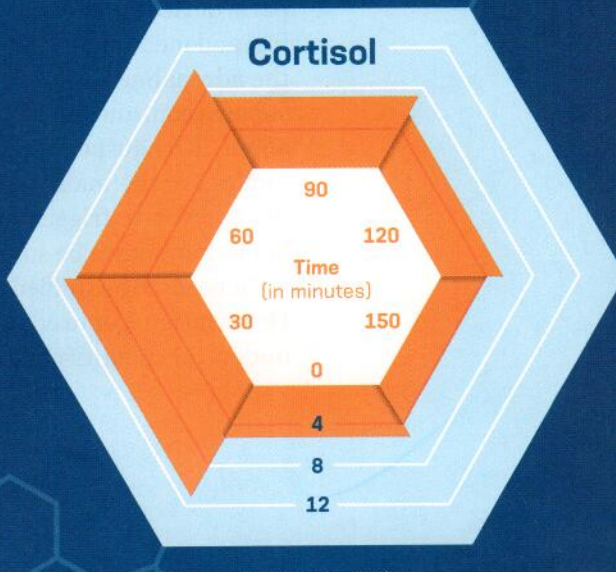


Figure 22.12

**Hof continues to train recruits to use his novel methods**

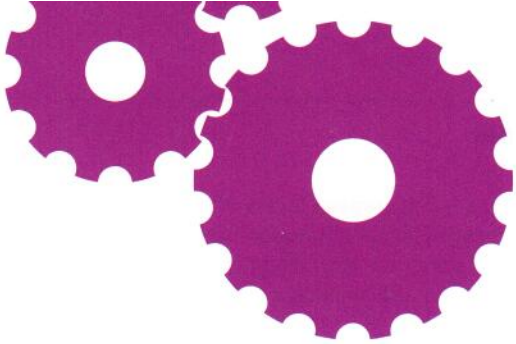
# The Iceman Cometh

In 2014, Pickkers and Kox published the results of their experiment in the *Proceedings of the National Academy of Sciences*, one of the world's most highly respected and cited peer-reviewed journals. They are conducting follow-up studies to determine whether one or more of the three parts of Hof's technique—cold exposure, breathing, and meditation—is primarily responsible for the adrenaline release and subsequent immune suppression, and exactly how these effects come about. Kox suspects that the breathing techniques are the main factor, since Hof's breathing appears to trigger the release of hormones, but he cannot yet be sure.

"It needs to be studied a whole lot more," agrees Hof, who is eager to continue putting his method under the magnifying glass of the scientific process (**Figure 22.12**). "By meticulous experiments and measurements—not speculation—we want to show this works. I'm very thankful to the professors at Radboud who dared to go into this."

Whether Hof's technique can help individuals with autoimmune disorders is still up for debate. Although the training worked for young, physically fit men, the team does not know whether it will work for older people with autoimmune diseases who already have compromised organ systems. "We would not advise people to do this [right now]," says Pickkers, until there are additional studies. "We have to be careful there are no unwanted side effects or risks."

But he is optimistic about the future and still sounds surprised about how well the training worked. "We confirmed that, indeed, using the techniques of Wim Hof, humans are able to modulate their autonomic nervous system and influence their immune response," says Pickkers. "It is remarkable."



## REVIEWING THE SCIENCE

- A **hormone** is a signaling molecule distributed through the body by the circulatory system. Because hormones move only as quickly as the blood moves, they tend to coordinate functions that are slower and longer-lasting than those under the influence of the nervous system.
- A single hormone may affect many different kinds of target cells, potentially triggering a different response in each. Hormones act on target cells either by moving through the plasma membrane to the cell's interior or by acting on receptors embedded in the plasma membrane.
- The **endocrine system** is made up of the glands and specialized cells that produce hormones. The **hypothalamus** coordinates the endocrine system and integrates it with the nervous system. The **adrenal glands** produce hormones responsible for the fight-or-flight response.
- The vertebrate **immune system** possesses three layers of defenses against **pathogens**.
  - The first layer consists of **external defenses**: physical and chemical barriers, including the skin and the linings of the respiratory and digestive systems.
  - The second line of defense is the **innate immune system**. Several types of blood cells and molecules produce the **nonspecific responses** of the innate immune system, including **phagocytes** such as macrophages and neutrophils, which engulf and destroy pathogens. Tissue damage stimulates **inflammation** and blood clotting.
  - The third line of defense is the **adaptive immune system**, providing long-term defenses in the form of **specific responses** to pathogens and parasites. These responses are mediated by powerful proteins called **antibodies**, or by cells.
- The **lymphatic system** provides the primary sites for adaptive immunity. White blood cells called **lymphocytes** confer specific immunity. Immature lymphocytes differentiate into **B cells** in the bone marrow and **T cells** in the thymus. Each lymphocyte has special membrane proteins that bind only to a specific antigen of a specific pathogen.
- The **primary immune response** from the adaptive immune system is relatively slow and mild. The **secondary immune response** is a faster, stronger response to a pathogen that has been encountered one or more times.
- **Active immunity** can be acquired through natural exposure to a pathogen or through a vaccine. **Passive immunity** comes from receiving antibodies that were not made by our own bodies, such as when a fetus acquires antibodies from its mother.

## THE QUESTIONS

### The Basics

1. Hormones are
(a) secretory cells.
(b) endocrine glands.
(c) signaling molecules.
(d) target cells.

2. Which of the following is *not* true of hormones?
(a) They are distributed through body fluids.
(b) They must be present in large amounts to be effective.
(c) They are produced by specialized cells.
(d) They act on target cells.

3. Adrenaline
(a) is produced in the adrenal glands.
(b) increases the amount of glucose in the bloodstream.
(c) suppresses immune system activity.
(d) all of the above

4. The _____ is the immune's system second line of defense.
(a) innate immune system
(b) adaptive immune system
(c) combination of physical and chemical barriers to pathogen entry
(d) all of the above

5. Which of the following is/are *not* a part of the innate immune system?
(a) phagocytes
(b) antibodies
(c) inflammation
(d) clotting

**6** Link each of the following terms with the correct definition.

| | |
|---|---|
| **ADAPTIVE IMMUNE RESPONSE** | 1. The glands and specialized cells that produce hormones. |
| **ENDOCRINE SYSTEM** | 2. The blood cells and molecules that provide a nonspecific response to pathogens. |
| **INNATE IMMUNE RESPONSE** | 3. The organ that coordinates the endocrine system and integrates it with the nervous system. |
| **HYPOTHALAMUS** | 4. Long-term defense against pathogens centered in the lymphatic system. |

**7** Circle the correct terms in the following sentence:

The first time you are exposed to a pathogen, the [**primary, secondary**] immune response is activated. The [**primary, secondary**] immune response to a pathogen is stronger and more rapid. You acquire [**active, passive**] immunity to a pathogen when your own body creates the antibodies against that pathogen. [**Active, Passive**] immunity comes from the antibodies produced by another person, such as your mother when you were in utero or nursing. Vaccines are an example of [**active, passive**] immunity.

**8** Beginning with a perceived threat (for example, a spider), identify the correct order of events by numbering them from 1 to 5.

___ a. Target cells amplify the hormonal signal to produce a response.

___ b. The liver breaks down glycogen to glucose, and the heart increases its rate and the force of its contractions.

___ c. Adrenaline reaches target cells in the liver and heart.

___ d. The hypothalamus signals the adrenal glands that a threat is present.

___ e. The adrenal glands release adrenaline into the bloodstream.

**9** Identify which of the below are characteristics of antibody-mediated (A) or cell-mediated (C) immunity.

___ a. relies on Y-shaped proteins to identify pathogens.

___ b. B-cells produce proteins specific to a pathogen

___ c. lymphocytes matured in the thymus identify infected cells.

___ d. Antigens on the pathogen allow it to be identified as non-self.

___ e. Infected cells are destroyed so that an infection cannot spread to other cells

## Try Something New

**10** Wim Hof and his trainees had increased levels of the stress hormone cortisol and decreased immune function during the experiments described in this chapter. How might these changes negatively affect their endocrine and immune systems over the long term?

**11** Describe in your own words what a B cell is.

**12** Increased body temperature (fever) is part of the body's innate immune response. Fever is uncomfortable and can be dangerous if very high. It is often treated with over-the-counter medicines like acetaminophen, ibuprofen, naproxen, or aspirin. What are possible negative effects of this treatment?

## Leveling Up

**13** **Life choices** While clotting is an important component of the innate immune response, it can also be dangerous. For example, a blood clot may block arteries to the heart or brain, leading to a heart attack or stroke. Aspirin reduces blood clotting by interfering with the body's production of a lipid called thromboxane A2. This lipid normally helps platelets clump together (see Figure 22.10), so aspirin, by inhibiting its production, reduces clotting and "thins the blood." Some doctors may prescribe a daily dose of aspirin for patients at risk of heart attack or stroke. Review the U.S. Preventive Services Task Force recommendations on daily aspirin therapy (http://www.uspreventiveservicestaskforce.org/uspstf/uspsasmi.htm), and then answer the questions below.

(a) Do you fall into one of the categories for which daily aspirin therapy is recommended? If yes, which one? If no, is there an aspirin therapy category that you think you'll be in eventually?

(b) How strong is the evidence supporting aspirin therapy in the category you identified in question (a), if any? (See the "Grade" column in the task force recommendations.)

(c) With this information in hand, do you plan to take aspirin daily?

(d) Will you speak with your doctor before taking aspirin daily? Why or why not?

(e) Do you know anyone who has had a heart attack or stroke? Do they take aspirin daily?

**14 Doing science** Pickkers and Kox say that their next experiment will attempt to determine whether one or more of Hof's techniques—cold exposure, meditation, and breathing exercises—is primarily responsible for the increased cortisol release and decreased immune response. Kox predicts that the breathing exercises will prove to be most important. (You can see a video of the trainees undergoing cold exposure and a trainee during an experiment at http://www.pnas.org/content/111/20/7379.full.) Imagine that it is your responsibility to design the next experiment for Pickkers and Kox. Please include answers to the following questions in the description of your experimental design.

(a) What are your experimental hypotheses?

(b) Give at least one prediction for each of your hypotheses.

(c) Identify your control group and treatment group(s). How many subjects will be in each group? Justify your sample size.

(d) Give a detailed description of the treatment for each group.