After herpes zoster, immunocompetent persons frequently experience chronic pain and considerable suffering. Zoster-associated pain has a complex pathophysiology that begins with viral damage and increased sensitization of peripheral sensory neurons. The enhanced afferent barrage from these neurons sensitizes spinal neurons and leads to loss of synapses from descending inhibitory fibers, resulting in central neuropathic pain and allodynia. Antiviral therapy of acute zoster limits this sequence of pathophysiologic mechanisms. There is no clear consensus regarding the optimal means of determining the benefits of antiviral therapy in the management of pain of herpes zoster. A novel statistical approach utilizing rates of disappearance of pain of differing pathophysiologic mechanisms is proposed.

Herpes zoster occurs when latent varicella-zoster virus (VZV) reactivates and multiplies within a sensory ganglion and travels along the sensory nerve to the skin. This is a common disease, particularly among the elderly. Epidemiologic data indicate there are 1.5–4.0 cases per 1000 persons per year [1]. Pain is the most troublesome symptom of herpes zoster and the reason for most physician consultations. In a large observational trial of valacyclovir, pain preceded the rash of herpes zoster in 84% of patients and was present during the acute exanthem phase in 89% [2]. Pain preceding or accompanying the dermatomal rash is termed acute pain. In some persons, especially the elderly, pain in the distribution of the affected sensory nerve can persist for days, weeks, months, or occasionally years after the skin manifestations of the condition have resolved [3]. Traditionally this persisting chronic pain is termed postherpetic neuralgia (PHN) and is defined as pain persisting after the lesions have healed or pain persisting 4 weeks after the onset of lesions, regardless of degree of healing.

Unlike pain accompanying acute tissue damage, which stimulates a person to avoid further damage to the area, persistent pain offers no biologic advantage and leads only to suffering and distress. As a result of activity in spinohypothalamic and pontine-hypothalamic pathways, the stress response is initiated and, once this stress response is extended it becomes dysregulated and maladaptive [4]. This leads to fatigue, impaired functioning, and adaptive behavior that is experienced as sickness. In turn, this promotes negative thinking and a vicious circle of stress and disability, rendering an individual incapable of performing as usual in the home, community, or workplace [4]. Thus, chronic pain is a major burden to the individual in terms of suffering and to the healthcare system and society at large.

To consider the rationale behind the wide range of interventions that have been used in acute herpes zoster and to formulate optimal approaches, it is helpful to understand the pathophysiologic mechanisms that contribute to the pain associated with herpes zoster. In one patient it is impossible to determine the contribution of different pain mechanisms occurring simultaneously, but modeling of the kinetics of pain in a population that has experienced herpes zoster could enable a more rational approach and an improved effect of therapy for an individual patient.

Pathophysiology of Pain in Herpes Zoster

The pain of herpes zoster is a form of neuropathic pain that results from damage to the nervous system. It is a conscious sensation resulting from complex sensory processing within the highest levels of the central nervous system (CNS) [5].

Pain accompanying acute herpes zoster. The neuropathology and acute inflammation of acute herpes zoster are maximal within the dorsal root ganglion of the affected dermatome but extend peripherally along the length of the sensory nerve and sometimes proximally to the adjacent motor and sensory roots and the spinal cord. This damage to neurons caused by VZV replication in acute herpes zoster results in an increase in the sensitivity and responsiveness of nociceptors (peripheral sensitization) [6]. This is a consequence of the initial inflammatory response to neuronal destruction and an associated release of cytokines. Of importance, the pain of acute herpes zoster is not produced by stimulation of the high threshold sensory receptors (nociceptors) and the functionally specialized nerve fibers that transmit sensations after noxious stimuli.

Central sensitization. Although peripheral sensitization is important in the generation of the acute pain of herpes zoster, it does not explain why the area of cutaneous hypersensitivity extends beyond the affected dermatome. Such allodynia or hyperalgesia results from “central sensitization” or changes in...
duced within the dorsal horn of the spinal cord as a consequence of the stimulation of nociceptors [7]. When sensory axons are injured during herpes zoster, there is a brief very high frequency discharge that causes long-lasting depolarization of the spinal neurons during which the response of the dorsal horn cell to all inputs is accentuated (termed wind-up) [6]. More prolonged neural dysfunction (or even death) of dorsal horn neurons could result from calcium entry following impulse-induced glutamate stimulation of N-methyl-d-aspartic acid receptors [8]. Any consequent reduction in disinhibition of dorsal horn cells might convert temporary central sensitization to a permanent state without the need for further nociceptor input.

Pathologic changes contributing to prolonged pain. Several pathologic changes could contribute to prolonged or even indefinite pain after herpes zoster. One is the development of small neuronal sprouts as nerve growth factor. In the other, chemicals induce an attempt to regenerate the damaged peripheral axons. These sprouts, termed “ectopic neural pacemaker nodules” [9], are capable of prolonged spontaneous pain impulses that may contribute to the continual reinforcement of central sensitization and hyperexcitability of dorsal horn neurons.

Deafferentation of dorsal horn neurons probably also plays a role in the pathogenesis of long-term central sensitization. As a cell loses its effective peripheral input (i.e., becomes deafferented), it compensates by becoming more excitable and increases the rate at which it spontaneously fires impulses in high-frequency bursts. The increased excitability eventually results in the cell responding to stimuli traveling in adjacent axons to nearby healthy cells within the spinal cord. This has the effect of enhancing the “receptive field” of the deafferented cell and their overreaction mimics the response to noxious stimuli.

There is some neuropathologic evidence of the above mechanisms of pain, although only a few postmortem studies have looked specifically at patients who had herpes zoster. Striking atrophy of the dorsal horn was described in persons who had severe PHN but not in those without such pain [10]. This structural change may reflect loss of inhibitory fibers within the dorsal horn.

Summary of pain mechanisms. In essence, the pain of herpes zoster results from a sequence of changes in neuronal sensitivity starting at the point of neural damage in the periphery and moving centrally to affect one cell after another within the pain pathway. Once central sensitization occurs, attempts to influence the pain purely by influencing peripheral nociceptor function are unlikely to be successful. Furthermore, once established, such neuropathic pain is notoriously difficult to control. Treatment of the acute illness is thus chiefly directed at minimizing the risk of the prolonged pain.

The cascades of responses that lead to pain after acute neuronal injury occur very rapidly; neurotransmitter release within seconds, wind-up and sensitization within minutes, sprouting and remodeling within hours, and structural responses over days to months [11]. This means that every attempt must be made to reduce further neuronal damage as soon as is practicable in the course of the acute illness. It also impacts upon the way in which the pain resolution curve in a population with herpes zoster should be interpreted and analyzed (see below).

Means of Reducing Chronic Pain and Other Complications in Herpes Zoster

Steroids. Although in some well-controlled trials, corticosteroids were beneficial for acute zoster pain and allowed patients to return to normal activity more quickly, they do not affect the development or duration of PHN [12]. No evidence supports the use of oral nonsteroidal antiinflammatory agents in acute herpes zoster pain or PHN.

Nerve blocks. Although there are numerous anecdotes (many dating back several decades) attesting to the efficacy of somatic or sympathetic nerve blocks for the relief of acute pain during herpes zoster [13], there are still no prospective large-scale controlled studies of their efficacy in preventing PHN.

Analgescics. It is good medical practice to provide adequate analgesia during the acute phase of herpes zoster and opioids impede transmission of nociception in the dorsal horn (among other actions). However, no data confirm that adequate analgesia for acute herpes zoster alters the development of PHN.

Antidepressants. Tricyclic antidepressant drugs inhibit the reuptake of noradrenaline (norepinephrine) and serotonin in the CNS and are thought to increase the inhibition of nociceptive signals within the dorsal horn of the spinal cord. Often considered the mainstay of treatment of established PHN, their use as adjunctive therapy (with acyclovir) in acute herpes zoster was studied in a small trial [14]. Although the trial design was flawed (patients were warned that if they received amitriptyline they might observe dryness of the mouth and other side effects; hence the study was not truly double blind), the results indicated that early therapy with low-dose amitriptyline might reduce the prevalence of PHN.

Antivirals. Since neuropathic pain mechanisms in herpes zoster begin very early after nerve damage, the most appropriate means of minimizing pain is prevention of further nerve damage by the use of antiviral drugs that stop VZV replication. Several nucleoside analogues have virologic benefits and improve cutaneous healing of acute herpes zoster, although their effects on PHN incidence or duration are less clear. The first drug with such efficacy in vitro that could be administered orally was acyclovir. Although the effect of acyclovir on PHN has been controversial (1 [15] of the 4 placebo-controlled studies [15–18] showed no benefit), a meta-analysis of all 4 studies showed oral acyclovir (800 mg 5 times/day) in acute herpes zoster reduced the duration of zoster-associated pain (ZAP), particularly in elderly patients (figure 1A) [19].

For more than 50 years, valacyclovir, the highly bioavailable prodrug of acyclovir, at a dosage of 1 g 3 times a day for 7 days, has been compared with acyclovir in patients with acute
herpes zoster. The duration of pain from enrollment was significantly shorter in the valacyclovir recipients and a smaller proportion had pain persisting >30 days after start of treatment; ** PHN, pain persisting after rash has healed; *** acute pain, pain in the first 30 days from treatment initiation. ZAP, zoster-associated pain.

Figure 1. Estimates of hazard ratios and 95% confidence intervals for meta-analysis of studies of treatments of herpes zoster by various pain milestones. A, Acyclovir vs. placebo (reproduced from [14]) and B, valacyclovir vs. acyclovir [15]. *PHN (postherpetic neuralgia), pain persisting >30 days after start of treatment; ** PHN, pain persisting after rash has healed; *** acute pain, pain in the first 30 days from treatment initiation. ZAP, zoster-associated pain.

Intent-to-treat analyses of a randomized controlled trial of valacyclovir (1 g 3 times/day) or famciclovir (500 mg 3 times/day) in immunocompetent patients aged ≥50 years with herpes zoster showed that the 2 drugs did not differ in their effects on resolution of ZAP or PHN, on rash healing, or in safety profiles [23]. In the United States and United Kingdom, current wholesale prices for a course of valacyclovir are considerably cheaper than the equivalent course of famciclovir, suggesting that valacyclovir is, at present, the more cost-effective option. No comparison of valacyclovir and the dosage of famciclovir licensed for treatment of herpes zoster in many European countries (250 mg 3 times/day) have yet been undertaken.

Measurement of Pain

Although persons who are still in pain from herpes zoster several months after the acute episode have a different quality of pain from that during the acute phase, these are the extremes of the pain continuum. In a percentage of the population (which probably depends on age), there will be sustained central hypersensitivity starting almost simultaneously with the acute pain. Furthermore, it is probable there is a subgroup of patients in whom central mechanisms are only slowly “reversible” (possibly as a result of pathologic changes): This too commences during the first few days or weeks of the acute illness. Hence, the pain present almost immediately from the outset in some persons with herpes zoster is caused by two or three different pathophysiologic mechanisms. The vast majority of patients with central hypersensitivity will also have acute pain; all with irreversible events in the dorsal horn cells will have a degree of less permanent central hypersensitivity. Each pain category will affect a different proportion of the population and each will decline naturally at different rates. Figure 2 illustrates the pain types.

Although the various types of pain found in herpes zoster undoubtedly overlap, a person cannot describe the part played by each type in overall discomfort or determine when one type of pain ends. In population studies, the predominant pain at individual time points will influence the pain resolution curve.

Clinical trials of antiviral therapies have attempted to assess their effect on the duration of pain. Usually the statistical analysis utilized is a Kaplan-Meier product limit method that estimates the distribution of time to cessation of pain in the population under study. The difficulty with this approach is in determining the effects of therapy upon the acute pain (peripheral mechanisms) compared with the chronic pain (central mechanisms). The dilemma in any such analysis is defining when acute pain ends and chronic pain (PHN) begins.

The method traditionally used has been a phase-specific stratified analysis that defines PHN by one of two starting points: the time when skin lesions have healed (usually judged by either complete crusting of the lesions or loss of all crusts) or 4 weeks from onset of lesions, regardless of degree of healing. The dis-
advantage of this approach is that the analysis of cessation of PHN will necessarily involve only a subset of the study population originally randomized, namely, those with persistent pain. This will lead to a reduction in the validity of the statistical analysis since any effects of treatment during the acute illness upon the factors that influence development of central pain mechanisms cannot be assessed. The cohort of patients with PHN is thus not likely to be of similar baseline characteristics. In particular, this will be the case if the point of rash healing defines PHN, yet one treatment group heals faster than another, or if one group has more patients whose pain ceases during the acute phase [24].

One suggestion to overcome this difficulty is to analyze pain as a continuum that starts at the onset of herpes zoster and lasts until the end of the follow-up period (≥6 months) [24]. This is a true intent-to-treat analysis that excludes any selection bias since it follows the original randomization scheme throughout. Analysis of the continuum of pain (ZAP), however, fails to determine whether there are treatment effects specific to the acute pain or chronic PHN. In order to clarify this matter, a proposal has been made to analyze the effects of antiviral therapy on specific phases of ZAP [25]. A recent classification of the pain associated with herpes zoster has divided the continuum of ZAP into three phases: acute herpetic neuralgia (any pain that persists up to 30 days from the onset of the rash), subacute herpetic neuralgia (pain present beyond day 30 that resolves within 4 months [120 days] of rash onset), and PHN (any pain persisting ≥120 days from onset of rash) [26]. It is tempting to equate these three phases with the three types of pain pathophysiology alluded to above.

The proposed analysis [25] is piece-wise regression modeling of the hazard function followed by estimation of the two change points (where the ZAP curve changes its exponential decline owing to the predominance of a different type of pain). In this way the change points and hazard rates for specific phases and populations can be determined. The transition times in the classification suggested by Dworkin and Portenoy [26] were 30 and 120 days, but these would differ depending upon the proportion of persons in a particular population who develop central pain of one type or another. Arani et al. [25], the authors of the new analysis method, have also suggested use of log-survival function plots, which are linear in time, to visually detect differences in hazard rates (slopes) between treatment groups in specific phases of ZAP. Figure 3, for example, illustrates the survival function in which groups differ only in the acute phase. The traditional phase-specific stratification (figure 3A) might lead to the erroneous conclusion that the survival functions are distinct in the PHN phases. The corresponding log-survival plot (figure 3B), however, shows that the functions are parallel in phases 2 and 3, indicating equivalent hazard rates.
Use of a model such as that discussed addresses the central issues of pain in herpes zoster and enables pain to be better defined in different populations. It also enables determination of whether therapy during the acute phase of herpes zoster will merely change the proportion of those who develop central pain and PHN or whether therapy will alter the speed with which such pain resolves long after the intervention has been removed.

References