Herpes zoster results from reactivation of endogenous varicella-zoster virus (VZV) that has persisted in latent form within sensory ganglia following varicella (chickenpox). More than 90% of adults in the United States have serologic evidence of prior VZV infection. Consequently, latent VZV is present in the sensory ganglia of virtually every older adult who was raised in the continental United States. Thus, almost every older adult in the United States is at risk of developing herpes zoster.

Herpes zoster actually begins with chickenpox, the clinical manifestation of primary VZV infection. During chickenpox, infectious virus that is present in large amounts in chickenpox vesicles enters the endings of sensory nerves in the skin, travels up the sensory nerves to the dorsal root and cranial sensory ganglia where the nerve cell bodies are clustered, and establishes lifelong residence (ie, latent infection) in those sensory neurons. Consequently, the dorsal root and cranial sensory ganglia of everyone who has had chickenpox are latently infected with VZV—they contain the genomic DNA of VZV, but not infectious virus.

This latent VZV eventually reacts, presumably in a single sensory neuron, to cause herpes zoster. The reactivated virus multiplies and spreads within the ganglion, infecting many additional neurons and supporting cells—a process that causes intense inflammation and neuronal necrosis. The virus then travels from the sensory ganglion back down the nerve to the skin, where it produces the characteristic dermatomal rash of herpes zoster.

The skin lesions of herpes zoster and chickenpox are histopathologically identical: both contain multinucleated giant cells with eosinophilic intranuclear inclusion bodies. The rash of herpes zoster is similar to chickenpox, except that it is restricted to one area of the skin on one side of the body—namely, the der-
matome innervated by the ganglion in which the latent virus reactivated. Also, the lesions of herpes zoster consist of closely grouped vesicles on an erythematous base, whereas those of chickenpox are individual and randomly distributed. These differences reflect intraneural spread of virus to the skin in herpes zoster, in contrast to viremic spread in chickenpox.

In temperate climates, chickenpox occurs in epidemics in the late winter and early spring, whereas herpes zoster occurs sporadically throughout the year. Immunocompetent individuals usually have herpes zoster only once, presumably because an episode of herpes zoster boosts immunity to VZV, essentially “immunizing” against another episode.

Course of Illness
Herpes zoster typically begins with severe unilateral pain that persists for several days before the rash appears. This presentation of herpes zoster reflects the pathology caused by multiplication and spread of the reactivated VZV in the affected sensory ganglion. The prodromal pain of herpes zoster can mimic the pain of appendicitis, biliary or renal colic, cholecystitis, duodenal ulcer, glaucoma, myocardial infarction, pleurisy, or prolapsed intervertebral disk and, therefore, can lead to serious misdiagnosis. Herpes zoster is virtually impossible to diagnose until the characteristic vesicular dermal rash appears.

When the herpes zoster rash develops, skin lesions appear in successive crops and quickly evolve from erythematous macules to papules and then to delicate intraepithelial vesicles (blister) filled with clear fluid. After polymorphonuclear leukocytes, macrophages, and lymphocytes infiltrate the vesicles, the fluid becomes cloudy and the vesicles become pustules. These pustules subsequently dry to form flat adherent crusts.

Vesicles and pustules are usually present for 7 to 10 days, while crusts persist for 2 to 3 weeks. Healing (re-epithelialization) is almost always complete within 4 weeks of rash onset. However, pain, which reaches maximum intensity early in the second week, may persist beyond rash healing, resulting in a debilitating complication known as postherpetic neuralgia (PHN).

Postherpetic Neuralgia
The incidence and severity of herpes zoster increase with age, as does the risk of developing PHN. Manifestations of PHN vary from person to person. While it is rarely described identically by two afflicted individuals, patients frequently describe it as the worst pain that they have ever experienced.

Clinically significant PHN was described by R. Edgar Hope-Simpson in 1975 as long-lasting pain of sufficient severity to interfere with activities of daily living, decrease quality of life, and cause patients to seek medical attention. Such clinically significant PHN complicates the more serious cases of herpes zoster, which are characterized by severe pain and extensive rash during the acute phase of the disease.

Patients with PHN often have a central area of cutaneous scarring and sensory loss surrounded by an area of hyperesthesia and allodynia, a particularly distressing sensory abnormality in which stimuli that are not normally painful (eg, light touch) elicit pain and unpleasant sensations.

Allodynia is present in the majority of patients with PHN and is responsible for a large portion of their disability. Even the light touch of clothing may cause severe pain and discomfort, resulting in decreased quality of life and reduced capacity to carry out activities of daily living. For example, afflicted individuals may find it impossible to leave their home because it is too painful to put on a shirt.

Individuals with prolonged PHN have pathologic evidence of neuronal loss and scarring in the portion of the sensory ganglion and spinal dorsal horn corresponding to the area of affected skin. Thus, death of primary neurons in the involved sensory ganglion and of secondary neurons in the corresponding dorsal horn of the spinal cord during the acute phase of herpes zoster appear to be responsible for many of the sensory abnormalities that characterize PHN.

Herpes Zoster vs Herpes Simplex
The pathogenesis of herpes zoster and herpes simplex share a number of characteristics that may cause the two diseases to be confused clinically. Thus, it is important to differentiate them (Figure 1).

Like VZV, herpes simplex virus (HSV) is latent in sensory neurons. However, sensory neurons latently infected with HSV are located primarily in the first and second divisions of the trigeminal ganglion and in the sacral sensory ganglia, reflecting the most common sites of primary HSV infection. Most episodes of recurrent herpes simplex involve these same anatomic sites.

In contrast, neurons latently infected with VZV are present in essentially all sensory ganglia. However, the frequency of herpes zoster in individual dermatomes corresponds to the density of lesions in chickenpox. Thus, herpes zoster most often involves the first division of the trigeminal ganglion and dermatomes on the trunk.

When HSV reactivates, it does not appear to multiply and spread within the ganglion. Instead, it remains confined to the neuron in which it reactivated. Thus, when HSV travels back down the sensory nerve to the skin, it usually produces lesions in the area innervated by that individual neuron and thus involves a very small portion of the dermatome. Remarkably, the neuron in which latent HSV reactivates does not appear to be killed in the process but survives to permit repeated reactivation. Thus, multiple recurrences of HSV (eg, herpes labialis or cold sores) are common and usually involve the same anatomic location.

Conversely, recurrences of herpes zoster are relatively uncommon in immunocompetent persons. When they do occur, they rarely involve the same dermatome. When VZV reactivates, it does not remain confined to a single neuron, as does HSV, but multiplies and spreads in the ganglion to infect many neurons. Consequently, it reaches the skin via the axons of many neurons, and the resulting rash involves a large portion of the dermatome. Reactivation of latent VZV also results in extensive damage to the ganglion, which is believed to explain the frequent development of PHN.
Recurrent herpes simplex is almost never associated with sensory loss or PHN. Many individuals have experienced hundreds of cold sores in a lifetime without developing sensory loss or PHN.

Herpes simplex and varicella-zoster viruses also differ in their epidemiology, particularly in the role of asymptomatic infection and asymptomatic virus shedding. A large proportion of primary and recurrent HSV infections are asymptomatic. Consequently, transmission of HSV, whether oral or genital, is usually the result of asymptomatic virus shedding.

In contrast, most primary and recurrent VZV infections are symptomatic, and asymptomatic virus shedding does not appear to occur with VZV. Susceptible individuals acquire chickenpox from someone with symptomatic chickenpox or herpes zoster, though respiratory transmission makes chickenpox contagious for a day or more before the appearance of skin lesions. Only about 4% of chickenpox cases are so clinically mild as to be undiagnosed.

The mechanisms of HSV and VZV latency are also different, and this difference may have significant clinical implications. Neurons latently infected with HSV express a unique class of viral RNA molecules (“latency-associated transcripts”) but do not express any HSV proteins. Thus, in theory, the immune system has no means of recognizing neurons latently infected with HSV. In contrast, neurons latently infected with VZV express several “immediate early” and “early” VZV proteins. Therefore, in theory, the host immune system may be able to recognize neurons latently infected with VZV and limit reactivation.

In addition, the important role of postreactivation multiplication and spread of VZV within the ganglion provides another target for host immune responses, which may limit VZV replication and spread and, thereby, prevent the development of herpes zoster even when latent VZV has reactivated. The well-recognized syndrome of herpes zoster without rash—zoster sine herpete—may represent an example of such limitation of postreactivation replication and spread of VZV by host immune defenses, as described in the following section.

*Cell-Mediated Immunity*

In 1965, Hope-Simpson published a landmark study on all cases of herpes zoster and chickenpox that occurred in his medical practice during the previous 16 years. He recorded the sporadic nature of herpes zoster and the absence of any temporal relationship between its onset and exogenous exposure to VZV. He also documented the increased frequency and severity of herpes zoster with increasing age, as well as the relative rarity of second episodes of herpes zoster.

To explain these observations, Hope-Simpson proposed that in addition to establishing latent VZV infections in sensory neurons, chickenpox elicits an immune response that limits the ability of the latent virus to reactivate and cause herpes zoster. The level of this immunity to VZV gradually declines over time but is periodically boosted by subclinical infections resulting from exogenous exposure to VZV (eg, when caring for a child with chickenpox) and by episodes of reactivation limited by rapidly mobilized immune responses so that no rash develops.

As described by Gelb in this supplement to *JAOA*—The Journal of the American Osteopathic Association, these boosts in VZV-specific immune response help slow the age-related decline in host resistance to herpes zoster. However, VZV-specific immunity eventually falls below some critical threshold, which allows the latent virus to reactivate and cause herpes zoster.

Every aspect of Hope-Simpson’s remarkable theory has been validated,

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<td>Symptomatic reactivation of latent virus</td>
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Figure 1. Comparison of herpes zoster and recurrent herpes simplex.
and it has been demonstrated that the critical element of the host immune response is cell-mediated immunity (CMI) to VZV (Figure 2). Antibody to VZV, which can protect against primary exogenous VZV infection (ie, chickenpox), appears to play no role in host resistance to herpes zoster. Instead, it is VZV-CMI that limits the ability of latent VZV to reactivate and cause herpes zoster.

Levels of VZV-CMI decline with age in immunocompetent individuals in association with the age-related increase in the incidence and severity of herpes zoster, whereas levels of antibody to VZV do not decline substantially with increasing age. Moreover, the incidence of herpes zoster markedly increases after hematopoietic stem cell transplantation, a circumstance in which VZV-CMI is depressed while VZV antibody levels are maintained with intravenous γ-globulin.

The age-specific incidence of herpes zoster is also markedly increased in patients with human immunodeficiency virus infection or Hodgkin disease, in organ transplant recipients, and in patients receiving immunosuppressive therapy in whom VZV-CMI is suppressed but levels of antibody to VZV are relatively well maintained. In contrast, patients with X-linked agammaglobulinemia whose VZV-CMI responses are relatively intact are not at increased risk of herpes zoster. Therefore, it is clear that the level of CMI to VZV determines the risk and severity of herpes zoster and PHN, whereas antibody to VZV plays no clinically significant role.

**Shingles Prevention Study**

As described by Gelb, Hope-Simpson’s hypothesis suggested that herpes zoster might be prevented or attenuated in elderly patients if their waning CMI to VZV could be boosted with a VZV vaccine. This hypothesis was the basis of the Shingles Prevention Study, a randomized double-blinded placebo-controlled trial conducted by the US Department of Veterans Affairs to evaluate the efficacy and safety of a high potency live attenuated VZV vaccine (zoster vaccine) for the prevention of herpes zoster and PHN.

The study enrolled 38,546 immunocompetent adults aged 60 years or older who had a history of chickenpox or had resided in the continental United States for more than 30 years. Study participants had no history of herpes zoster. Subjects at each of the 22 study sites were separately randomized by age strata (aged 60-69 years and aged 70 years or older) to receive a single dose of zoster vaccine or placebo.

As noted by Gelb, zoster vaccine stimulated VZV-CMI and reduced the burden of illness caused by herpes zoster—a severity-by-duration measure of the total pain and discomfort caused by herpes zoster—by 61.1% (P < .001). Zoster vaccine also reduced the incidence of clinically significant PHN by 66.5% (P < .001) and the incidence of herpes zoster by 51.3% (P < .001). The zoster vaccine was well tolerated and did not induce or cause herpes zoster in this population.

An Immunology Substudy of the Shingles Prevention Study involved a subset of participants who had immunologic assessments before and after vaccination. Blood samples were collected from 1396 subjects at two study sites before vaccination and at 6 weeks and 1, 2, and 3 years thereafter. The samples were tested for VZV-CMI by interferon-γ enzyme-linked immunospot assay (ELISPOT) and responder cell frequency (RCF) assays, and for antibody to VZV by glycoprotein enzyme-linked immunosorbent assay.

Six weeks after vaccination, the immune responses in the vaccine recipients as measured by all three assays were significantly greater than those in placebo recipients.

**Figure 2. The pathogenesis of herpes zoster according to Hope-Simpson, 1965.** Source: Modified from Hope-Simpson R. Proc R Soc Med. 1965;58:9-20.
were significantly increased compared with those of the placebo recipients. The vaccine-induced increases in VZV-CMI persisted during the 3-year follow-up period, although they decreased in magnitude over time.6

The immune responses among different age groups were also measured to determine the effect of increasing age on immune responses to VZV. When baseline (preimmunization) values of VZV-CMI and VZV antibody among subjects in various age groups were compared, the age-related decline in VZV-CMI levels known to occur beginning early in adulthood was found to continue among older adults in the Shingles Prevention Study.6 The estimated annual decline in the level of VZV-CMI per year of increase in age was 2.7% for RCF and 3.9% for ELISPOT. In contrast, levels of antibody to VZV did not decline with increasing age.6

The VZV-CMI responses to zoster vaccine, measured 6 weeks after vaccination by both RCF and ELISPOT assays, also decreased with age, and average levels were significantly lower in subjects aged 70 years or older than in subjects aged 60 to 69 years. RCF and ELISPOT responses at week 6 decreased by 3.5% and 3.8%, respectively, per year of age. In contrast, the effect of age on the antibody response to zoster vaccine was negligible.6

At baseline, VZV-specific immune responses were lower, on average, in subjects in whom herpes zoster developed than in those in whom it did not, regardless of group assignment (ie, placebo or vaccine). Cox regression analyses also revealed a significant inverse relationship between the immune responses 6 weeks after vaccination and the risk of herpes zoster.6

Severity of illness among subjects in whom herpes zoster developed was inversely correlated with the level of VZV-CMI measured at the first clinic visit following rash onset.20 Subjects with higher levels of VZV-CMI at this early time point had lower herpes zoster severity of illness scores. The average levels of VZV-CMI were also significantly lower in subjects in whom PHN developed than in those in whom it did not.20

A similar correlation was not observed between levels of antibody to VZV and severity of herpes zoster. In fact, VZV antibody levels were highest in the group of individuals with the most severe disease and in those who developed PHN.20 The increased level of antibody most likely reflected the more extensive replication of VZV in subjects with more severe disease. Thus, higher levels of VZV-CMI at the onset of herpes zoster correlated with reduced severity of disease and with a lower incidence of PHN, whereas higher levels of antibody to VZV did not.20

Comment

The Shingles Prevention Study7 and its Immunology Substudy20 demonstrated that administration of zoster vaccine to subjects aged 60 years or older reduced the incidence and severity of herpes zoster and the incidence of PHN. This clinical response was correlated with a vaccine-induced increase in VZV-CMI. In the placebo recipients, the age-related increase in the incidence and severity of herpes zoster and in the incidence of PHN was shown to be correlated with an age-related decline in VZV-CMI, but a comparable age-related decline in levels of antibody to VZV was not observed.

Finally, the study7 demonstrated that increased levels of VZV-CMI at rash onset were correlated with a reduction in the severity of herpes zoster and in the incidence of PHN, whereas increased levels of antibody to VZV were not. These results strongly support the hypothesis that the increase in the frequency and severity of herpes zoster that accompanies increasing age is caused by an age-related decline in VZV-CMI. These results also indicate that the clinical efficacy of zoster vaccine is the result of its capacity to increase the waning levels of VZV-CMI observed in older adults.7

References