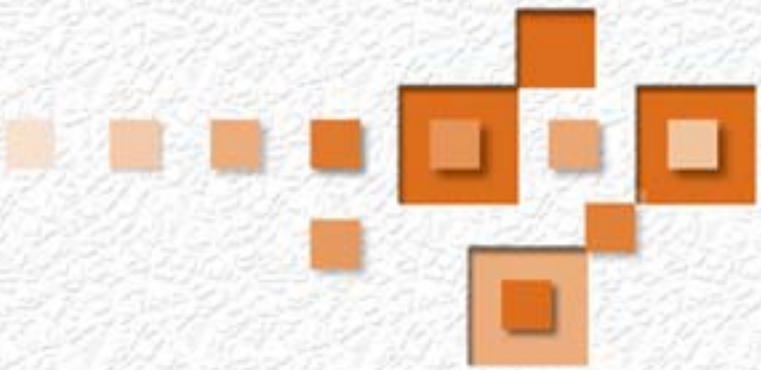
DEADLY DISEASES AND EPIDEMICS

CHICKEN POX



Patrick Guilfoile, Ph.D.

Consulting Editor: Hilary Babcock, M.D., M.P.H.
Infectious Diseases Division, Washington University School of Medicine,
Medical Director of Occupational Health (Infectious Diseases),
Barnes-Jewish Hospital and St. Louis Children's Hospital

Foreword by David Heymann
World Health Organization

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Foreword

Communicable diseases kill and cause long-term disability. The microbial agents that cause them are dynamic, changeable, and resilient: They are responsible for more than 14 million deaths each year, mainly in developing countries.

Approximately 46 percent of all deaths in the developing world are due to communicable diseases, and almost 90 percent of these deaths are from AIDS, tuberculosis, malaria, and acute diarrheal and respiratory infections of children. In addition to causing great human suffering, these high-mortality communicable diseases have become major obstacles to economic development. They are a challenge to control either because of the lack of effective vaccines, or because the drugs that are used to treat them are becoming less effective because of antimicrobial drug resistance.

Millions of people, especially those who are poor and living in developing countries, are also at risk from disabling communicable diseases such as polio, leprosy, lymphatic filariasis, and onchocerciasis. In addition to human suffering and permanent disability, these communicable diseases create an economic burden—both on the workforce that handicapped persons are unable to join, and on their families and society, upon which they must often depend for economic support.

Finally, the entire world is at risk of the unexpected communicable diseases, those that are called emerging or re-emerging infections. Infection is often unpredictable because risk factors for transmission are not understood, or because it often results from organisms that cross the species barrier from animals to humans. The cause is often viral, such as Ebola and Marburg hemorrhagic fevers and severe acute respiratory syndrome (SARS). In addition to causing human suffering and death, these infections place health workers at great risk and are costly to economies. Infections such as Bovine Spongiform Encephalopathy (BSE) and the associated new human variant of Creutzfeldt-Jakob Disease (vCJD) in Europe, and avian influenza A (H5N1) in Asia, are reminders of the seriousness of emerging and re-emerging infections. In addition, many of these infections have the potential to cause pandemics, which are a constant threat to our economies and public health security.

Science has given us vaccines and anti-infective drugs that have helped keep infectious diseases under control. Nothing demonstrates the effectiveness of vaccines better than the successful eradication of smallpox, the decrease in polio as the eradication program continues, and the decrease in measles when routine immunization programs are supplemented by mass vaccination campaigns.

Likewise, the effectiveness of anti-infective drugs is clearly demonstrated through prolonged life or better health in those infected with viral diseases such as AIDS, parasitic infections such as malaria, and bacterial infections such as tuberculosis and pneumococcal pneumonia.

But current research and development is not filling the pipeline for new anti-infective drugs as rapidly as resistance is developing, nor is vaccine development providing vaccines for some of the most common and lethal communicable diseases. At the same time providing people with access to existing anti-infective drugs, vaccines, and goods such as condoms or bed nets—necessary for the control of communicable diseases in many developing countries—remains a great challenge.

Education, experimentation, and the discoveries that grow from them are the tools needed to combat high mortality infectious diseases, diseases that cause disability, or emerging and re-emerging infectious diseases. At the same time, partnerships between developing and industrialized countries can overcome many of the challenges of access to goods and technologies. This book may inspire its readers to set out on the path of drug and vaccine development, or on the path to discovering better public health technologies by applying our present understanding of the human genome and those of various infectious agents. Readers may likewise be inspired to help ensure wider access to those protective goods and technologies. Such inspiration, with pragmatic action, will keep us on the winning side of the struggle against communicable diseases.

David L. Heymann
Assistant Director General,
Health Security and Environment
Representative of the Director General for Polio Eradication,
World Health Organization,
Geneva, Switzerland

1

What Is Chicken Pox?

A 27-year-old woman came to the emergency room in a hospital in England with a mild fever, a rash, and breathing difficulty. She was diagnosed with chicken pox that had developed into pneumonia and was rushed to intensive care. During her hospitalization, her breathing difficulty worsened. She was given oxygen, and eventually a tube was placed in her throat and attached to a respirator to aid her breathing. Her fever worsened. After several days, she developed bacterial infections in her lungs and in her bloodstream, both of which were treated with antibiotics. She remained in intensive care for 20 days; finally, she was transferred to a regular hospital room, and was discharged 8 days later. Although she felt better, a week after her discharge from the hospital she still had limited lung function. Aside from being a cigarette smoker, she did not have any risk factors that would have reduced her immunity and made her vulnerable to developing simultaneous infections.[1] In some individuals, as this case shows, chicken pox can lead to serious complications, such as pneumonia.

Chicken pox is a sudden onset, very contagious disease that is characterized by a widespread, blister-like rash. It typically infects children in temperate regions; adults are more frequently infected in tropical areas. Chicken pox is caused by the varicella-zoster virus, a type of **herpesvirus**. Herpesviruses are a group of viruses that include the herpes simplex virus, which causes cold sores, and the Epstein-Barr virus, which causes mononucleosis. Usually chicken pox is relatively mild, although the symptoms can be unpleasant and uncomfortable. However, it can be a serious, sometimes even fatal infection. Before the widespread use of the chicken pox vaccine in the mid-1990s, there were more than 100 deaths

per year from complications related to chicken pox infection in the United States.[2]

Chicken pox is of particular concern when it affects individuals over the age of 20, because complications are more likely to occur. Complications of chicken pox, serious enough to require hospitalization, were estimated to occur in about 10 cases out of 10,000 in children 14 years old and younger, but about 127 cases per 10,000 in adults 20 and older.[3] These complications include **pneumonia**, secondary bacterial infections, and damage to the central nervous system. In addition, chicken pox is likely to be more serious in patients who have some type of immune deficiency, including patients with certain types of cancer.

CHARACTERISTICS OF THE VIRUS

The varicella-zoster virus belongs to the herpesvirus family, a group of more than 100 viruses that infect a wide variety of animals including fish, reptiles, birds, and mammals. Herpesviruses share the ability to invade animal tissues, cause infection, and subsequently remain dormant until they reemerge and cause a new infection in the same host.

The varicella-zoster virus is a member of the alpha-herpesvirus subfamily, and the alpha-2 herpesvirus **genus**. The varicella-zoster virus is most closely related to the equine herpesviruses that infect horses, and the pseudorabies virus that infects pigs. Even though the varicella-zoster virus is most similar to animal viruses, the only known host for the varicella-zoster virus is humans, although some laboratory animals can be infected, at least for short periods of time. However, these animals do not develop an infection that mimics all the symptoms of an infection in humans. The varicella-zoster virus is also related, but not as closely, to the human herpes simplex viruses that cause cold sores and genital lesions. Genetic comparison of mammalian herpesviruses suggests they have been evolving from a common ancestor for approximately 75 million years.[4]

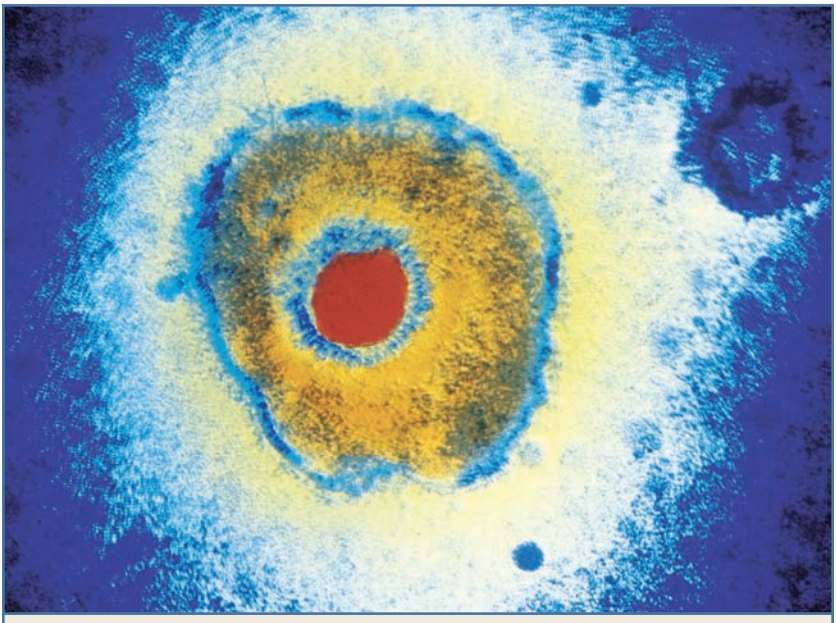

Figure 1.1 Electron micrograph of the varicella-zoster (chicken pox) virus. (©Institut Pasteur/Phototake)

Like other herpesviruses, the varicella-zoster virus contains double-stranded DNA located inside a protein structure called a **capsid**. **Tegument proteins** are also present inside the capsid; these proteins are critical for **replication** (copying) of the viral DNA inside host cells. The capsid is wrapped in an **envelope** made of fats. This envelope comes from membranes manufactured by the infected cell.[5] Embedded in the envelope are several viral proteins required for attachment and entry into human cells, the viral **glycoproteins**. Glycoproteins are proteins that are decorated with sugar molecules. This fatty envelope also means that the virus is less stable in the environment than other viruses that lack an envelope. Once it is outside the body it dries out and can no longer invade human cells, so it is unable to cause infection.

Like most viruses, the varicella-zoster virus is very small (150 to 200 **nanometers**), roughly one-tenth the size of a typical bacterial cell. Also, like most viruses, this microbe can replicate very rapidly, requiring only about 8 to 10 hours between entry into the cell and the appearance of new viruses in that cell, based on studies of infected cells in the laboratory.[6] The infection of a single cell with one virus probably results in the production of hundreds of new varicella-zoster viruses, although the exact number has been difficult to determine experimentally. The virus typically passes from cell to cell when the cell membrane of an infected cell fuses with the membrane of an adjacent, uninfected cell. Consequently, the viruses rarely separate from cells, so they are hard to count.

Unlike many viruses, the varicella-zoster virus does not appear to **mutate** (change its DNA) at a rapid rate. There are no identified subtypes of the virus, and there have not been any identified strains that appear to have enhanced or lower **virulence**. Virulence is associated with the ability to cause disease; more virulent **pathogens** are more readily able to cause disease, or cause a more serious form of the disease.

As noted above, the varicella-zoster virus is related to the herpes simplex Type 1 virus. For example, these viruses share many genes, and the order of genes in the **genomes** of both viruses is similar. However, since the varicella-zoster virus has a smaller genome, it lacks some of the genes found in the herpes simplex Type 1 virus and other herpesviruses.[7] Because of these genetic differences, the life cycle of these two viruses is somewhat different. For example, the varicella-zoster virus normally reactivates once in a person's lifetime, leading to the development of **shingles.** Shingles, which occurs when the original varicella-zoster virus emerges and causes new disease symptoms, often occurs decades after a person is first infected with the varicella-zoster virus. In contrast, herpes simplex Type 1 virus infections are characterized by frequent

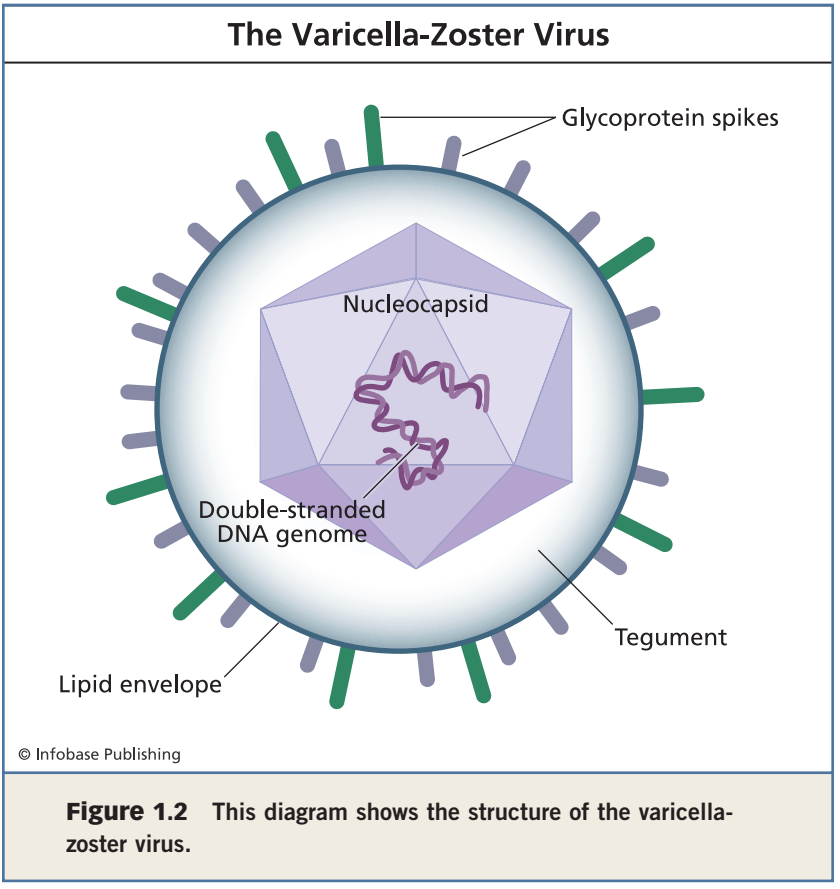

Figure 1.2 This diagram shows the structure of the varicella-zoster virus.

reactivations, seen as the eruption of cold sores. Further research should identify the genes responsible for these differences in life cycle.

TRANSMISSION OF CHICKEN POX

Most commonly, the virus is passed from one person with chicken pox to an uninfected, susceptible person. The virus initially infects the respiratory tract, because the virus is inhaled, or picked up from direct contact with the fluid from the sores of a person with chicken pox. An adult with shingles can also

transmit the virus, although rarely, causing chicken pox in a susceptible person.

In many countries, chicken pox is more common during certain seasons. In the Northern Hemisphere for example, the incidence of chicken pox has been highest during the spring (March to June). In several developed countries (e.g., the United States, United Kingdom) the average age of infection has dropped in recent decades, perhaps reflecting a larger proportion of children using day care centers, where they may be exposed to the virus prior to the start of school.

Before the development and widespread use of a chicken pox vaccine, it was estimated that 3 to 4 million cases of chicken pox occurred each year in the United States, and that 90 percent of those cases were in children under 13 years of age. With the widespread use of the vaccine, the number of cases has been reduced approximately 90 percent, to somewhere between 400,000 and 600,000 cases per year.[8]

Close contact with an infected person leads to the development of chicken pox. A second child in a household with one chicken pox case has a 70 to 90 percent risk of contracting the disease. Often the second child develops a more severe case of chicken pox, with more lesions. This is probably because he or she is infected with a higher dose of the virus than the first child, who may have acquired the disease during a brief interaction with an infected child at school. An infected person can transmit the disease for approximately two days before the characteristic rash develops, and a person remains infectious until all the chicken pox sores become crusted over, usually about a week. Normally, a person only gets chicken pox once in his or her lifetime, although there have been a few reports of multiple infections,[9] and one study from California that suggested that upwards of 10 percent of chicken pox infections may be reinfections.[10]

The pattern of transmission is quite different in the tropics. As noted above, in temperate regions, prior to the widespread

use of a vaccine, the number of cases approximated the annual birth rate, meaning that relatively few individuals (only about 5 percent) reached adulthood without contracting chicken pox. In contrast, in the tropics, approximately 50 percent of individuals reach adulthood without having chicken pox.[11] There have been a number of possible explanations for the low rates of chicken pox during childhood in the tropics, including limitations on virus transmission at higher temperatures. However, the phenomenon appears to be a consequence of reduced transmission of chicken pox in rural areas. In 1998, researchers from the United Kingdom and India studied about 400 people living in urban and rural areas of India. They found that 96 percent of urban dwellers had evidence of chicken pox infection by age 25. In contrast, only 42 percent of people living in rural areas contracted chicken pox by age 25.[12] In rural areas people live farther apart and may be less likely to come in contact with an infected person.

SYMPTOMS OF CHICKEN POX

The symptoms of chicken pox are variable, depending on the age of the patient and whether the person has an intact immune system. As a rule, the illness is mildest in young children with a normal immune response, and most severe in people who are older, and among those who are immunocompromised. For example, in the 1990s, the mortality rate from chicken pox in the United States was 15 times higher in adults, as compared with children. As another example, patients with leukemia (a cancer that affects the white blood cells that fight infections) are much more susceptible to chicken pox, and more frequently develop serious complications.

In a typical childhood infection, the disease has a substantial **incubation period** (an average of about 14 days) prior to the development of the first symptoms. A mild fever is common, usually less than 102°F (39°C), but occasionally as high as 106°F (41°C). This fever, along with headache, pain in the abdomen, and a general feeling of ill health often are present a day or

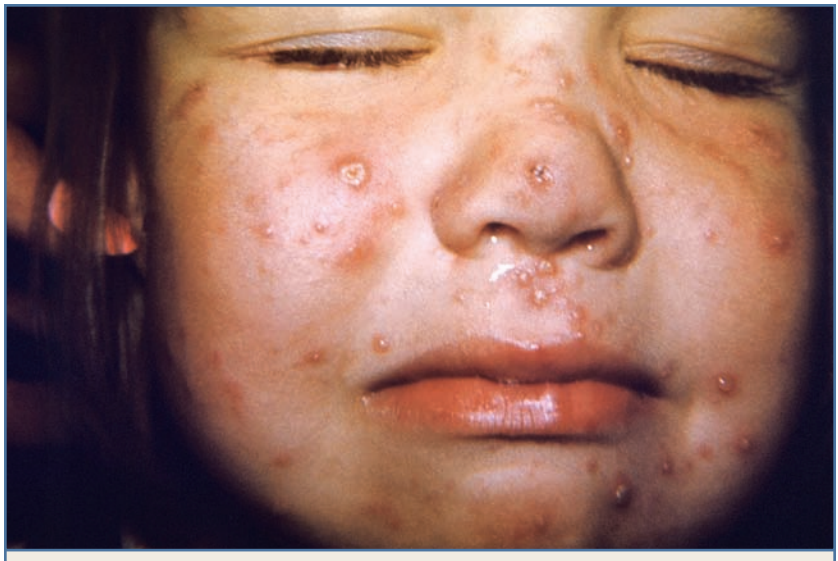

Figure 1.3 Child with chicken pox. (Dr. John Noble, Jr./Centers for Disease Control/ U.S. Department of Health and Human Services)

two in advance of the primary symptom, a widespread rash. The rash is composed of little fluid-filled sacs, which are surrounded by reddened skin. These lesions often first appear on the face or torso and eventually extend to the extremities. In an otherwise healthy child with no previous exposure to the virus, about 100 to 300 of these lesions typically develop, although the range is broad, with as few as 10 lesions and as many as 1,500. New vesicles, or pox, generally develop for 3 to 5 days, until the immune system wins the battle with the virus and new lesions no longer form. Eventually, the pox lesions crust over and fall off. Usually there is not much scarring, although the skin often loses its pigmentation for a time at the site of the lesions.

COMPLICATIONS OF CHICKEN POX

Chicken pox in a young child rarely leads to complications. However, the older a person is when they contract chicken pox,

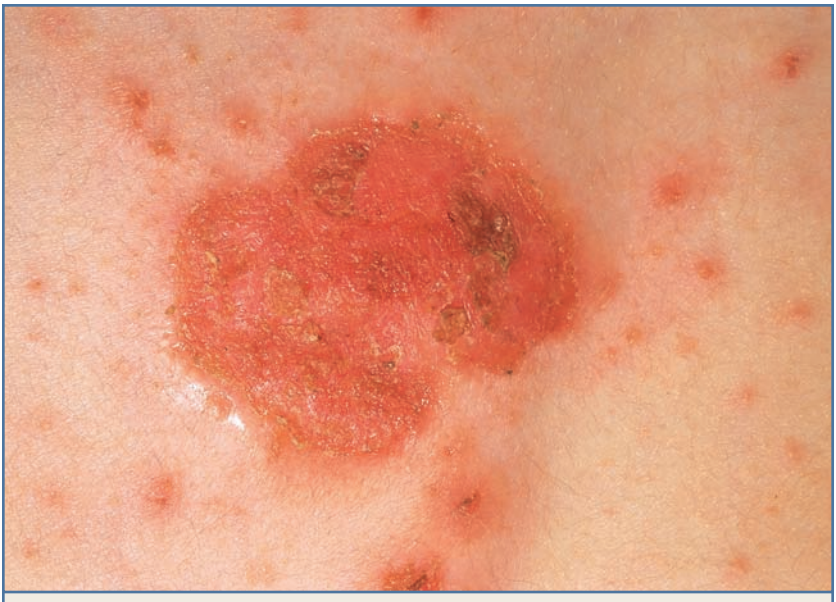

Figure 1.4 An infected chicken pox lesion. In some cases, infections of the chicken pox blisters can lead to serious complications, even death. (© Pulse Picture Library/CMP Images/Phototake)

the greater the chance of serious complications. One example of a complication following chicken pox is a bacterial infection of the skin at the site of a chicken pox vesicle. The most serious infections are caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. These infections can range from local infections of a few chicken pox vesicles to infections that involve tissues throughout the body. The widespread infections can be very serious, even life threatening.

Another potential complication is Reye's syndrome. This illness causes damage to the liver and may cause serious alterations to the nervous system. Reye's syndrome has been linked to cases of chicken pox where a patient took aspirin to treat symptoms of the disease. As a consequence of this connection, since 1980 public health authorities have recommended that children

who have viral illnesses such as chicken pox not take aspirin. As physicians and parents became aware of this connection, the number of cases of Reye's syndrome has dropped dramatically in the United States, from 555 cases in 1980, to fewer than 36 cases per year since 1987. This was an important advance in public health, because the death rate, following a diagnosis of Reye's syndrome, was nearly one in three.[13]

In adults, one of the more serious and frequent complications of varicella-zoster infection is chicken pox pneumonia. Pneumonia is associated with fever, cough, wheezing, shortness of breath, and difficulty breathing. As noted in the case study at the beginning of this chapter, this form of pneumonia can lead to serious disturbance of respiratory function and prolonged

VISION CORRECTED BY CHICKEN POX

Typically, an illness does not improve a patient's health. An exception to that rule was a report of a case of chicken pox in an 11-year-old girl from England, who was nearsighted and required glasses for distance vision. The girl initially went to her family doctor with a complaint of pain in her right eye, and hazy vision. Three weeks earlier, she had had chicken pox. She was given a treatment for inflammation of the eye, and sent home. A week later, she went back to the eye clinic, still complaining of hazy vision. An examination showed that the vision in her right eye had suffered as a result of scarring due to chicken pox. However, a year later, her eyesight was rechecked, and the vision in her right eye was found to have markedly improved. Over the year, the scarring in her right eye partially healed. As a result, the surface of her eyeball had become flattened, largely correcting the vision in that eye. This correction was so significant that she no longer needed glasses; she relied on her left eye for near vision, and her right eye for distance vision.[14]

hospitalization. The death rate for healthy adults who contract pneumonia following chicken pox is estimated to be as high as 30 percent.[15]

Complications involving the nervous system occur most commonly in adults or children under five years of age. Usually these disorders begin a few days after the first signs of the typical chicken pox rash. These complications include **encephalitis** (inflammation of the brain), which can result in loss of consciousness and seizures. Another serious neurological complication of chicken pox is **cerebellar ataxia**, a disturbance of the brainstem that causes affected patients to move in an uncoordinated manner, show uncontrolled movements of the eyeballs (nystagmus), and experience a loss of balance.

In adults, another rare complication of varicella virus infection is uncontrolled bleeding. In these very isolated incidents, patients develop bleeding disorders due to a loss of **platelets** following chicken pox. (Platelets are components of the blood that aid in blood clotting.) In severe cases, these bleeding disorders can even be fatal. Most of the time, though, a patient with a bleeding disorder due to chicken pox recovers without any lasting harmful effects.

Kidney damage is another rare complication of chicken pox. It is not clear if this is due to the varicella virus itself, or to subsequent infection with the bacterium *Streptococcus pyogenes* following chicken pox. A few other complications such as arthritis and inflammation of the heart have been reported following chicken pox, but these complications occur so rarely that it is not clear if they are caused by the varicella-zoster virus.

Other serious complications of varicella-zoster infection may occur during pregnancy. If the pregnant woman develops chicken pox during the first 20 weeks of a pregnancy, in about 1 percent of cases, the infection results in severe malformations of the fetus. These deformities frequently include shortened limbs, eye defects, and brain damage. In addition, if the mother

develops chicken pox a few days before or after giving birth, there is also a risk of serious harm to the infant. Up to 30 percent of these infections may be fatal to the infant, although there is some question about the accuracy of these figures.[16]

Individuals who are immunocompromised are more likely to develop serious complications, including a varicella-zoster virus infection that spreads throughout the entire body, which can lead to damage to the lungs, liver, and other organs. Prior to the development of effective treatments, one-third to one-half of children with several types of cancer developed these disseminated infections, which were fatal about 10 percent of the time.[17]

In addition, patients who received organ transplants or those who receive steroids for treating arthritis or other conditions are at increased risk for severe varicella infections. This is also true for people with acquired immunodeficiency syndrome (AIDS) or genetic immunodeficiencies. Even in the absence of complications, individuals suffering from immunodeficiences tend to have a longer period of illness, with a more extensive rash and more lesions.

PROBLEMS DIAGNOSING CHICKEN POX

Historically, one of the primary sources of confusion for diagnosing chicken pox was **smallpox**. Both diseases are characterized by raised bumps and rashes that spread across the body, although smallpox was a much more serious illness that caused about one death for every three infections. However, since the eradication of smallpox in 1977, confusing these two diseases is no longer a problem for physicians or their patients.

The remaining illnesses that may sometimes be confused with chicken pox include a variety of diseases that manifest with some type of rash. For example, impetigo is a skin infection caused by bacteria of the genus *Streptococcus,* which sometimes has the appearance of small bumps at and near the place where the bacteria entered the skin. A diagnosis is made

by taking some skin scrapings and looking for the presence of ball-like bacteria, strung together in chains, in those wounds. The presence of these bacteria indicates a disease called impetigo, rather than chicken pox. This diagnosis is critical because the treatment of chicken pox and a bacterial skin infection are very different.

Scabies, a skin disease caused by an infestation with a small mite, can cause raised pimples that resemble chicken pox. Rickettsialpox, a bacterial infection transmitted through the bite of a mite, also causes a rash and can sometimes be mistaken for chicken pox. A viral infection called hand-foot-and-mouth disease can produce a rash that may appear to be similar to chicken pox.

Other conditions that may be confused with chicken pox included rashes resulting from some type of allergic reaction, or the bites of midges or mosquitoes which, if prevalent enough, could give an appearance of widespread raised bumps on the skin similar to chicken pox.

CHARACTERISTICS OF SHINGLES

Most viruses have a hit-and-run lifestyle. They get in the body, cause an acute infection, and then are permanently evicted by the immune response. Varicella-zoster virus has a very different natural course. It does cause chicken pox, a short-term, acute infection. However, instead of being completely eliminated from the body as the disease wanes, the virus invades nerve cells, where it lies dormant until the immune defenses break down, perhaps decades after the initial infection. This second outbreak is called shingles (the medical term is Herpes Zoster, or Zoster). Shingles is a painful illness with an outbreak of chicken pox–like sores along the path of a nerve.

Shingles is particularly common in individuals with certain types of cancer such as leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma. It is also common in individuals who are immunosuppressed as a result of receiving an organ transplant,

and in patients with HIV infection. However, most people who get shingles do not have an underlying medical condition, although the elderly are most likely to be victims. There is now a Zoster, or shingles, vaccine for people over 60 years old. This manifestation of the varicella-zoster virus will be described in more detail in Chapter 7.

2

The History of Chicken Pox

Chicken pox, like many other infectious diseases, has left its mark on human history. For example, Sayyid Basir Hindi, a key figure in the early years of the Baha'i faith during the mid-1800s, was blind as a consequence of a chicken pox infection at the age of seven. He was considered a mystic, and it is likely that his blindness helped create an aura that contributed to his success as a religious leader.[1]

Chicken pox has likely been a human affliction for thousands of years. For example, there is suggestive evidence of chicken pox in ancient Babylonia more than 2,000 years ago.[2] As a typically mild illness, though, chicken pox did not make it into historical accounts until the 1500s, when Giovanni Filippo, an Italian doctor, provided a description of this disease, and distinguished between chicken pox and scarlet fever. In 1694, Richard Morton, an English doctor, reported on a mild form of smallpox that he called chicken pox. However, many doctors confused smallpox and chicken pox because of the initial similarity of the rashes in both conditions. It was not until 1767 that another English physician, William Heberden, first made a definitive distinction between the two diseases, including a list of criteria that distinguished smallpox and chicken pox.[3]

For a number of years, there was still some confusion about the distinction between chicken pox and smallpox. William Osler, for example, in 1892, had to argue that "there can be no question that varicella [chicken pox] is an affection quite distinct from variola [smallpox] without at

Figure 2.1 In 1767, English physician William Heberden became the first person to make a definitive distinction between chicken pox and smallpox. (National Library of Medicine/U.S. National Institutes of Health)

present any relation whatever to it. An attack of one does not confer immunity from an attack of the other." He then went on to describe a case of a five-year-old boy who was admitted to a hospital with a case of chicken pox. He was on the same floor as smallpox patients and developed smallpox eight days later. The fact that a patient was able to simultaneously get infected with

both diseases was strong support that smallpox and chicken pox were entirely different afflictions.[4]

In 1904, Ernest Tyzzer provided further experimental evidence that chicken pox and smallpox were different diseases, while studying a chicken pox outbreak at a prison in the Philippines. Tyzzer noticed that many of the patients with chicken pox had either scars from a previous smallpox infection, or from smallpox vaccination. This made it extremely unlikely that these individuals were suffering from another case of smallpox, because it was well documented that either vaccination or infection normally protected a person from contracting smallpox again. Tyzzer was also aware that smallpox would cause signs of infection in monkeys and in the corneas of rabbits. Consequently, he placed fluid from prisoners with chicken pox into the eyes of rabbits and injected the fluid from chicken pox lesions into monkeys. No signs of infection developed, further affirming the distinction between chicken pox and smallpox. He also studied the lesions microscopically and observed the presence of very large cells in the skin lesions of patients with chicken pox. These cells were not found in cases of smallpox, so this provided a potential means of distinguishing the two ailments.

THE IDENTIFICATION OF THE VARICELLA-ZOSTER VIRUS

A starting point to the identification of the varicella-zoster virus was the work by Johann Steiner, who in 1875 inoculated children with fluid from a patient with chicken pox, after which the children developed the disease; this made it clear that chicken pox was an infectious disease. Investigations by a number of researchers in the 1920s through the 1940s showed that unusual structures were present inside skin cells from patients with chicken pox. Based on investigations with other infectious agents, these unusual structures were identified as the hallmark of a viral infection.

As with all scientific discoveries, many scientists contributed to the final understanding. In the case of any pathogen, the definitive identification normally requires that the pathogen be separated from all other organisms in a culture. This is normally followed by infection of laboratory animals to see if they show symptoms of the disease, and then the re-isolation of the pathogen from the laboratory animals.

THE ORIGIN OF NAMES FOR CHICKEN POX AND SHINGLES

The history of the name "chicken pox" itself is somewhat unclear. Thomas Fuller, in 1730, attributed the name to the type of lesions expected if a chicken pecked the skin. Another explanation was that the lesions look similar to chickpeas (although the term chicken pox was apparently used prior to the origin of the term "chickpeas"). Yet another explanation is that the term chicken pox is derived from the Old English word gican, meaning "itch." There was also a suggestion that chicken pox derived from the name of a coin of small value, the "chequeen." Perhaps the most plausible explanation is that the name came from chicken pox being a minor infection, in comparison with smallpox, which was much more likely to be fatal. This was suggested by Samuel Johnson, in his dictionary, in 1755, and subsequently by other authors.[5]

Similarly, the history of the name varicella is also disputed. Some have claimed that it is derived from a term that means a minor form of smallpox. Others have felt that the term is derived from the word *varus* meaning "pimple."[6]

The origin of the word "shingles" is more generally accepted; it comes from the Latin term *cingulus* for "girdle." The derivation of the synonym for shingles, "zoster," is also generally accepted. The term comes from the Greek, where *zoster* means "belt." Both terms highlight the usually band-like distribution of shingles lesions on the body.[7]

The first attempts to do this, by Ernest Tyzzer, involved laboratory animals and were unsuccessful. Later, in 1944, Ernest Goodpasture and Katherine Anderson tried to grow the virus in cultures in the laboratory. They used skin taken from a woman who had undergone surgery for breast cancer, with the idea of using the tissue as a culture medium for the virus. After the skin was removed from the patient, it was treated with iodine and alcohol to remove contaminating bacteria, cut into small pieces, and placed on blocks of sterile cork for further manipulation. Then, a needle and syringe was used to remove some of the fluid from shingles lesions from a two-and-a-half-year-old child. The skin from the woman was subsequently injected in multiple places with this fluid, and the skin was then grafted to 12 nine-day-old chicken embryos. Finally, these researchers microscopically examined the grafts for the presence of characteristic cells associated with chicken pox. They found those characteristic cells, suggesting that the presumed virus could be grown in culture. This work opened the door for future experiments.[8]

However, it was laborious to graft human skin to chicken embryos, so researchers, most notably Thomas Weller, tested new methods of growing the varicella-zoster virus in the laboratory. His initial attempts to grow the virus using tissues from human embryos or chicken eggs were unsuccessful. Consequently, on the suspicion that the virus had an affinity for human skin, he attempted to grow the virus in samples of fetal skin tissue. Saliva from children with chicken pox was used to inoculate the tissue cultures. This also failed, however. (An explanation came later when it was determined that the virus is rarely found in the saliva.) By 1952, using cells from human embryos and human foreskin, Weller finally had a system that consistently allowed infection of human cells with varicella-zoster virus. For these experiments he used fluid from chicken pox lesions to infect the human cells. The lesions had a much

higher concentration of the virus, and were therefore more effective in infecting cells in the laboratory than saliva.[9]

As noted, there was no animal model for the varicella-zoster virus that allowed for growth of the virus and mimicked the symptoms of the human disease. Therefore, to verify the identity of the virus, Weller would have needed to infect human volunteers, something that would be unethical. Instead, Weller did the next best thing and used **antibody** tests to verify that the virus growing in his cultures was the same type of virus that was found in children with chicken pox infections. He did this by taking **serum** (the liquid portion of the blood) from people who had recently recovered from chicken pox. This serum contained specific antibodies against the virus that caused the disease. These antibodies reacted against the virus and therefore demonstrated that the virus, grown in culture, was the same virus that caused chicken pox. This result was first demonstrated in 1954 and subsequently confirmed with additional reports published in 1958.[10]

THE SAME VIRUS CAUSES CHICKEN POX AND SHINGLES

In 1892, James Bokay, a professor in what is now the country of Hungary, studied five cases of people who developed chicken pox after they were exposed to people with shingles. He suggested that the agent that caused shingles might therefore be the same as the agent that causes chicken pox.

About 30 years later, B. Lipschutz showed that when the vesicles from people with chicken pox or shingles were examined with a microscope, the appearance of the cells and other features were similar between the two diseases. In 1925, K. Kundratitz took material from the lesions of patients with shingles and transferred it to children who had never had chicken pox. These individuals developed a disease identical to chicken pox.

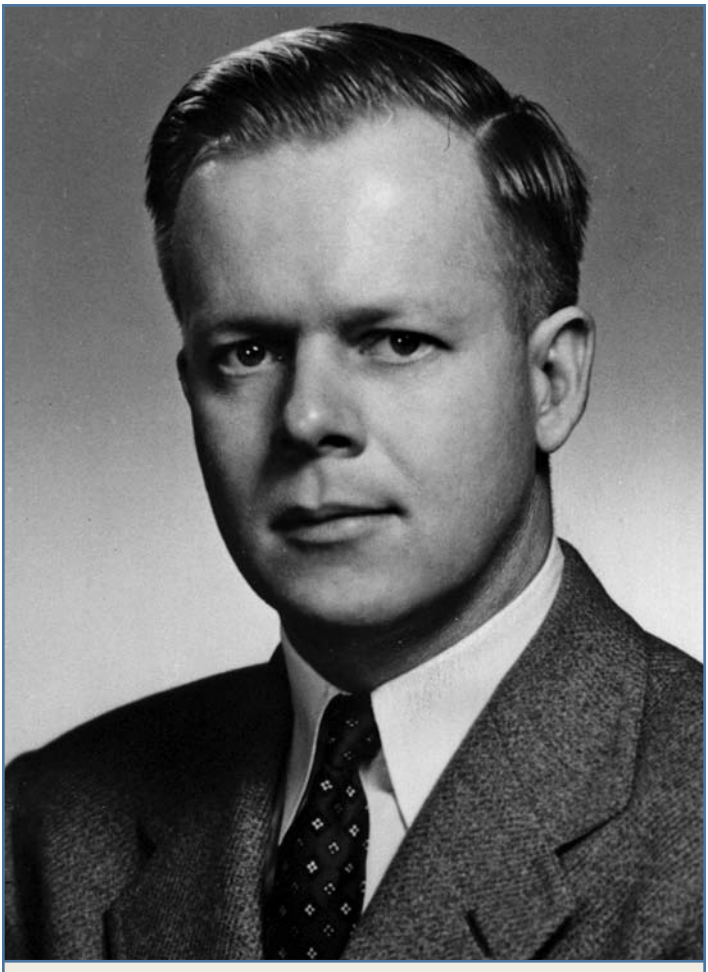

Figure 2.2 Dr. Thomas Weller, the first person to grow the varicella-zoster virus in cell culture. (National Library of Medicine/U.S. National Institutes of Health)

During the 1920s and 1930s, antibody tests were used to compare the agents of chicken pox and shingles. People who had chicken pox developed antibodies that reacted against shingles skin lesions. Similarly, people with shingles developed

antibodies that reacted against chicken pox skin lesions. By the 1940s, the **electron microscope** was becoming widely used (this was the only microscope powerful enough to view viruses). Seen through the electron microscope, the viral particles in shingles vesicles appeared to be identical to the viral particles in chicken pox vesicles.

More definitive evidence that the virus causing chicken pox and the virus causing shingles were identical came from growth of the viruses in culture. Antibodies from patients with shingles reacted against viruses in culture from patients with both shingles and chicken pox. The converse was also true; antibodies from patients with chicken pox reacted against viruses in culture from patients with both shingles and chicken pox.[11]

Further work focused on whether the virus that causes shingles was the result of a new infection of the varicella-zoster virus, or whether it involved reactivation of virus from the original chicken pox infection. By the 1980s, genetic techniques were becoming powerful enough to address that question. **Enzymes** had been discovered (called **restriction enzymes**) that cut DNA at specific sequences. Individual varicella-zoster viruses that infect different people may have slightly different DNA sequences, and if these sequence alterations affect the sites cut by restriction enzymes, digestion with these restriction enzymes will produce unique patterns from the viral DNA isolated from different individuals. Similarly, if the same virus strain causes chicken pox and then shingles, using this technology it should be possible to determine that the viruses are identical. Researchers did this experiment, isolating DNA from the varicella-zoster viruses from a patient who had chicken pox. They subsequently isolated DNA from varicella-zoster viruses from the same patient when he or she later developed shingles and found that the patterns generated by the restriction enzymes were identical, suggesting that the same exact strain of the virus that first caused chicken pox later became reactivated and caused shingles.[12]

This technique of using restriction enzymes was somewhat crude, in that it only could measure DNA sequence differences that affected sites cut by restriction enzymes; this allowed only a small portion of the viral genome to be scanned. Subsequently, a technique was used to scrutinize each individual portion of a genome (each individual nucleotide). This technique was called **DNA sequencing**. The DNA sequence of the virus used to vaccinate an infant was compared to the DNA isolated from a virus that later caused shingles in the same patient. The viral DNA was very similar, providing confirmation that the virus responsible for chicken pox and shingles in an individual is the same strain, from the original chicken pox infection or vaccination.[13]

In the history of the study of chicken pox and shingles, awareness grew of the potentially serious nature of varicella-zoster infections, at least in some people. This led to research into the development of effective treatments and preventative measures.

3

Chicken Pox in Young Children

A three-year-old boy had a play date with a two-year-old girl. After an afternoon of constructing paper plate masks of monkeys and playing "jungle," the boy went home. The next night, his mother noticed the start of a characteristic chicken pox rash on his left shoulder. Two weeks later, the girl developed the disease as well. Both children had a mild fever and felt lethargic and ill for a week or so, starting around the time the rash first developed. They recovered without any complications or long-term health concerns.

Until the widespread vaccination of children in the United States in the 1990s, it was estimated that 95 percent of all American children developed chicken pox before adulthood.[1] Consequently, the childhood form of chicken pox is widely regarded as the natural form of the disease, at least in temperate regions of the world.

THE CAUSE OF CHICKEN POX SYMPTOMS

Generally, symptoms associated with an illness result either from some factor produced by the pathogen, or the body's response to the pathogen. In the case of chicken pox, it appears that the symptoms result both from viral damage, and from the body's response to infection.

The characteristic pox lesions are the result of viral damage to the skin cells. Infections with the virus start in the bottom layers of the skin (the dermis) and move toward the surface. Initially, skin cells located near the blood vessels show signs of infection, probably as a result of their contact

with infected cells of the immune system called **T-cells**. Following infection, these skin cells become swollen. Eventually, these cells degenerate and release virus-filled fluid into the surrounding tissue resulting in the formation of the characteristic chicken pox lesions. The fluid in these vesicles contains a high concentration of the varicella-zoster virus.[2]

Fever is another common symptom of chicken pox. A region of the brain, the hypothalamus, controls body temperature in humans. A variety of substances, either released from pathogens, or from cells in the body in response to infection, can cause fever. In the case of chicken pox, **interferons** are one of the products produced by cells in response to viral infection, and interferons are known to stimulate the production of a fever. Interferons become present at high concentrations in the blood following infection with the varicella-zoster virus. Some of these interferons enter the brain and lead to a change in the biochemistry of the hypothalamus that, in turn, alters the temperature set point for the body. This is an example of an immune system reaction (the production of interferons) leading to symptoms of illness.[3]

THE CELL BIOLOGY OF CHICKEN POX

The molecular details of how the varicella-zoster virus actually causes disease are not entirely clear, largely because of the lack of a simple animal model of chicken pox. Therefore, until quite recently, much of what was known or hypothesized about the ability of the virus to cause disease was based on studies of humans with chicken pox and a study of an animal model for another viral disease. For example, studies of how the mousepox virus causes disease in mice led to inferences about chicken pox in humans. More recently, studies of chicken pox in mice have provided more detailed information. These studies have involved the use of a strain of mouse with a condition called **severe combined immunodeficiency** (SCID).[4] These mice have little natural immune response, so they can readily

accept human cells and human tissues, unlike mice with a normal immune system. These mice have had human immune system cells injected into their systems, and human skin grafts attached to their bodies. The result is a mouse with portions of the human immune system, and sections of human skin, to mimic some elements of chicken pox infection in humans. These human tissues and cells allow the varicella-zoster virus to establish an infection in mice and allow for a study (at least in part) of what happens during an infection in humans.

In addition, studies of cases of human infection, where the time between infection and symptoms of the disease were shortened, also provided information about the natural history of the virus in the body. In these cases, patients either had fluid from chicken pox lesions directly transferred to their skin, or infants got chicken pox from their mother right after birth and, being infants, had a poorly developed immune response that allowed the virus to replicate rapidly.

Based on these studies and other information, it appears that the initial infection occurs in the throat or upper respiratory tract. From there, the virus invades the lymph nodes near the site of infection and replicates, likely in the tonsils in the throat. Originally, based on studies of the mousepox virus, it was thought that the virus then spread through the blood to the internal organs, like the liver, and replicated there for some time, before it spread to the skin. This was based, in part, on the long incubation period between infection and symptoms (averaging about 14 days, with a range of 10 to 20 days). Now, based primarily on studies in the SCID mouse containing human skin and immune cells, it appears that the virus infects a type of human immune cell called **memory T-cells**.

T-cells are white blood cells that play several critical roles in the immune response. Memory T-cells are long-lived T-cells that are initially produced in response to a particular infection. These memory T-cells can also shuttle the virus to the skin. Once there, the virus apparently infects skin cells

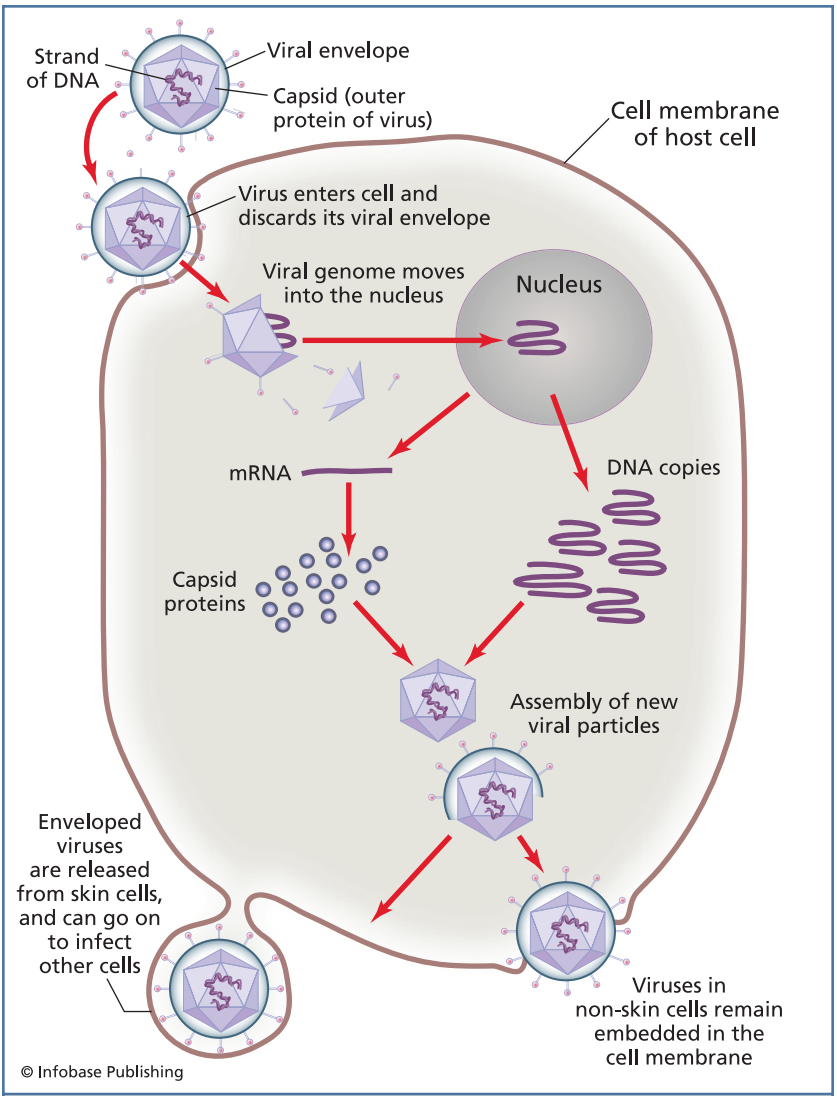

Figure 3.1 This diagram shows the process of viral infiltration into cells. The virus's DNA enters the host cell's nucleus and uses the nucleus to replicate. After new viruses are produced they leave the host cell—sometimes destroying the host cell—and proceed to infect other cells.

and begins replicating. Initially, the virus replicates slowly in the skin cells. This is thought to be in part because of the chemicals the skin cells naturally produce (antiviral molecules like interferon alpha). As the virus infects skin cells, it prevents infected cells from making those antiviral chemicals. Eventually, enough cells are infected, and enough viruses are produced, that skin damage becomes evident in the form of lesions and a rash. The continued formation of additional skin lesions is likely the result of new memory T-cells being infected, traveling to and establishing infections in new sites in the skin, and causing more damage.[5] As noted above, the entire process from infection to the appearance of a skin rash is typically about 14 days. Normally, new lesions develop on the skin for three to five days, and the person remains infectious until all the lesions crust over.

HOW THE VIRUS ESTABLISHES INFECTION

Due to the limitations of animal models of chicken pox, many aspects of the biology of the virus are still somewhat unclear, including some of the details of how the varicella-zoster virus actually causes disease. However, molecular analysis of the virus is beginning to reveal some of these secrets about the natural history of chicken pox infection.

Several of the proteins on the surface of the virus (the viral glycoproteins gE, gI, and gB in particular) are involved in **endocytosis**, the process by which the virus enters a host cell. Cell entry is a prerequisite for establishing an infection, because the varicella-zoster virus can only replicate inside human cells. In addition, the entry of the virus through this pathway is apparently essential for proper assembly of the virus, so this is a critical stage in the life cycle of the virus.

These viral glycoproteins interact with a molecule on the surface of the human cell called **heparin sulfate** (a molecule consisting primarily of sugar molecules in chains). As a

consequence of this binding, other molecules on the surface of the virus (**mannose-6-phosphate**) interact with the **mannose-6-phosphate receptors** on the host cells, and the viral nucleocapsid enters the cell. Cholesterol in the cell membrane also appears to be essential for viral entry.[6] Along with the nucleocapsid, viral tegument proteins, located in the space between the envelope and the nucleocapsid, are also released into the cell. These tegument proteins then travel to the nucleus, where they will play an important function in the replication of the virus.

Subsequently, this inner region of the virus, the nucleocapsid, migrates to the cell nucleus, where it fuses with the nuclear membrane, releasing the viral DNA into the nucleus. The viral DNA contains ends with sections of single-stranded DNA.

THE MOLECULAR DETAILS OF THE VIRAL LIFE CYCLE

Sophisticated methods have been used to determine how the viral particles are put together inside the host cell during infection. For example, one aspect of the viral life cycle is that the virus acquires an initial envelope, loses it, and then gets a second envelope that contains the viral glycoproteins.

One experiment that helped establish this idea involved monitoring varicella-zoster virus infected cells using electron microscopy. Antibodies that detected the glycosylphosphatidylinositol (gpI) protein were added; this protein is found in the envelope of mature viruses. As the virus left the nucleus, no gpI protein was detected.

However, viruses were identified, by electron microscopy, as acquiring a second envelope when they interacted with the trans-golgi network (a series of membrane-bound compartments responsible for ensuring that different molecules end up in the correct cellular location), and this second envelope did contain the gpI protein.[7]

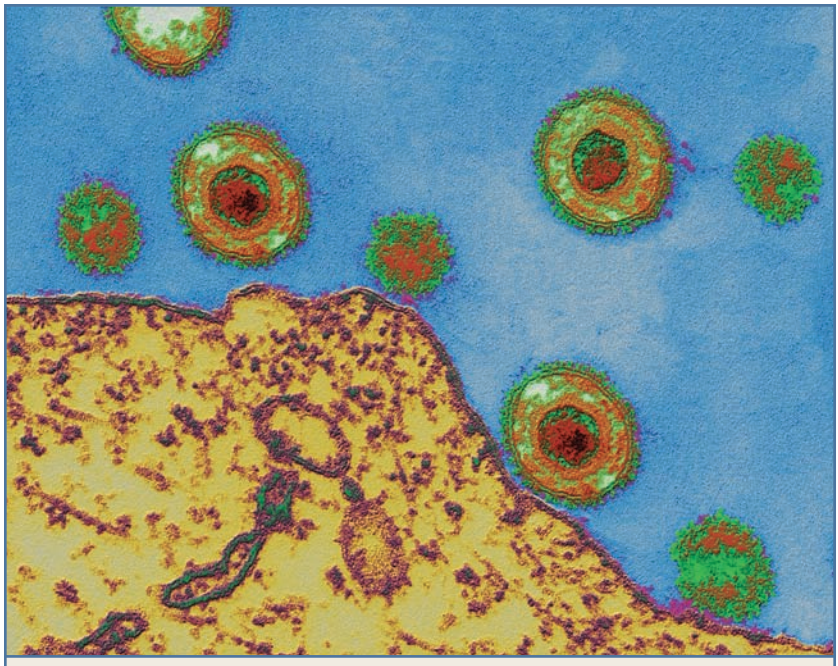

Figure 3.2 Varicella-zoster virus invading human cells. The rounded viruses are sectioned through to show DNA genetic material (red) surrounded by a protein coat (green). At lower left is part of an infected cell (yellow). (© Eye of Science/Photo Researchers, Inc.)

These regions at the end of the viral genome come together, forming a circular viral DNA molecule. The tegument proteins then bind to the viral genome and allow for the production of new viral proteins. The first proteins produced are called the immediate early (IE) proteins, which include **transcriptional activators** and **transcriptional repressors**. Transcriptional activators are proteins that enhance the conversion of the information in the DNA genome into another molecule called RNA. The information in RNA is ultimately converted to proteins. Transcriptional repressors are proteins that inhibit the conversion of the information in DNA to RNA. In particular, IE62,

a transcriptional activator, is critical for the production of all other varicella-zoster proteins.

Subsequent stages in the production of the viral proteins are tightly regulated so that the proteins are produced in a specific order. As they accumulate inside the nucleus, the IE proteins then turn off the synthesis of additional IE proteins and facilitate the production of the next group of proteins, the early (E) proteins. These E proteins catalyze the production of the viral DNA through a mechanism called **rolling circle replication**. Rolling circle replication is a process by which DNA molecules are made from a circular DNA template. The DNA is synthesized in a manner somewhat analogous to string being pulled off a spool. Finally, the late (L) proteins are produced, which are the structural proteins required to build the nucleocapsid and the proteins that populate the envelope.[8]

The DNA synthesis by the E proteins results in the production of a long DNA "string"containing a number of genomes. This long DNA molecule is cut into single genomes, which are then ready for packaging into a viral particle. The initial assembly of the varicella-zoster virus occurs in the nucleus of the cell. This involves the capture of the DNA genome by the capsid proteins. The **nucleocapsid** (viral DNA plus the capsid) then exits the nucleus, pulling a portion of the nuclear membrane with it. This nuclear membrane forms a temporary envelope. The capsid is now inside a cellular structure called the **endoplasmic reticulum**, which is part of the transportation system in the cell. The virus envelope then fuses with the endoplasmic reticulum membrane, releasing the virus, lacking an envelope, into the cytoplasm of the cell.

Separately, the glycoproteins that will become embedded in the envelope of the virus are being processed. These proteins are modified though the addition of sugars, including mannose-6-phosphate in the endoplasmic reticulum. Once modified, they are released into a structure called the **trans-golgi network**. The trans-golgi network is part of the transportation system in the

cell. It is a series of membrane bound compartments responsible for helping to ensure that different molecules end up in the right cellular location.

It appears, at this point, that the remainder of the life cycle of the virus inside the cell depends on the cell type that is hosting the virus. The virus is only adorned with an envelope in skin cells; in all other cells, the virus ultimately lacks an envelope.

In skin cells, the virus nucleocapsid enters the trans-golgi network compartment, which contains a number of viral proteins, as well as a lipid envelope that is synthesized by the cell. The virus becomes encased in this envelope and is released from the cell. The viruses now have two possible fates: to be released into the environment, where they can go on to infect other people, or to enter into neurons, where the virus can lay dormant for years. It is theorized that only enveloped viruses can enter nerve cells, because they contain the mannose-6-phosphate molecule, which allows them to interact with nerve cells.

In other cells where the virus replicates, it does not end up with an envelope, but this is not essential, because the virus can move directly from cell to cell, thereby infecting new cells even without the envelope.[9] In this case, the viral nucleocapsid again interacts with the trans-golgi network. However, in non-skin cells, once the virus interacts with the trans-golgi network the virus gets targeted for a cellular structure called the endosome. In the endosome, any envelope is removed, and some of the viruses are completely destroyed. Any remaining viable virus is released to the cell surface, but does not exit the cell, limiting the damage caused by runaway viral replication.

Why is the pathway different in skin cells? Skin cells are in the last stage of their life, producing large amounts of **ceramides** (lipids that waterproof the skin) in preparation for their death and transport to the outermost layer of the skin. Therefore, the endosome pathway is largely turned off in skin cells and the enveloped viruses pass directly to the surface of the skin, with the envelope intact.

IMMUNE SYSTEM CELLS AND THE CONTROL OF CHICKEN POX

There are several types of white blood cells that play a role both in spreading the virus and ultimately controlling the virus during infection. T-cells play a role in both the direct destruction of pathogens and the coordination of the other branches of the immune system. During a chicken pox infection, these cells play a role in spreading the virus to the skin, as well as, ultimately, controlling the virus.

During the initial stage of infection in the respiratory tract, T-cells become infected with the varicella-zoster virus. Some of these cells then eventually travel to the skin, where they transfer the virus to the skin cells. In this situation, the virus takes over a normally protective immune system cell and uses it as a shuttle to a site where it can cause infection.

As a specific immune response begins to develop during the course of infection, T-cells play a critical role in eliminating the disease. One type of T-cell, a cytotoxic T-lymphocyte, will target and destroy cells infected with the varicella-zoster virus. Another type of T-cell, the CD4+ T-cell, helps marshal other T-cells and other components of the immune system to fight the infection. Ultimately, some of these T-cells become memory T-cells and provide long-term protection against additional chicken pox infections and outbreaks of shingles.

Another type of immune system cell, the B-cell, plays a less prominent role during chicken pox infections. These cells produce antibodies; during a chicken pox infection, high levels of antibodies are produced against chicken pox. However, these antibodies do not appear to be critical in fighting the infection; for example, patients who lack the ability to produce antibodies as a result of a genetic condition are often able to control a chicken pox infection.

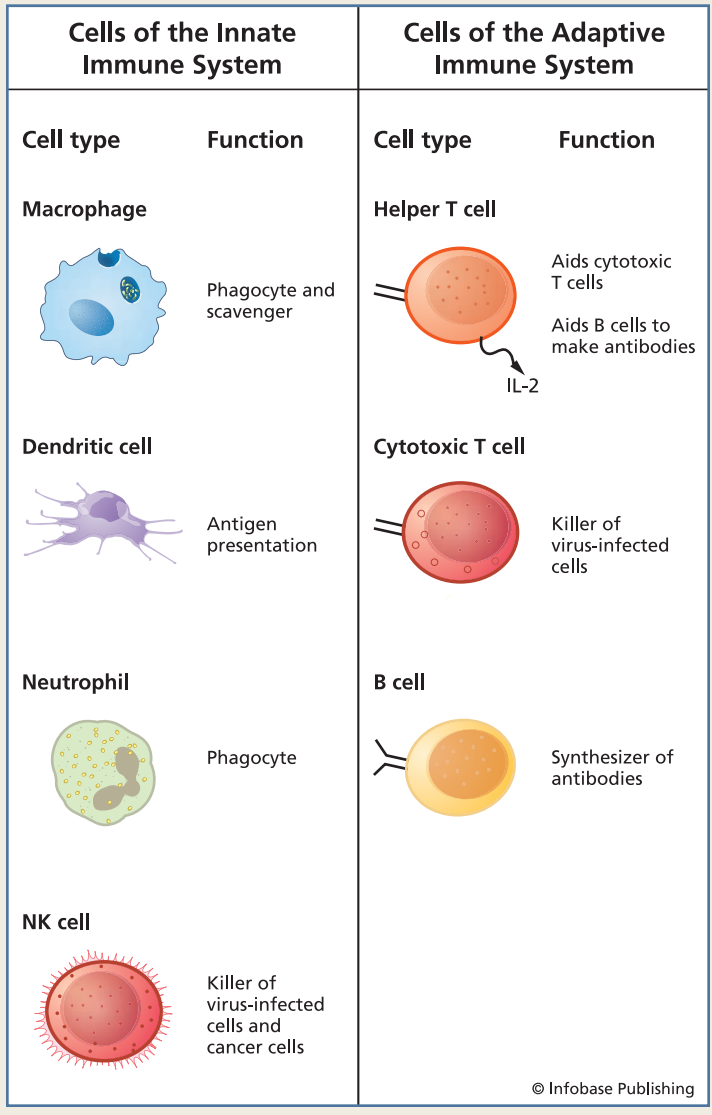

Figure 3.3 The immune system has two arms: the innate immune system and the adaptive immune system.

CELL-TO-CELL SPREAD OF INFECTION

Viruses that are located on the surface of infected cells are capable of fusion with uninfected cells, and this leads to the spread of infection. The glycoproteins on the surface of the virus, particularly gB, gE, gH, and gL, are thought to be critical for the fusion of uninfected cells with infected cells.[10]

IMMUNE SYSTEM RESPONSE TO CHICKEN POX

There are two branches of the immune system that coordinate the response to a chicken pox infection. One branch is called the **innate immune system**; the other branch is called the **adaptive immune system**. The innate immune system has the capability to respond to any pathogen and is always available, so it serves as the first line of defense against infection. However, the adaptive immune responses are more effective at ultimately eliminating pathogens, such as the varicella-zoster virus.

In the case of chicken pox, the innate immune response consists primarily of natural killer cells and a chemical released by immune system cells and skin cells called interferon-alpha. Natural killer cells recognize other cells infected with the varicella-zoster virus and kill the cells and the viruses contained within those cells. These natural killer cells destroy infected cells by releasing a protein called **granulysin**. This protein creates pores in the membrane of the infected cell and these pores lead to a loss of cellular material and, ultimately, death of the cell.

Interferon-alpha is also produced by natural killer cells, another type of white blood cell called a monocyte, and by skin cells. This chemical inhibits the replication of varicella-zoster virus, thereby limiting the growth of viruses in the body.

From studies of immunocompromised children who had an intact innate immune response, but who developed a severe case of chicken pox, it was clear that adaptive immunity was critical for ultimately clearing up a chicken pox infection. The adaptive immune response is primarily through **cell-mediated**

immunity. This means cells of the immune system specifically recognize chicken pox–infected cells and then seek out and destroy these cells. The cells that do the hunting are called **cytotoxic T-lymphocytes** (CTLs). These cells recognize viral proteins that are displayed on the surface of infected cells. The CTLs then bind to the surface of the infected cell and release toxic proteins (like granulysin) that destroy the infected cells and the viruses those cells contain. This dramatically reduces viral replication, and is a critical step in the control of chicken pox infections by the immune system.

Another adaptive immune response that is important in the control of many infections is the production of antibodies. However, antibodies do not appear to play a major role in the control of chicken pox. Individuals with mutations that prevent them from producing antibodies are generally able to control a chicken pox infection. Yet, the administration of antibodies during an early stage of infection can reduce the severity of the disease, so antibody production by immune system cells may play some role in controlling varicella-zoster virus growth and spread in the body.[11]

IMMUNE EVASION

Every successful pathogen has evolved systems for avoiding the host immune response, and the varicella-zoster virus is no exception. This virus, as an internal cellular parasite, automatically avoids some aspects of the immune response, such as antibodies that only affect free pathogens in the bloodstream. This is probably why antibodies are not very important for controlling infection. In addition, this virus has several other strategies for evading other aspects of the host immune response.

For example, one key defense against viruses involves **antigen presentation**, where an infected cell places sections of the virus on the surface of the cell. These virus parts alert immune system cells, such as cytotoxic T-lymphocytes, which then home in on and destroy the infected cells. The varicella-zoster virus is

able to suppress the ability of infected cells to display parts of the virus on the cell surface by trapping the display molecules inside the cell. Consequently, these virally infected cells remain invisible to the immune system, and the virus can continue to grow inside these cells.

There is another pathway for infected cells to display "chunks" of the virus on their surface cells. This pathway is enhanced through the production of interferon gamma by T-cells. The varicella-zoster virus has the ability to suppress this display system as well. The suppression only works for infected cells, though, so adjacent cells can produce these display proteins, meaning that once the production of interferon gamma begins, it limits the ability of the virus to infect adjacent cells.[12] The virus also inhibits the activation of another protein in infected cells that would otherwise activate an antiviral response, including the production of interferons.[13]

In addition, the virus takes up residence in nerve cells, and these cells are subject to little scrutiny by the immune system. Consequently, the presence of the varicella-zoster virus inside nerve cells is another important mechanism by which the virus avoids the host immune response.

VARICELLA-ZOSTER VIRUS ENTRY INTO NERVES AND LATENCY

Entry into nerve cells probably plays a critical role in the life cycle of the varicella-zoster virus. It appears that the viruses that enter nerves have an envelope, and enveloped viruses only come from skin cells. These enveloped viruses have mannose-6 phosphate on their surfaces, and nerve cells have a large quantity of mannose-6 phosphate receptors on their surface. So the complementary surfaces of the virus and the nerve cell result in the virus binding to nerve cells. Once bound, the virus enters the nerve cell.

Once inside the nerve cell, a different pattern of gene expression occurs, as compared with the gene expression that

occurs in other type of cells. In particular, the only genes that are expressed are ones that, in other cells, are expressed early in the course of infection. None of the genes that are normally expressed later in infection are expressed in nerve cells. This suggests that the varicella-zoster virus, inside nerve cells, is very restricted in terms of the proteins that are produced. As a consequence, the presence of the virus inside these cells probably does not cause much of a perturbation in normal cellular function. This contributes to **latency**, a condition in which the virus can remain inactive for years, until the immune system weakens, rendering the person vulnerable to a flare-up of the viral infection.[14]

4

Chicken Pox in Infants and Adults

A woman in Italy developed chicken pox when she was 15 weeks pregnant, in a case reported in 2003. Subsequent ultrasound examinations showed that the fetus was not developing normally. The infant was delivered by Caesarean section at 37 weeks and was very small (below the tenth percentile in length and weight). The infant had hydrocephalus (an enlarged head) with extensive damage to the brain and one eye. This young boy had breathing difficulty requiring the use of a ventilator, and seizures that were treated with medication. In spite of intensive care, the infant died three days after birth. An autopsy suggested that the child had suffered chicken pox while in the uterus at 15 weeks, and a case of shingles shortly before birth. These bouts with the varicella-zoster virus caused much of the child's brain to be destroyed. Although congenital chicken pox is rare (3 to 4 cases per 100,000 pregnancies) this case shows the potentially devastating nature of chicken pox during pregnancy.[1]

The outcome of any illness is the result of the balance between the virulence of the pathogen and the vigor of the immune response. In the case of chicken pox, individuals who develop more severe cases of chicken pox are not as able to mount a strong immune response against infection. Unlike many other viruses, the varicella-zoster virus strains do not differ in virulence, so the immune system of the patient is the key variable in the outcome of a chicken pox infection.

Infants have an undeveloped immune system. Consequently, they have less ability to fight infections. However, during pregnancy, the mother transfers to the fetus antibodies against diseases she has encountered during her lifetime. These antibodies help the infant fight off any of the diseases his or her mother had previously encountered. This includes chicken pox, if the mother had developed the disease or been vaccinated prior to pregnancy. However, if the mother had not previously developed chicken pox, but came down with a case of chicken pox during pregnancy, the fetus gets a double whammy. On the one hand, the mother has not developed an immune response, so antibodies cannot be transferred. (It normally takes a week or two after infection before an antibody response develops). On the other hand, the virus is present at high levels in the body of both the mother and the fetus, and the fetus lacks many of the innate immune responses normally required to fend off infection.

The result of a maternal chicken pox infection can be, at least in a small number of cases, a condition called **congenital varicella syndrome** (CVS). This can result in the infant's death shortly after birth, or serious damage that can lead to permanent impairment. In one small sample, CVS involved malformation of at least one arm or leg (72 percent of 25 cases), scarring of the skin (72 percent of 25 cases), damage to the eyes (44 percent of 25 cases), and brain damage (48 percent of 25 cases). CVS is most likely to occur if the mother develops a chicken pox infection in the first or second trimester of her pregnancy. Fetuses with significant abnormalities resulting from CVS can be detected in the uterus using ultrasound. The rate of CVS has been reported at about 0.7 percent in women who develop chicken pox during the first stages of pregnancy. (Overall, though, the rate of CVS is very low, taking into account all pregnancies. For example, by one estimate, there are approximately 4 million births per year in the United States,

and about 44 cases of CVS, which is a rate of about one-one-thousandth of 1 percent.)[2]

If the mother develops chicken pox in the third trimester of pregnancy, CVS is less likely to develop. However, if the mother contracts chicken pox within five days of giving birth, the child may develop a severe case of chicken pox called disseminated neonatal varicella. Treatments are available for both the fetus and the mother, which may help to reduce the risk of serious side effects from neonatal varicella.[3]

In contrast with chicken pox, the development of shingles during pregnancy does not seem to have adverse consequences for the fetus. One study analyzed 366 mothers who developed shingles early in their pregnancy. None of their infants had any sign of varicella-zoster infection.[4] This is not surprising, because a woman who develops shingles has previously had chicken pox, so she can mount an immune response that would reduce viral growth. In addition, during a shingles attack, the virus has a limited distribution in the body and, therefore, less opportunity to infect the fetus. The fetus also gains protection from antiviral antibodies transferred to the fetus, as a consequence of the mother's previous chicken pox.[5]

CHICKEN POX IN ADULTS

The situation resulting in more serious chicken pox cases in adults is somewhat analogous to that of infants. Compared to the immune response in healthy children, the immune response in older adults, at least the type of immune response that limits chicken pox, is substantially reduced. The immune response continues to tail off with greater age, so the greater the age at the first encounter with chicken pox, the more serious the disease.

In adults, several factors related to the immune response are in play. For example, interferons are key to inhibiting the varicella-zoster virus during early infection.[6] One of these interferons, called interferon alpha, is produced more

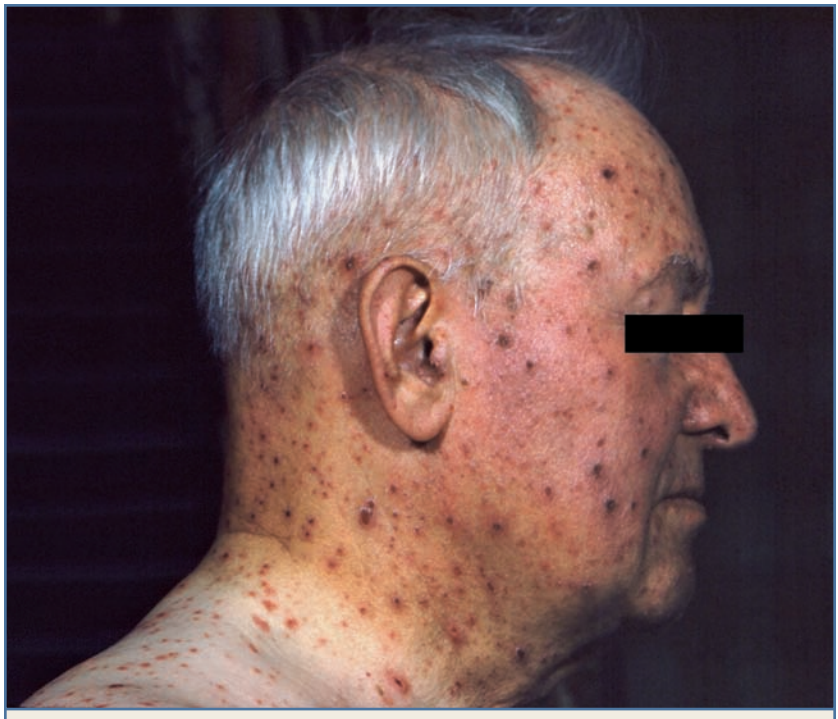

Figure 4.1 An adult with chicken pox. Chicken pox is often a more serious disease in adults, with often a higher number of lesions, and a higher incidence of complications. (Dr. Alexander D. Langmuir/Centers for Diseases Control and Prevention/ U.S. Department of Health and Human Services)

abundantly in children than in adults, who appear to lack sufficient levels of this immunity-fostering agent. This might be one factor in the generally more severe symptoms of chicken pox in adults. Similarly, another critical interferon, interferon gamma, is also found at lower levels in adults than in children. As with interferon alpha, this may help explain the poorer control of chicken pox in adults versus children. In general, interferons prevent the replication of the varicella-zoster virus in infected cells. If interferons are produced at only low levels,

the virus can replicate to higher levels, causing a more severe infection in adults.

Another factor relates to cell-mediated immunity. In this process, cells of the immune system recognize virally infected cells and destroy them. This form of immunity also appears to be critical for the control of chicken pox. Adults, as a group, have a reduced ability to produce immune cells that target chicken pox–infected cells. This also contributes to the greater severity of chicken pox symptoms in adults.[7]

All components of the immune system work together. So the effect of lower levels of interferon and the reduced functioning of cell-mediated immunity conspire to make chicken pox in adults with a normal immune system much more serious than chicken pox in children with a normal immune system. In adults, the virus replicates to higher levels and, consequently, more damage is done to organs and tissues in the body, and the risk of complications is substantially greater. In adults, the rate of hospitalization following chicken pox is about 10 times higher than in children who are infected, and the death rate from chicken pox is 15 to 20 times higher in individuals who are older than 20, compared to the death rate in children.[8]

USING ANIMAL MODELS TO BETTER UNDERSTAND CHICKEN POX

One of the longstanding challenges in understanding chicken pox and shingles in any age group has been the lack of an animal model of the disease that reproduces the characteristics of this affliction in humans. During the twentieth century, a variety of animals were tested as possible models for chicken pox and shingles. For example, several nonhuman primates (green monkeys, patas monkeys, macaque monkeys, pygmy marmosets) were infected with the varicella-zoster virus, but none developed the disease, and no evidence of the virus remained in their tissues. However, a six-month-old gorilla in a zoo did

contract chicken pox, as confirmed by the symptoms of the illness, DNA analysis of virus isolated from the gorilla, and antibodies that reacted against the chicken pox virus. The source of chicken pox was not clear, as none of the animal handlers had evidence of chicken pox, and the gorilla was separated from the public by glass. It was likely that the illness was contracted from a handler with inapparent illness (for example, a very mild infection with few blisters), although another source, such as the activation of a virus already present in the gorilla, could not be excluded.[9]

As a consequence of these studies and observations, as well as the difficulty and expense of working with these animals, nonhuman primates are not considered a useful animal model for the study of chicken pox and shingles.

One more useful animal model for chicken pox has been the guinea pig, which can be infected with the vaccine strain of the varicella-zoster virus (which had been passaged in guinea pig cells). The virus could be recovered from the guinea pigs for up to three weeks following infection, but the infection did not cause symptoms and did not result in the long-term survival of the virus in nervous system tissue. One potential problem with the use of guinea pigs to study chicken pox is that they have a higher body temperature than humans (102.7°F/39.3°C in guinea pigs versus 98.6°F/37°C in humans), and the virus replicates less well at these higher temperatures. One attempt to overcome these problems involved the use of mutant guinea pigs that lacked hair and consequently had a lower body temperature (100.9°F/38.3°C). Infection of this strain of guinea pigs did result in a rash in almost 90 percent of the animals, although the rash was not identical to that seen in human chicken pox. In addition, there was evidence that the virus does infect cells of the nervous system in these animals. This strain of guinea pigs has subsequently been used to study the immune response in chicken pox, and to test candidate vaccines. Although guinea pigs do model some aspects of chicken pox

Figure 4.2 Mouse with severe combined immunodeficiency (SCID). SCID mice have little natural immune response, so they can readily accept human cells and tissues. Based on research using SCID mice containing human skin and immune cells, researchers have discovered that the varicella-zoster virus infects a type of human immune cell called memory T-cells. (Linda Bartlett /National Cancer Institute/ U.S. National Institutes of Health)

infection, there are limitations, and consequently, additional models have been explored.[10]

Another important model of chicken pox involves the use of SCID mice. Because of a mutation in a gene required for normal development of cells of the immune system, these mice lack immune responses. Consequently, it is possible to graft human tissue to or to inject human cells into these mice and they do not reject the transplants. As a result, human pathogens, which normally do not infect mice, can cause disease in this mouse strain, by infecting the human cells and tissues.

In some experiments, the mice have had human skin grafts attached to their skin, and have had human immune cells injected into their circulatory system. This has provided useful information about the growth of the virus in the skin, and the role of immune system cells in the spread of the virus.

Another important issue that has been addressed with SCID mice has been the study of the interaction of the varicella-zoster virus with nerve cells. In one set of experiments, human embryonic stem cells from the nervous system were injected into the brains of SCID mice. These mice were then infected with the varicella-zoster virus. It was found that the virus did infect the human nerve cells, and it was possible to determine detailed information about which genes are expressed in nerve cells. This information could be useful in better understanding the latency of varicella-zoster virus in nerve cells in the body, and the steps leading to the development of shingles.[11] Collectively, these animal models will likely lead to a better understanding of, and improved treatments for, chicken pox in humans of all ages.

5

How Is Chicken Pox Diagnosed and Treated?

A man in his mid-20s went into the emergency room, complaining of intense chest pain, which had worsened over the previous two days He was initially examined for a possible heart attack, but his vital signs were normal. The next day, the pain had begun extending to his back. The following day he started to develop a rash along his left, lower chest, which the man attributed to brushing against some shrubbery a few days earlier. Further analysis of his condition led to a diagnosis of shingles. His symptoms persisted for several weeks. Had the drug acyclovir been administered when he first complained of painful symptoms, it is likely that the length of his illness would have been shortened.[1]

One of the keys in proper treatment of chicken pox or shingles is proper diagnosis. In the case of chicken pox, there are several methods for identifying whether a person has this disease. The symptoms, particularly the distinctive rash, which is often accompanied by fever, provide a reasonable basis for assuming that a patient has chicken pox. These symptoms, especially if accompanied by a history of exposure to other individuals with chicken pox, are usually considered a clear indication of chicken pox. For shingles, the rash appears in a narrow band, which only spans one side of the body. The rash is often preceded by pain in that region two or three days prior to the development of a rash. Again, because this pattern of symptoms is so distinctive, additional tests are rarely needed.

However, for definitive diagnosis, there are several laboratory tests available. These tests may be important in cases where a patient has a

severe form of the disease, or where there is danger of transmission of chicken pox to susceptible patients. It is therefore critical to verify for certain whether a person has chicken pox.

COLLECTION OF SAMPLES FOR TESTING

Proper collection of the virus is one of the keys to a rapid, proper diagnosis. Skin lesions, particularly those produced early in the course of the disease, are one of the best sources of the virus for laboratory testing. To collect the material, the surface of a chicken pox lesion is cleaned with alcohol to remove contaminating bacteria, and then opened with a sterile needle or other sharp object. Then the material from the lesion is expressed (or squeezed out) with a cotton swab to remove both the liquid and some skin cells. As with all clinical samples, the best results are obtained if they are delivered to the laboratory without delay.[2]

DETECTION OF THE VIRUS USING ANTIBODIES

The most common method for identifying the varicella-zoster virus is an antibody staining method. In this technique, the swab containing material from a chicken pox sore is rolled on to a microscope slide. That material is then chemically fixed to the slide, so it will not wash away in subsequent steps. An antibody, specific for the varicella-zoster virus, is then added to the slide. If the virus is present, the antibody binds very tightly to the material on the slide. This antibody has a dye attached to it. If the virus is present in that sample, it can be detected by visualizing the dye. Typically, the dye is fluorescent. Consequently, if the slide is viewed with a microscope that can visualize fluorescent signals, the virus will be detected as brightly glowing particles on the slide. If the virus is not present, there will be no binding of antibodies, and no glowing particles on the slide. In recent years, this technique has improved, as antibodies have been developed that are very specific to varicella-zoster virus, and which do not react to the presence of other viruses.

DETECTION BY VIRUS ISOLATION

In some cases, varicella-zoster virus can be grown in culture in the laboratory as a way to determine if the virus is the cause of an infection. The virus is added to cells grown in culture; after one to three days, antibody tests are used to determine if the virus is present in cultured cells. These procedures are cumbersome, require the presence of viable virus, and are time consuming, so culture is rarely used as a diagnostic method.

DETECTION OF VIRAL DNA

Increasingly, tests to detect viral RNA or DNA are used for identification of viruses. One of the most common of these tests is called the **polymerase chain reaction** (PCR). This technique is analogous to a molecular copy machine, amplifying a specific bit of DNA from a virus a millionfold or more, to the point where it can be readily detected.

PCR can detect, theoretically, a single DNA molecule. It also can detect both living and dead viruses, which is an advantage in chicken pox, because many of the viruses in lesions are not viable. In addition, by using PCR, researchers can use the small DNA sequence differences to distinguish the virus strains that are used in the vaccine from those circulating in the community.

PCR amplification requires the presence of viral DNA; at least in some cases, clinical specimens can be used directly, without purification. PCR requires a sample for testing, and reagents that can be used to make DNA in a test tube. The PCR itself involves three steps. Initially the PCR reaction mixture is heated to a temperature high enough to cause the two strands of DNA to separate. Next, the reaction is cooled down to the point where small, single-stranded DNA segments called primers bind to the viral DNA if it is present. Primers, as the name suggests, initiate or prime the synthesis of new DNA. In the third and final step, the temperature is raised again, and **DNA polymerase**, an enzyme that makes DNA, begins to operate.

Figure 5.1 A biologist prepares a polymerase chain reaction (PCR) assay, a test that allows researchers to identify viruses by detection of viral DNA. (James Gathany/Centers for Disease Control and Prevention/ U.S. Department of Health and Human Services)

The DNA polymerase uses the primers as starting points for DNA synthesis. The key to this method is the use of primers that uniquely recognize the varicella-zoster virus DNA, and not the DNA from any other virus or other pathogen. The use of proper primers makes this test highly specific for chicken pox. Recent innovations in PCR include the development of methodologies allowing for more rapid detection of the virus and differentiating the strains used for vaccination from those that naturally cause disease in the population.[3]

DETECTION USING MICROSCOPY

Although rarely used now, a variety of other tests had been used in the past to detect chicken pox infections and the

varicella-zoster virus. These included electron microscopy, where a very high-powered microscope was used to directly visualize the virus. Another technique involved isolating cells from a chicken pox lesion, and using a light microscope to identify characteristic shapes of cells that are associated with the disease. Although rapid and inexpensive, this method does not distinguish between varicella-zoster virus and herpes simplex virus infections.

DETECTION BASED ON IMMUNE RESPONSES

There are other laboratory tests that detect a reaction to the virus, or the specific effects the virus has on cells or tissues, rather than the virus itself. Most of these tests determine whether a person has specific antibodies to the varicella-zoster virus. These types of tests have two possible applications. One application is to test selected adults, such as health care workers, women who are contemplating pregnancy, and others who are at risk of serious complications from chicken pox. By determining whether or not antibodies are present, it is possible to determine whether the person is likely still susceptible to the disease. If the person does not have antibodies present in their blood, it is a sign they have not been exposed to chicken pox. In these cases, a person may be vaccinated or given medications to reduce the severity of disease if they have been exposed to the virus, but do not yet show symptoms.

Two types of tests for antibodies directed against the varicella-zoster virus are commonly used. In one technique, called an **enzyme-linked immunosorbent assay** (ELISA), proteins from the virus are used to coat small wells in a rectangular plastic plate. A serum sample from a patient is then added to the wells. If antibodies to the varicella-zoster virus are present, they will bind to the proteins in the well and not be washed away in the next step. Following washing, another antibody is added that binds to human antibodies. In some cases, an additional antibody is added that binds to the human-binding

Figure 5.2 A microbiologist uses an enzyme-linked immunosorbent assay (ELISA) test to identify a virus by the detection of antibodies to the virus. (James Gathany/Centers for Disease Control and Prevention/U.S. Department of Health and Human Services)

antibody. This last antibody contains a molecule that, under the appropriate conditions, produces a signal that can be detected and is used to determine whether antibodies to the varicella-zoster virus are present.

Another method for detecting antibodies to the varicella-zoster virus is called the latex **agglutination** test (agglutination means clumping). This diagnostic method uses viral proteins that are bound to latex beads. To perform the test, a drop of serum from a patient is placed on a glass slide. The latex agglutination reagent is then added. If antibodies to the varicella-zoster virus are present on the slide, the latex particles will visibly clump or agglutinate after a few minutes, as the antibodies in the serum bind to the latex particles. This clumping is a sign that the patient has had a previous exposure to the varicella-zoster virus and made antibodies.

Tests that provide a more accurate measure of immunity to chicken pox determine the extent of cell-mediated immune response to the virus. These tests are more time consuming (requiring several days), more cumbersome, and more expensive, so they are rarely used in normal clinical practice. Examples of these tests include proliferation assays and cytotoxicity assays.

To perform a proliferation assay, a blood sample is taken from the patient, and the white blood cells are separated. These white blood cells are then grown in an incubator in laboratory culture medium. If the patient has developed a cell-mediated immune response to the varicella-zoster virus, when proteins from the virus are added to the culture, some of the white blood cells in the culture will grow and divide. This can be detected by the ability of these dividing cells to take up a radioactive compound and incorporate this molecule into their DNA. After several days, the amount of radioactivity in cells that were exposed to the virus, and a control group of cells that were not exposed to the virus, are compared. If the cells exposed to the viral proteins are much more highly radioactive, it is an

indication that the patient has a strong cell-mediated immune response directed against the virus.

Cytotoxicity assays can also be used to determine if a person has a cell-mediated immune response directed against the virus. These tests are done by taking cells from the patient and infecting them with the varicella-zoster virus. These cells are then incubated with radioactive chromium, which is retained inside the cells unless they are killed. The virus-infected, chromium-laced cells from the patient are then added to white blood cells from the same patient. These white blood cells had been previously exposed to varicella-zoster virus proteins to activate any cells that respond specifically to the varicella-zoster virus. If some of these white blood cells have been produced in response to a previous chicken pox infection, they will attack and kill the virus-infected cells, and radioactivity will be released into the culture medium and be readily detected.

The other application for testing the immune response is to verify that a person does, currently, have a case of chicken pox. By detecting specific antibodies against the virus, and comparing the amount of antibody at the time of initial symptoms and at a later time, it is possible to verify a current infection. This is done either by looking at the change in the amount of antibody, or by looking at the change in the type of antibody. Initially the level of a type of antibody, called IgM, increases in the very early stages of an infection. As an infection progresses, another type of antibody, called IgG, becomes predominant. Therefore, if a patient initially has a high level of chicken pox anti-IgM antibody, and he or she later develops a high level of anti–chicken pox IgG antibody, this change indicates that the person has a current case of chicken pox.[4]

TREATMENT: ANTIVIRAL DRUGS

It is often a challenge to treat viral infections, because viruses must live inside cells in order to replicate. It is difficult to get drugs into cells, but even if that obstacle is overcome, another

basic issue in the biology of viruses may pose another obstacle. Viruses use components of human cells to reproduce. Consequently, it is hard to target a virus for destruction without harming the host that harbors the virus. As a result, for many viral infections, there are no drug treatments that have any effect on the course of the illness.

Fortunately, in the case of chicken pox and other diseases caused by herpesviruses, there are several medications available that can reduce the severity and duration of the illness. They include drugs that have been used for a number of years, as well as several drugs that are being tested for use in humans.

Three related drugs—acyclovir, famciclovir, and valacyclovir—are nucleotide analogs. They mimic nucleotides, the building blocks of DNA, but do not function properly, when they are inserted into DNA. In fact, insertion of these nucleotide analogs into DNA prevents the DNA from being further extended, and this stops the virus from making copies of itself.

This is a potential problem, because both human cells and the varicella-zoster virus need to make DNA. However, the virus possesses a gene not found in human cells. This gene codes for an enzyme called thymidine kinase. Thymidine kinase encoded by this gene converts acyclovir and related drugs into an active form. Therefore, the drug will only be active in cells infected with the virus, and will not harm cells that are not infected.

Acyclovir is particularly effective against the herpes simplex viruses. It is not as effective against the varicella-zoster virus, which requires about 12 times more of the drug to inhibit the virus. A related drug, valacyclovir is very similar to acyclovir, but is more easily absorbed by the body when taken orally. Famciclovir is a newer, related drug. It lasts about 10 times longer in the body than acyclovir, but requires a concentration 5 to 10 times higher than acyclovir to inhibit the varicella-zoster virus.

Foscarnet is another drug that has been approved for use to treat varicella-zoster infections. This drug interacts with the enzyme that makes DNA (DNA polymerase) in the

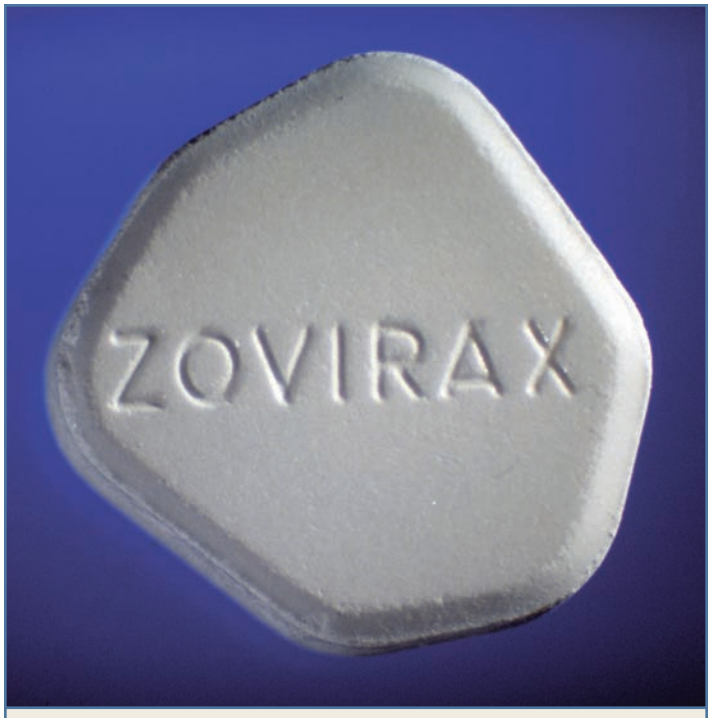

Figure 5.3 The chemical structure of acyclovir (Zovirax), the most common treatment for chicken pox and shingles, resembles one of the building blocks for DNA and acts by inhibiting DNA synthesis of the varicella-zoster virus. (© Leonard Lessin / Photo Researchers, Inc.)

varicella-zoster viruses, preventing the virus from making new DNA. This drug does not have to be acted on by an enzyme in order for it to function. A major benefit of this drug is that viruses that are resistant to acyclovir and related drugs are generally still susceptible to foscarnet. Foscarnet, however, often causes kidney dysfunction and other side effects and so is only used in select cases.

The treatment with these antiviral agents (acyclovir has been studied most intensively) is generally quite effective when

given within 24 hours of the first lesions on the skin. Their effectiveness has been demonstrated in studies showing that the number of vesicles is reduced, the number of days where new lesions are produced is reduced, and the symptoms (such as fever) were reduced in intensity.[5] Treatment with acyclovir was also shown to reduce the severity of disease in children who had a compromised immune system, and had value in some cases if taken continuously to prevent infection.[6]

TREATMENT: VARICELLA IMMUNOGLOBULIN

Another treatment available for chicken pox infections is the use of varicella **immunoglobulin**. Immunoglobulins are another name for antibodies, proteins produced by immune system cells that bind to pathogens. The binding of antibodies to the varicella-zoster virus can prevent the virus from entering and infecting cells.

Varicella immunoglobulin consists of blood serum from human donors who had high levels of antibodies to the varicella-zoster virus. It is prepared by taking blood from these donors, removing the red blood cells, and keeping the liquid. The liquid is then treated with ethyl alcohol, which concentrates the antibodies. Solvents and detergents are then added to the preparation to inactivate any blood-borne viruses that could otherwise be transmitted to the patient.

An early study of the effect of varicella immunoglobulin on preventing chicken pox was reported in 1962. Children who were members of a family where one case of chicken pox developed were either treated or left untreated as controls. Of the participants, 242 were given immunoglobulin, and 209 were left untreated. About the same percentage of children (around 87 percent) developed chicken pox whether or not they received the immunoglobulin. Although the attack rate was not reduced, the severity of symptoms was lower in patients who received injections of immunoglobulin, particularly at higher doses.[7]

In a later test of the effectiveness of varicella immunoglobulin, six households with at least three children were studied. In this case, a more potent serum was used, prepared from patients who had recently recovered from an attack of shingles. Within 72 hours of the time one of the children developed chicken pox, one of the children was given the varicella immunoglobulin, and the other a placebo, or inactive infusion (it was not known to the investigators which child had been given which treatment). Subsequently, it was noted that in each of the six families studied, one additional child developed chicken

VARICELLA-ZOSTER RESISTANCE TO ANTIVIRAL DRUGS

Varicella-zoster viruses rarely show resistance to the drugs, like acyclovir, that are used to treat chicken pox or shingles. However, in some patients, especially those who are immunocompromised, resistance to antiviral drugs has been reported. Typically, these patients are treated for long periods of time with the drug, and this can select for resistant viruses, especially because a defective immune system often leads to exceptionally large numbers of viruses in the body, resulting in a larger pool of viruses that can develop mutations.

For the common drugs, like acyclovir, the mutations that lead to resistance occur either in the thymidine kinase gene, or the DNA polymerase gene. The thymidine kinase enzyme is required to convert the drugs, like acyclovir, to an active form. The DNA polymerase enzyme incorporates acyclovir into a growing DNA chain. Consequently, mutations in either of the genes that encode these proteins can result in resistance to these drugs. Fortunately, for patients with acyclovir-resistant viral infections, there is at least one option. The drug foscarnet is usually active against viruses that are resistant to other drugs, although it can cause significant side effects.

pox. In each case, it was the child who received the placebo. Although this was a small trial, it did help establish the efficacy of the immunoglobulin at preventing chicken pox, if the immunoglobulin contained a high enough concentration of antibodies directed against the varicella-zoster virus.[8]

Early trials in children who had leukemia, and who were therefore susceptible to severe cases of chicken pox due to their suppressed immune systems, suggested that the immunoglobulin did not prevent the development of chicken pox. A later trial was then conducted with more a more potent formulation of immunoglobulin. In this small trial, eight children at risk for more severe chicken pox were treated with a high-potency preparation of immunoglobulin. Three of the children in the study developed a very mild case of chicken pox with 50 or fewer lesions, and the remaining five did not develop the disease, even though they lived in households where another child had developed chicken pox.[9]

Based on these and other studies, patients who are candidates for this treatment have been exposed to chicken pox, are susceptible to it, and are at high risk for severe symptoms following chicken pox infections. These people include mothers and infants who developed chicken pox within five days of delivery, adults without previous exposure to chicken pox, and children or adults who are immunocompromised. The treatment has been found to be effective if administered within 96 hours of exposure to the virus; it is not clear if later administration reduces the symptoms or severity of infection.

Varicella immunoglobulin is injected into the muscle at a rate of approximately 125 units per 20 pounds of patient weight. It can be administered multiple times if a susceptible person has several exposures to the virus. Severe reactions occur in approximately one in every 1,000 treatments. These reactions include **anaphylactic shock**, a serious condition that can normally be treated in a medical setting. Mild reactions are common, including pain and irritation at the site of injection.[10]

While useful in treating some cases of chicken pox, immunoglobulin treatment does not seem to be useful for preventing or reducing the severity of the symptoms of shingles.

TREATMENT-RELATED CONCERNS

The use of aspirin to treat the symptoms of chicken pox is now strongly discouraged. Starting in about 1980, it became clear that there was an association between Reye's syndrome, aspirin, and chicken pox. Reye's syndrome is a serious complication that can follow aspirin use during a viral illness. It often starts with nausea and vomiting, and a loss of mental alertness. The condition can quickly worsen, leading to paralysis and loss of consciousness. The mortality rate can be 30 percent or higher. Prior to an understanding of the cause of Reye's syndrome, there were more than 100 cases per year in the United States associated with the use of aspirin in children with chicken pox. Although the cause of the link between aspirin and Reye's syndrome is not entirely clear, one set of experiments, in 1984, suggested a possible explanation. These experiments showed that the varicella-zoster virus grew in culture to higher numbers in the presence of high concentrations of aspirin. Larger numbers of viruses are likely to cause more severe infections, and that might contribute to the symptoms observed in Reye's syndrome.[11]

There was also a concern about whether treatment with antiviral drugs might limit the growth of viruses to the extent that an insufficient immune response would develop, and the infected person might still be susceptible to a subsequent chicken pox infection. The data available so far does not indicate that this is a problem. This may be due, at least in part, to the fact that the varicella-zoster virus replicates fairly extensively before symptoms develop. Because the drugs are not typically given until symptoms develop, there is adequate time for an immune response to develop before the drugs start to limit further growth of the virus.[12]

6

How Is Chicken Pox Prevented?

Dr. Michiaki Takahashi was a virologist in Japan who had studied a variety of pathogens, including measles virus and polioviruses. In 1964, his three-year-old son developed a severe case of chicken pox, with a high fever and vesicles covering his entire body. This eventually inspired him to start developing a vaccine that could prevent this normally mild, but sometimes very serious, illness. His work on the chicken pox vaccine began in 1972, and two years later he succeeded in developing a vaccine strain of the virus. Another 21 years would elapse before the vaccine was approved for use in the United States, in 1995.

Preventing chicken pox required the development of a vaccine. Because most cases of chicken pox are relatively mild, creating a vaccine had not been a priority among public health officials until fairly recently. However, an increasing awareness of potential complications from chicken pox, along with an expanding pool of immunocompromised people who were vulnerable to severe cases of chicken pox, finally led to the licensing of a commercial vaccine.

The eventual production of the vaccine required a substantial amount of preliminary work in order to determine how best to grow the virus in culture, and to determine conditions for separating the virus from the cells used for growth. Once these problems were surmounted, work on the varicella-zoster vaccine began in earnest in 1972 by the Japanese doctor Michiaki Takahashi.

Figure 6.1 Child being vaccinated. The chicken pox vaccine was approved for use in the United States in 1995. (James Gathany/Centers for Disease Control/ U.S. Department of Health and Human Services)

The virus used for vaccine development was isolated from an otherwise healthy three-year-old boy in Japan, who had a case of chicken pox. It was named the Oka strain, based on the name of the boy who contributed the virus to science. Previous work had shown that the virus retained its ability to cause disease for at least a year when held at a low temperature, so the virus was stored in the laboratory at -94°F (-70°C) until it was needed.

From studies of how the body defends itself against chicken pox infection, it was clear that a live virus vaccine would likely be needed. A live vaccine typically stimulates a stronger immune response, as compared to a vaccine that just contains parts of a virus, or an inactivated virus. Specifically, a live vaccine stimulates a cell-mediated immune response as well as an antibody

response; a vaccine with an inactivated virus normally only stimulates an antibody response. Consequently, Dr. Takahashi and his group had their work cut out for them. To produce a live virus vaccine, the virus has to be weakened but still be able to grow to a limited extent in the body. Typically, weakening, or attenuating, a virus requires growing it under unusual conditions, and it can be a matter of both good experimental design and good luck to find the right conditions.

In the case of the Oka vaccine strain, the virus was initially grown in culture flasks in human embryonic lung cells, at a lower-than-normal temperature. After several days, when the cells showed definite signs of infection, they were treated with an enzyme that caused them to float off the bottom of the flask. The loose cells, full of the varicella-zoster virus, were then added to a new batch of human embryonic lung cells. This process was repeated 11 times.

After the eleventh passage in human cells, some of the infected human cells were added to another type of cell—guinea pig embryonic fibroblast cells. These cells were one of the few types of nonhuman cells that were known to allow for the growth of the virus. The logic was that, in order for the virus to successfully grow in such an unusual type of cell, it must undergo genetic changes that will make it less harmful to humans. As with the human cells, the same process of waiting a few days until the cells showed some signs of infection was employed, before some of the cells were transferred to new flasks of uninfected cells. This process was repeated six times for the initial vaccine trials. The virus that was eventually used in the vaccine was grown for 12 cycles in guinea pig cells.[1]

At the end of this process, the virus was tested for a lack of virulence in laboratory animals. Not surprisingly, no pathogenicity was observed, because the virus normally does not infect laboratory animals. The next step was to test the virus in human volunteers. Healthy children, with no history of chicken pox, were given various dosages of the vaccine. In almost all

cases, the vaccine appeared to promote immunity and did not cause disease.

Next, the vaccine was tested on children in a hospital. Many of the children in this particular hospital had medical conditions that made a chicken pox infection life threatening. Consequently, when the first case of chicken pox was reported in the hospital, the other children were vaccinated. None of the vaccinated children developed chicken pox. These initial trials supported the usefulness of the vaccine and eventually helped lead to the widespread use of this preventative measure.

Before the virus could be produced for mass vaccination, one major problem still had to be addressed. The growth of the virus in the guinea pig cells was relatively poor, meaning that it was difficult to produce the large volumes of the virus required for mass vaccination. Ultimately, several human cell lines were used, instead, for final growth of the virus. This involved five cycles of growth in one of two cell lines.[2]

Additional studies were conducted by Dr. Takahashi and his group to determine the efficacy of the vaccine prepared with this modified method. These studies included vaccination of children in families in Japan where one child developed chicken pox. Normally, chicken pox spreads quickly within a family; however, in this study, none of the vaccinated children developed chicken pox, whereas all the unvaccinated children developed chicken pox. Other studies further supported the efficacy of the vaccine in protecting against chicken pox.

Further analysis of the vaccine included the sequencing of the entire genome of the vaccine strain of the virus, and the parental strain from which it derived. Altogether, 42 mutations were identified in the vaccine strain, as compared to the parental strain. These mutations meant that the vaccine strain and the original parental strain differed by 0.016 percent—a small difference, but enough to turn the virus from a pathogen into a medicine.[3]

The vaccine was first approved in Japan in 1989, and then in the United States in 1995; it has subsequently been approved for use in many countries in Europe. Data from the first randomized trial in the use of the vaccine in the United States was reported in 1984. The study involved children who had not previously been exposed to chicken pox. In this test, children in the same household were randomly given either the vaccine or a placebo. During the first year of follow-up, the vaccine was 100 percent effective; over 7 years, 95 percent of the children who received the vaccine had not developed chicken pox. In another vaccine trial in Europe, those children who received the highest dose of the vaccine had a low rate of chicken pox (3 percent); in contrast, among those children who did not receive a vaccine, 26 percent developed chicken pox. Additional studies have subsequently shown 85 to 90 percent protection against chicken pox, and 90 to 100 percent protection against severe cases of chicken pox.[4]

Since the vaccine became widely used in the United States, the number of cases of chicken pox has dropped dramatically. Prior to the availability of the vaccine, there were more than 4 million cases of chicken pox per year. By 2006, it was estimated that there were about 600,000 cases of chicken pox, about an 85 percent reduction. The number of deaths attributed to chicken pox dropped substantially once vaccination was implemented. In 1994, the year before the United States approved the vaccine, the number of deaths in the United States directly caused by the varicella-zoster virus was 124. By 2001, that number had dropped almost 80 percent, to 26. By 2006, that number was 19, a reduction of 85 percent compared to 1994.[5] A 1994 study suggested that each dollar spent on the vaccine generated $5.40 in savings for medical costs and indirect costs, such as loss of work.[6] In addition, there is evidence that people who are vaccinated are less likely to develop shingles, another important benefit of this medical intervention.

In 2005, a new vaccine formulation was approved called ProQuad. It consists of the varicella vaccine in the same shot along with the measles, mumps, and rubella vaccines (MMRV). It was approved based on a demonstration that the combined vaccine was as effective at promoting immunity as the separate vaccines.[7]

RASHES FOLLOWING VACCINATION

The varicella-zoster virus vaccine consists of a number of closely related viral strains, which differ by a few DNA mutations. The viruses in the vaccine, in general, show a reduced ability to replicate in skin cells and consequently are rarely transmitted from a person receiving the vaccine to another person.

However, about 5 percent of the children who are vaccinated develop a mild rash following vaccination, indicating that the virus, in these children, has some ability to replicate in the skin.

Researchers from the United Kingdom and the United States studied the viruses isolated from patients who developed a rash following vaccination. They found that in each individual vesicle or blister, there was only a single strain of varicella-zoster virus. However, different vesicles on the same person, or from different people, contained genetically distinct strains. This indicated that more than one strain of the genetically mixed strains in the vaccine was responsible for replication in the skin. However, virus strains with at least one of four specific mutations were found much more commonly in a skin rash. This implies that some of the viral variants in the vaccine are more able to replicate in the skin, and the vaccine would be even more useful if some of those variants were eliminated.[8]

SAFETY OF THE VARICELLA-ZOSTER VACCINE

Millions of doses of the vaccine have been administered since its approval in the United States and elsewhere, and the safety record of the vaccine has been very good. The most common side effects are pain at the site of injection and fever. These effects were reported in about 10 percent of the people who received a vaccination. Another common side effect, reported in about 5 percent of healthy children who have been vaccinated, is a mild rash that develops about two weeks after vaccination. There have been relatively few serious side effects from vaccination (such as pneumonia and chicken pox infection that spreads throughout the body). In almost all these cases, the patients had an undiagnosed immune deficiency.[9]

Three groups of people should not receive the vaccine:

1. People who are allergic to a vaccine component.

2. Women who are pregnant.

3. People who are immunocompromised.

However, some immunocompromised people do receive the vaccine with favorable results. For example, there is a compassionate use provision for vaccination of patients with leukemia with the chicken pox vaccine. These individuals have typically had a much lower rate of severe chicken pox, as compared to unvaccinated children with the same underlying disease (approximately 10 percent of vaccinated children get the disease, as compared with 45 percent of unvaccinated children).

This vaccine, like all live virus vaccines, is not recommended for pregnant women, although there have not been reports of harm to the woman or the fetus following vaccination. There have been some cases where women who had received the vaccine decided not continue their pregnancies, however.[10] Currently, no adverse effects associated with this vaccine are eligible for compensation from the National Vaccine Injury Program.

VACCINE SCHEDULE

When the vaccine was first approved in the United States in 1995, it was initially recommended that a single dose be given sometime between 1 year and 12 years of age. Subsequent determination that there was still some spread of chicken pox in the community led to a new recommendation that children be vaccinated twice.[11] It is now recommended that children receive a vaccine for chicken pox between 12 and 15 months of age, and again at the age of 4 to 6 years. For individuals who only received one dose of the vaccine, they should have a second "catch-up" vaccine as soon as possible.[12]

CONCERNS ABOUT VACCINATION

One of the issues raised regarding chicken pox vaccination is ensuring high levels of vaccine coverage. In the years prior to the approval of the vaccine, chicken pox was such a common illness that almost all United States residents developed chicken pox during childhood.

With vaccination, there have been dramatically fewer cases of chicken pox, so the likelihood of encountering chicken pox has decreased significantly. This means that a person who has not been vaccinated is less likely to develop chicken pox during childhood. Because chicken pox is a more serious illness in adults, it is critical to ensure that everyone possible is vaccinated.

7

What Is Shingles?

A 65-year-old man developed a burning sensation on his lower back, just at the waistline. It extended from the right side to the middle of the back. A day or two later, the characteristic rash developed, and was intensely itchy. His physician diagnosed shingles, and prescribed acyclovir. In spite of the treatment, the rash lasted about two weeks, was painful even to light touch, and the gentle pressure of fabric from a shirt caused irritation. The itchiness and pain lasted for several more weeks, but he recovered without further complications. To the best of his knowledge, there was no previous illness, unusual stress or other factors that might have triggered this attack.[1]

Shingles, or zoster, is caused by the reactivation of varicella-zoster virus, which often remains hidden for years in nerve cells in the body. In the United States, approximately 1 million people develop shingles each year, although the number is expected to drop substantially with the use of a recently approved vaccine.

As described previously, the varicella-zoster virus causes both chicken pox and shingles. After the initial chicken pox infection, usually in childhood, almost all the virus is destroyed by the immune system. However, some of the virus retreats to the nerve cells and remains inactive and hidden, but viable, often for decades. The victims of shingles are typically over 60 years old, although shingles can potentially occur in anyone, of any age, who has previously had a case of chicken pox.

Elderly people are at higher risk for shingles because their immunity in general, and their immunity to the varicella-zoster virus in particular, wane with time. In most cases, many years elapse between chicken pox and shingles; however in some select cases (e.g., an infant who developed

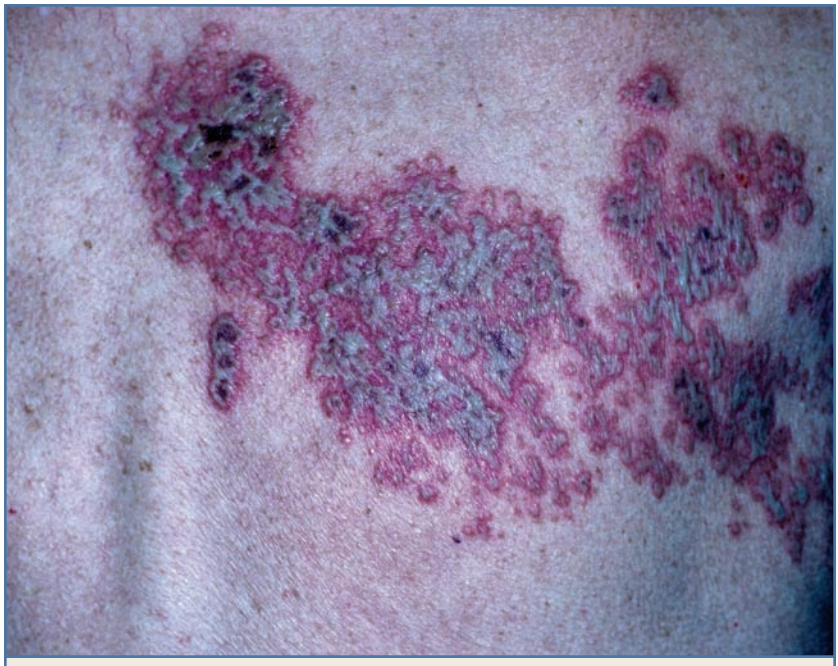

Figure 7.1 A typical presentation of a shingles rash. (© Dr. Ken Greer/Visuals Unlimited, Inc.)

chicken pox right after birth), shingles can develop within a year or less of a bout with chicken pox. Based on several studies, about 1 percent of the elderly would be expected to develop shingles in a given year. However, the risk rises with increasing age, probably related to declining immune responses. It has been estimated that 10 to 20 percent of the population will develop shingles at some point in their life if they have not been vaccinated to prevent the disease.[2]

It is not yet clear what causes the varicella-zoster virus to break out of its inactive state and cause disease again. There have been some cases of shingles following an X-ray or surgery, although no clear causal connection has been made between these events. There have also been anecdotal connections

between shingles and stress, and a consequently lower immune response. Several studies have addressed this issue. In one study, researchers matched 101 patients with shingles with 101 people who had not developed the disease. Both groups were similar in terms of age, sex, and racial composition. The patients who developed shingles had significantly more stressful life events within six months prior to their illness, compared to the matched group that had not developed shingles. (The connection was even stronger for stressful events within two or three months of their outbreak.) Similarly, another study, reported in 1990, tracked a large group of patients who had not yet developed shingles. The patients who experienced stressful life events were more likely to develop shingles, compared with individuals who did not experience the stressful events, although the association was not very strong.[3]

When individuals develop shingles, they often experience substantial pain prior to the development of the rash. When the rash develops, it is more localized, but also more dense, than a chicken pox rash. The rash is only found on one side of the body, in a narrow band. This band corresponds to the area supplied by a single nerve hub near the spinal cord. When reactivated, the virus travels out from the hub along the nerves to the skin. The affected band of skin is called a **dermatome**. Most shingles episodes affect a single dermatome. In immunocompromised patients, more than one dermatome can be affected. The most frequent sites are the torso or face. In shingles, the entire swath of the rash area can be red, sometimes with a thick network of lesions. As with chicken pox, new vesicles appear for up to seven days. The lesions produce infectious viruses, which can infect people not previously exposed to chicken pox.

For many people, especially those over 60, the rash is very painful. For some, it produces an itching, burning sensation, in others a stabbing or throbbing pain. For some people, the pain is constant, and in others, the pain comes and goes. The pain

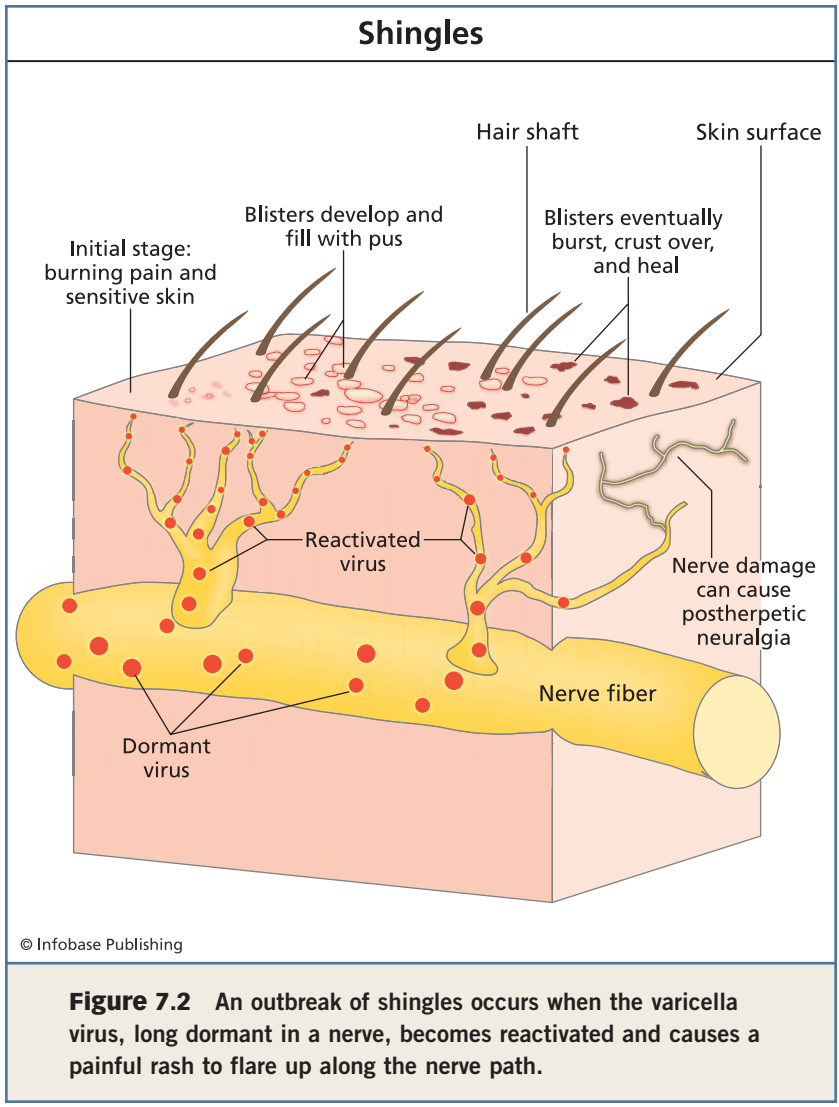

Figure 7.2 An outbreak of shingles occurs when the varicella virus, long dormant in a nerve, becomes reactivated and causes a painful rash to flare up along the nerve path.

results from either damage to the nerves or overstimulation of the sensory nerves. In most cases, after the lesions begin to heal, there are no permanent ill effects. The skin begins to crust over, and the new skin replaces the lesions after about four weeks.

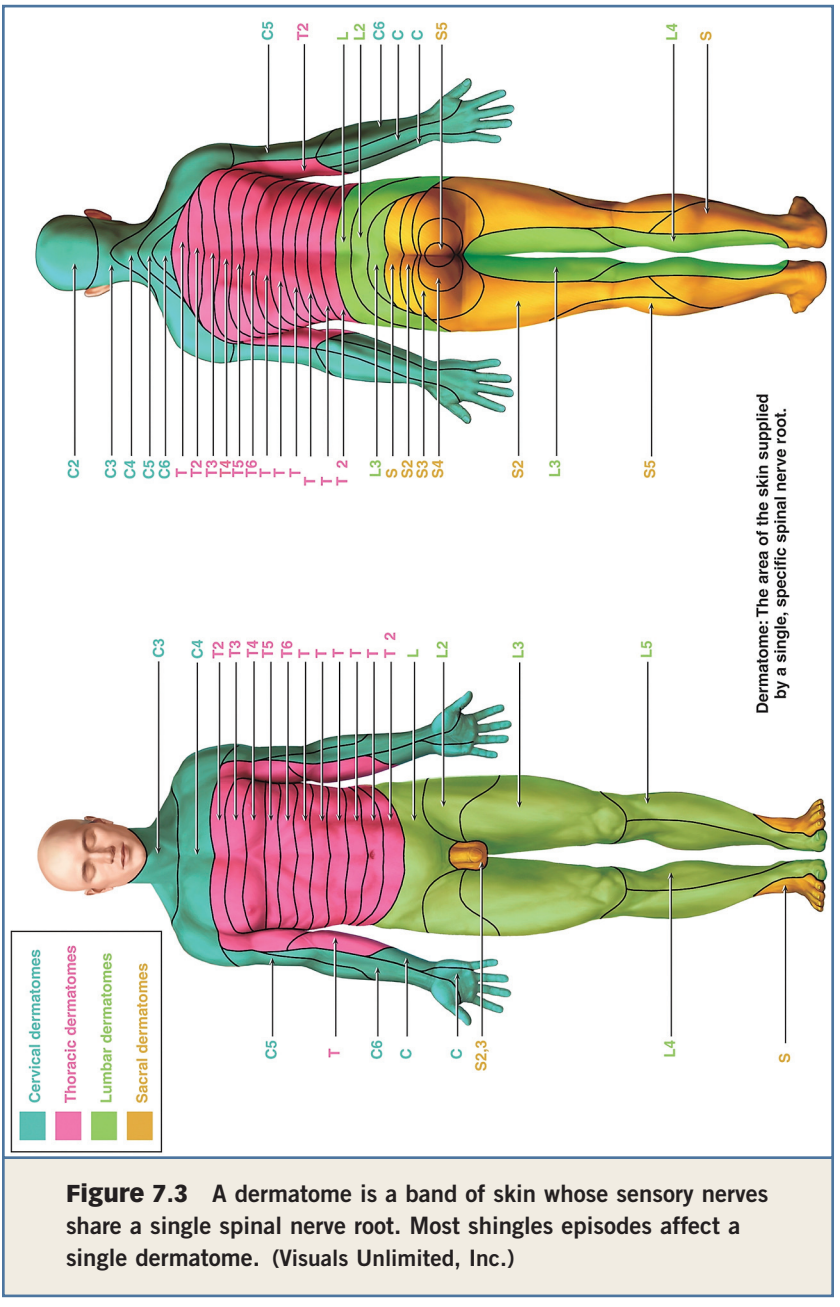

Figure 7.3 A dermatome is a band of skin whose sensory nerves share a single spinal nerve root. Most shingles episodes affect a single dermatome. (Visuals Unlimited, Inc.)

However, some people who develop shingles can develop long-lasting complications. One example is a condition called post-herpetic neuralgia (PHN). It occurs in 10 to 15 percent of patients who develop shingles. In those who are over 60 when they develop shingles, the incidence of PHN is greater than 50 percent. This is a syndrome that results in long-lasting, severe pain following an attack of shingles. The pain is described as a deep, burning pain that is constant; a sharp, stabbing pain that comes and goes; or a dull, blunt pain exacerbated by even a light touch. Some patients with PHN experience all three types of pain—a common description likening the pain to the feeling one gets from chewing aluminum foil, but with the sensation under the skin. In general, PHN occurs because the virus can damage or destroy the nerves where it is replicating. More specifically, the growth of the virus leads to inflammation that can damage the nerves. This inflammation can travel to adjacent nerves, and extend to the spinal cord or brain. This damage can lead to inappropriate signals in the nervous system that are perceived as pain. Also, as some of the damaged nerves regenerate, they become hyperactive and send out abnormal pain signals. This damage can take years for the body to repair, providing an explanation as to why the pain in PHN is often long-lasting.

Many other complications can occur. For example, the patient may lose all feeling in the area where they had an outbreak of shingles. Outbreaks that include the eyes may affect up to 25 percent of patients. Of those patients, 50 percent of the time, eye involvement causes repeat bouts of ocular disease, and in many of those cases, some degree of vision loss. Paralysis, deafness, meningitis, bronchitis, gastritis, colitis, pericarditis, pneumonia, hepatitis, arthritis, and scarring are all reported complications of shingles.

SHINGLES IN PATIENTS WITH IMMUNE DEFICIENCIES

Patients who are immunocompromised are at greater risk for contracting shingles, and for developing serious complications from the illness. For example, several studies have indicated an

THE EVOLUTION OF LATENCY FOR THE VARICELLA-ZOSTER VIRUS

Latency is a condition where a virus (or other pathogen) is kept in check and the net viral population size does not change. Herpesviruses, like the varicella-zoster virus, maintain a static latency during which the virus does not replicate but the viral DNA remains in cells in the body, waiting for a signal to replicate.

A paper from 2002 by researchers from the United Kingdom described some of the factors that might contribute the evolution of viral latency. Essentially, a parasite, like the varicella-zoster virus, needs a strategy that can ensure survival until a new host is available, and the virus can continue to replicate. One potential problem for the varicella-zoster virus is that once a person is infected, he or she is typically immune from a second infection. Because the virus is capable of spreading rapidly within a population, frequently 90 to 95 percent of the population will be immune by virtue of having contracted a case of chicken pox. Consequently, viruses that infect a person late in an epidemic will frequently not be able to find new, susceptible hosts to infect.

These researchers calculated that in populations with few susceptible hosts, viruses with a long latent period have a selective advantage over viruses without the ability to become latent. In these situations, a virus that can wait for years, until a new cohort of susceptible children is born, is more likely to survive and continue to be an effective pathogen.[4]

increased incidence of shingles in patients with systemic lupus erythematosus (SLE). SLE is a disorder of the immune system, where patients produce antibodies that attack their own cells and tissues. This derangement of immune function apparently creates an opening for latent varicella-zoster virus to replicate and produce symptomatic disease.

In patients who are infected with HIV, the risk of developing shingles is 15 to 25 times higher than the risk for individuals who are not infected with HIV. The risk for HIV-infected individuals developing shingles increases with age. HIV patients younger than 50 years of age have a risk for developing the disease of about 4 percent per year; HIV patients over 50 have a risk of about 25 percent per year for developing shingles. In addition, individuals with HIV infection are also prone to develop complications from shingles at higher rates than the general population. For example, HIV patients have a risk of developing severe complications of the nervous system at a rate of about 7 percent, as compared with a rate about 3 percent in the general population.[5] In addition, these patients are prone to unusually severe side effects that are rarely, if ever, seen in patients with normal immunity. For example, some HIV infected patients with AIDS develop progressive outer retinal necrosis, a condition that can lead to blindness following a shingles attack. Other HIV/AIDS patients have developed progressive multifocal leukoencephalopathy, a neurological disorder that damages the brain to the point where death normally follows within a month to a year from onset. HIV/AIDS patients were also likely to have repeated recurrences of shingles, something that occurs very rarely in people with an intact immune system.

There has been a strong association of shingles with certain types of cancers. Patients with Hodgkin's disease, non-Hodgkin's lymphoma, and leukemia had some of the highest shingles attack rates. For example, in one analysis of patients at a comprehensive cancer center in Ontario, Canada, published in 1988, 14 percent

of patients with Hodgkin's disease developed shingles; rates were also high for leukemia (10 percent) and non-Hodgkin's lymphoma (5 percent).[6] It is not entirely clear to what extent the elevation of the shingles incidence is due to the disease itself, or to the chemotherapy and radiation treatments that are often used to treat these diseases. As with patients with AIDS, individuals with these types of cancers often develop a severe case of shingles, and complications are common.

Although the data are sparse, there is also evidence that organ transplant recipients develop shingles at higher rates than the general population. These high rates of shingles are likely attributed to the immunosuppressive drugs taken to prevent rejection of the donated organ or tissue, and for bone marrow transplants, the radiation treatment required to destroy the recipient's bone marrow cells. For example, about one-third of patients receiving bone marrow transplants developed shingles within a year of receiving the transplant.[7] Elevated rates of shingles have also been reported in patients receiving kidney and heart transplants.

SHINGLES AS A MARKER FOR UNDERLYING DISEASE

Because shingles occurs at a higher rate, and with more complications, in patients with conditions that weaken the immune response, this raises the question of whether shingles may be a sign of a more serious underlying disease, such as cancer or diabetes. The information available suggests that is not the case, at least for these two diseases. In one large analysis of patients from Rochester, Minnesota, reported in 1982, there was no difference in cancer or diabetes rates for patients who developed shingles, versus those who did not. However, severe or recurrent cases of shingles, as described above, are likely a sign of an underlying immune deficiency like AIDS, because individuals with a normally functioning immune system typically get shingles no more than once.[8]

SHINGLES TREATMENTS

Because of the potential seriousness of the complications from shingles, attempts have been made to treat or prevent this disease. As with chicken pox, treatment for shingles consists of acyclovir, or similar drugs that prevent the virus from replicating, and these can reduce the seriousness of a shingles attack, if taken early enough.

Because PHN is so common in the elderly, a number of studies have been conducted to test various treatments for this condition. In general, a graded approach is used. Initially, patients are treated with a nonsteroidal anti-inflammatory drug, such as acetaminophen or aspirin. If those drugs do not sufficiently reduce pain, then an additional drug is added. One example is the tricyclic antidepressants such as amitriptyline. In addition to their antidepressant effects, these drugs also reduce the uptake of **neurotransmitters**, thereby reducing the transmission of pain signals. (Neurotransmitters are chemicals that relay signals to nerve cells.) However, there are a number of side effects of these drugs, such as confusion and drowsiness, which limits their usefulness.

If the tricyclic antidepressants are ineffective, or cause too many side effects, another option is a drug like gabapentin, which is one of several drugs used for preventing epilepsy. Limited trials have suggested a reduction in pain in patients suffering from PHN, compared to a placebo, and fewer side effects, compared to the tricyclic antidepressants. It is not clear how gabapentin works to reduce pain, but it may act on nerves in the spinal cord to prevent the transmission of pain signals.

If the combination of a nonsteroidal anti-inflammatory drug and one of these other drugs is not effective at reducing pain, then a physician may prescribe an opioid like codeine or oxycondone (oxycontin). Although side effects such as respiratory problems and drowsiness are common, and there is potential for addiction, these risks can often be managed.

Figure 7.4 Gabapentin, a drug originally developed to prevent epilepsy, may be used to treat pain associated with post-herpetic neuralgia, a complication of shingles. (© 2009 Foster & Smith, Inc. Reprinted as a courtesy and with permission from http://www.DrsFosterSmith.com)

Patients who still do not have pain relief following these treatments have a few other options. There are topical treatments, such as lidocaine, an anesthetic that can be applied to

areas of the skin where a patient is experiencing intense pain. Capsaicin (the active ingredient in hot peppers) can also be applied to the skin. Over time, it can reduce pain, but it does cause a burning sensation that can be intolerable to some people with PHN. There are also surgical interventions, methods of electrical stimulation, and other measures that have sometimes been helpful in treating cases of severe, unrelieved PHN. These techniques may involve cutting some nerves to reduce transmission of pain signals or strong electrical stimulation to alter the sensory input to the brain.[9]

PREVENTING SHINGLES

Prevention has become a more critical component in the medical care for shingles. In 2006, a shingles vaccine was approved for use in the United States for people over the age of 60. The vaccine has a much higher dose of the virus, compared to the vaccine used to prevent chicken pox. This high dose is used because older individuals tend to have a weakened immune response, so greater exposure to the virus is needed in order to stimulate a strong enough reaction to protect against shingles. The vaccine was shown to be safe in clinical studies. In a large-scale study, reported in 2005, nearly 40,000 volunteers, aged 60 to 69, were included. Those who were vaccinated had about 50 percent fewer cases of shingles. Those who were vaccinated and did develop shingles had less painful cases, and were less likely to develop complications.[10]

It is likely that, as the number of chicken pox cases continues to decline in the United States, vaccination for shingles will become more important. When chicken pox was common, people at risk for shingles would be exposed to the varicella-zoster virus whenever they encountered someone with chicken pox. This exposure would boost their immunity to the virus, and possibly prevent an attack of shingles. As chicken pox becomes rare, the likelihood of boosting the response to the virus decreases, and the risk of an attack of shingles

TAI CHI AND SHINGLES

Researchers have also studied some less conventional therapies to prevent or treat shingles. One report from researchers in California analyzed a study of the effect of tai chi on immunity to shingles. Tai chi is an oriental exercise that involves the slow repetition of martial arts movements. They studied a small group of 36 people over the age of 60, 18 of whom took tai chi three times per week, and 18 of whom did not. The study ran for 15 weeks. During this time, the participants' immune response to the varicella-zoster virus was determined. Those seniors taking tai chi had significant increases in their response to the virus compared to those not participating, suggesting they might be less susceptible to the development of shingles.[11]

Figure 7.5 Senior citizens practicing tai chi. (© Anne Clark/iStockphoto)

will likely increase. This phenomenon was reported from a study in Massachusetts, where the incidence of chicken pox declined following vaccination, but the incidence of shingles increased. Further study will be needed, though, to verify this association between chicken pox vaccination and shingles.[12] The shingles vaccine will likely be increasingly important as a means of providing a boost to the immune response, thereby reducing the risk of shingles in an individual. The vaccine is now recommended by the Centers for Disease Control for all adults over the age of 60, unless they are significantly immunocompromised.

8

The Future of Chicken Pox and Shingles

In the United States, with the widespread implementation of the chicken pox vaccine and the recent introduction of the shingles vaccine, it is expected that the number of cases of chicken pox and shingles will continue to decline. Vaccination has already substantially reduced the number of deaths and the associated medical costs for treating chicken pox in the United States.

As mentioned previously, one of the unanswered questions is what will happen to patients who do not receive the vaccine. Until recently in the United States, most people got chicken pox during childhood. In general, chicken pox becomes more serious the older one is when one contracts it. Therefore, it appears likely that unvaccinated people will be less likely to contract chicken pox in childhood, and may be more likely to get it later in life, when it will be a more serious disease. Consequently, it will be critical that public health authorities work to ensure that the vaccination rate is very high. Doing this would ensure that any chicken pox outbreak would not spread, because the virus cannot spread to vaccinated people, a phenomenon called herd immunity.

Another unanswered question is how long the vaccination protects against infection. So far, the protection from the vaccine seems durable, although the vaccine has not been available for a long enough period to

document that the vaccination protects for 40 to 50 years. In the United States, there are also some unanswered questions about the incidence of shingles in future years. As the elderly population is expected to grow substantially in the next decades, one would expect a substantial increase in the number of shingles cases. However, the approval of the shingles vaccine should help people maintain their immunity, and reduce the incidence and severity of the disease. In addition, those who received the chicken pox vaccine are less likely to develop shingles, based on early studies. Over time, this will likely reduce the overall number of shingles cases.

It will not be known for some time how long immunity from the shingles vaccine will last. The vaccine is approved for people over 60, but with a larger number of people living into their 80s and beyond, it is not yet clear if the vaccine will provide protection for 20 years or more.

In other parts of the world, the future of chicken pox and shingles is even less clear. Many other developed countries have not adopted the universal vaccination for chicken pox that has been put in place in the United States. In these countries, it would be expected that the incidence of chicken pox and shingles would not decrease as much as in the United States. In the less developed countries, where there is little or no vaccination, the long-term patterns of infection are likely to continue. In many of these countries, there is a higher rate of chicken pox in adults, when the disease is likely to be more serious. That is not likely to change in the near future.

Some general aspects of the biology of the varicella-zoster virus suggest hope for continued reduction of the incidence of the disease. The virus has a relatively low mutation rate, so it is unlikely that mutations will lead to the vaccine becoming ineffective.

As described in previous chapters, advances in molecular biology have led to a greatly enhanced knowledge of the natural history of the varicella-zoster virus. The sequencing of the

Figure 8.1 The Centers for Disease Control now recommends shingles vaccination for all adults over 60, unless they are significantly immunocomprimised. (Judy Schmidt/Centers for Disease Control and Prevention/ U.S. Department of Health and Human Services)

entire genome of the vaccine strain, the parental viral strain, and other isolates of the virus have aided in understanding how the virus causes disease.[1] The ability to use polymerase chain reaction and other techniques to identify the location of the virus during latency in the body has provided a better understanding of strategies the virus uses to remain hidden in the body, and should aid in the development of improved therapies and preventative measures for dealing with shingles.

One of the continuing limitations in understanding the biology of the varicella-zoster virus is the lack of an animal model that reproduces all aspects of the disease in humans. The SCID mouse model of chicken pox has been an important development, but still lacks some elements of

natural infections in humans (for example, the lack of a clear latent phase of infection). Consequently, additional tools for understanding all aspects of the biology of this pathogen will continue to be important. If the pace of recent advances continues, there is reason to hope for a continued reduction in the number of deaths, and the pain and suffering caused by chicken pox and shingles.

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Glossary

adaptive immune system A branch of the immune system that develops in response to a particular pathogen. It consists of both cell-mediated immunity and antibody production. This response is generally very effective, but it takes a week or more to develop, so the innate immune response is critical early in an infection.

agglutination A reaction that results in clumping. One method for detecting the varicella-zoster virus involves an agglutination reaction.

anaphylactic shock An allergic reaction where the blood vessels suddenly dilate, causing the blood pressure to drop and the bronchial tubes to close off, resulting in breathing difficulty. It can occur following exposure to an allergen and can result in death if not treated quickly.

antibody Proteins in the blood that are involved in responding to an infection. Antibodies can also be used to identify specific pathogens, such as the varicella-zoster virus. *See also* **immunoglobulins**.

antigen presentation A mechanism by which cells of the immune system recognize cells that are infected with a virus (or other pathogen). In this process, the infected cell places some parts of the virus on the cell surface. These viral fragments, in the context of a host molecule (the MHC), activate cytotoxic T-lymphocytes, which then destroy the infected cells.

B-cells A type of circulating white blood cell that produces antibodies. While apparently not a critical factor in the immunity to chicken pox, antibodies may play some role in control of the disease.

capsid A portion of the varicella-zoster virus. The capsid consists of proteins that completely surround and protect the DNA genome of the virus.

CD4+ T-cell A type of white blood cell that regulates the function of other components of the immune system. These cells play at least two roles during an infection of the varicella-zoster virus. Initially, they become infected with the virus and help transport the virus to the skin. As a specific immune response develops, these cells help coordinate the immune response that clears the virus from the skin.

cell-mediated immunity A type of specific immune response where cells of the immune system (cytotoxic T-lymphocytes) recognize cells infected with viruses or other intracellular pathogens and destroy those infected cells as a means of limiting infection.

ceramides Lipids produced by skin cells that provide a waterproofing coating for the skin.

cerebellar ataxia A potential complication of chicken pox in the cerebellum of the brain that results in disturbances in balance and gait and other critical functions.

chicken pox An illness characterized by a widespread rash. Chicken pox is caused by the varicella-zoster virus.

congenital varicella syndrome (CVS) A group of symptoms that may occur in the fetus following a maternal chicken pox infection during early pregnancy. Although rare, CVS can result in death or serious malformations of the fetus.

cytotoxic T-lymphocytes (CTLs) Cells that form a critical part of the specific immune response to chicken pox (and other viral infections). CTLs are a type of white blood cell that can recognize cells that are infected with a particular virus and target and destroy those cells to limit viral replication.

dermatome A band of skin whose sensory nerves share a single spinal nerve root.

DNA polymerase An enzyme that is used to make DNA.

DNA sequencing A technique for determining each letter of the genetic code in a gene, a virus, or an organism. This provides the most definitive method for comparing genetic information between, for example, different isolates of a virus.

electron microscope A microscope that uses an electron beam (rather than visible light) to visualize objects. Electron microscopes are powerful enough to visualize tiny objects (such as the varicella-zoster virus).

encephalitis A complication of chicken pox that involves inflammation of the brain

endocytosis A process by which cells take up materials from their environment. Some viruses, like the varicella-zoster virus, take advantage of this process and use it to enter the cells.

endoplasmic reticulum A channel-like structure inside human cells that is involved in the transport of materials to their proper location in the cell. In the life cycle of the varicella-zoster virus, the newly formed viral particles transit from the nucleus through the endoplasmic reticulum.

envelope A membrane that provides the very outer coat of the varicella-zoster virus. The envelope consists of lipids that come from the nuclear membrane of the infected host cell.

enzyme-linked immunosorbent assay (ELISA) A laboratory technique for detecting antigens or antibodies. For example, to detect antibodies to the varicella-zoster virus, a lab can manufacture a plastic plate that contains small wells coated with varicella-zoster virus proteins. Patient serum samples are added to the wells, and, if antibodies to the virus are present, those antibodies will bind, and can be detected through the addition of other chemicals.

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enzymes Proteins that catalyze a particular chemical reaction.

genome The entire set of genetic instructions for a virus or an organism. In the case of the varicella-zoster virus, the genome is a double-stranded DNA that consists of approximately 125,000 individual pieces of information (nucleotide base pairs).

genus A category in the classification of viruses that includes the most closely related members of a virus family or subfamily.

glycoproteins Proteins that have sugars attached to them. In the case of the varicella-zoster virus, glycoproteins on the surface of the virus play a critical role in the viral entry into cells, and in the human immune response that ultimately curtails the infection.

granulysin A protein produced by immune system cells that kills other cells that are infected with intracellular pathogens like viruses.

heparin sulfate A molecule on the surface of many human cells. It is composed of a chain of sugar molecules, which have sulfur attached. Heparin sulfate is a molecule that the varicella-zoster virus uses for binding to host cells and entering them.

herpesviruses A family of viruses that includes a number of human pathogens, including the varicella-zoster virus that causes chicken pox. These viruses contain a double-stranded DNA genome, which contains information that specifies 100 to 200 proteins. The DNA is encased in a protein capsid, which in turn is surrounded with an envelope made of lipids. The name *Herpes* comes from a Greek word meaning "to creep," describing the repeated cycles of infection that are typical of most illnesses caused by this group of viruses.

immunoglobulins Also known as antibodies. Proteins made by cells of the immune system that bind to and inactivate pathogens. Immunoglobulins are selected, in the body, in response to specific pathogens.

incubation period The time from infection or exposure to a virus until disease symptoms appear.

innate immune system A branch of the immune system that is always available to fight infection. It includes the chemical interferon-alpha, which is an important factor in reducing the ability of the virus to replicate. Although the innate immune response is the first line of defense, it is not as effective as the immune response that develops specifically to fight a particular infection.

interferons Chemicals produced by cells in the body in response to viral infection that reduce the ability of the virus to replicate. The name of these compounds derived from the fact that they interfere with viral replication.

latency A condition where a virus remains viable but is inactive. The varicella-zoster virus can remain inactive for years in nerve cells.

mannose-6-phosphate A sugar with an attached phosphate. In cells, mannose-6-phosphate is a targeting signal that sends proteins (or the varicella-zoster virus) to a cellular compartment called the golgi apparatus.

mannose-6-phosphate receptor A protein on the surface of cells that binds to mannose-6-phosphate. In relation to the varicella-zoster virus, this receptor aids in the uptake of the virus into nerve cells, establishing a latent infection.

memory T-cells A type of T-cell that is long lasting and retains the ability to react to the chemical signature of a specific pathogen, such as the varicella-zoster virus.

mutate To change. In a biological context, mutation generally describes a change in the genetic material, the DNA.

nanometer A measure of length, corresponding to one-billionth of a meter. This is the size range of most viruses, including the varicella-zoster virus, which is approximately 175 nanometers in size.

neurotransmitters Chemicals (like serotonin) that relay signals to nerve cells.

nucleocapsid A viral particle consisting of the protein capsid, which contains the viral DNA. In the case of the varicella-zoster virus, the nucleocapsid is an intermediate in the synthesis of the final viral particle.

pathogen A microbe, usually a bacterium or virus, that causes disease.

platelets Components of the blood that facilitate clotting. Chicken pox complications rarely include disruption of platelet function.

pneumonia An infection of the lungs or a portion of the lungs by a pathogen. This can be a serious complication, particularly in adults, following a bout of chicken pox.

polymerase chain reaction (PCR) A method for amplifying sections of DNA. Polymerase chain reaction tests can be used to determine whether the varicella-zoster virus is present in a patient sample.

replication Copying, reproducing. The replication of the varicella-zoster virus means that the virus is producing many copies of itself inside human cells.

restriction enzymes A type of enzyme that recognizes and cuts a particular DNA sequence. These enzymes have been used for many purposes, including the comparison of viruses isolated from the same person, or different people, to see if the viruses are similar or different.

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rolling circle replication A process of DNA replication in which a circular DNA molecule acts as a template for the production of linear DNA. The process begins with one strand of the circular DNA being cut and used as a template for the other DNA strand. The mechanism is somewhat like the unspooling of string, with a second strand of string being made and attached to the first strand of string, as it is pulled off the spool.

serum The liquid portion of the blood that contains antibodies. These antibodies can be used to identify pathogens and, in some cases, even treat diseases like chicken pox.

severe combined immunodeficiency (SCID) A strain of SCID mice has been used to study chicken pox. These mice lack almost all normal immune responses, and consequently, they do not reject transplants of human tissue. The human tissue in the mice is infected with the varicella-zoster virus, and the development of stages of infection can be studied in detail.

shingles Herpes zoster. A disease, usually characterized by a localized, banded, painful rash. It is caused by the varicella-zoster virus, the same virus that causes chicken pox. In the case of shingles, the same virus that originally caused chicken pox in a person reactivates in the person's nerve cells and travels to the skin, producing shingles.

smallpox A serious, frequently fatal disease caused by the variola virus. Prior to the eradication of this disease by a worldwide vaccine campaign, it could sometimes be confused, in its initial stages, with chicken pox.

T-cells White blood cells that play a number of critical roles in the immune response. During the early stages of a chicken pox infection, the varicella-zoster virus infects T-cells, which eventually travel to the skin.

tegument proteins These are proteins located between the viral nucleocapsid and envelope. They are critical for early stages in replication of the varicella-zoster virus.

transcriptional activator A protein that enhances the production of RNA from a DNA template in a cell.

transcriptional repressor A protein that inhibits the production of RNA from a DNA template in a cell.

trans-golgi network Part of a cellular system for sorting molecules in the cell. In the case of the varicella-zoster virus, the trans-golgi network is the place where the virus acquires an envelope studded with viral glycoproteins.

virulence A property of a pathogen that makes it more likely to cause disease, or to cause a more serious disease

Further Resources

Books

Arvin, Ann, and Anne Gershon, eds. *Varicella-zoster virus: Virology and clinical management*. Cambridge, Mass.: Cambridge University Press, 2000.

Royston, Angela. *Chickenpox (It's Catching)*. Chicago: Heinemann Library, 2002.

Web Sites

Centers for Disease Control and Prevention
http://www.cdc.gov

eMedicine
http://www.emedicinehealth.com/chickenpox/article_em.htm

KidsHealth
http://kidshealth.org/parent/infections/skin/chicken_pox.html

Mayo Clinic
http://www.mayoclinic.com/health/chickenpox/DS00053

VSV Research Foundation
http://www.vzvfoundation.org

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About the Author

Patrick Guilfoile earned his Ph.D. in bacteriology at the University of Wisconsin–Madison. He subsequently did postdoctoral research at that institution, as well as at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. He is a professor of biology at Bemidji State University in northern Minnesota. Currently on leave from his faculty position, he is serving as an associate dean at the University. His most recent research has focused on the molecular genetics of ticks and other parasites. He has authored or coauthored more than 20 papers in scientific and biology education journals. He has also written three other books in this series, along with a molecular biology laboratory manual, and a book on controlling ticks that transmit Lyme disease.

About the Consulting Editor

Hilary Babcock, M.D., M.P.H., is an assistant professor of medicine at Washington University School of Medicine and the medical director of occupational health for Barnes-Jewish Hospital and St. Louis Children's Hospital. She received her undergraduate degree from Brown University and her M.D. from the University of Texas Southwestern Medical Center at Dallas. After completing her residency, chief residency, and Infectious Disease fellowship at Barnes-Jewish Hospital, she joined the faculty of the Infectious Disease division. She completed an M.P.H. in Public Health from St. Louis University School of Public Health in 2006. She has lectured, taught, and written extensively about infectious diseases, their treatment, and their prevention. She is a member of numerous medical associations and is board certified in infectious disease. She lives in St. Louis, Missouri.