The varicella-zoster virus (VZV) causes two diseases – chickenpox and shingles. The hyphen in the virus’ name summarizes more than a century of confusion and debate stemming from an obvious fact – the two diseases have very different presentations. The typical case of chickenpox (varicella) is a child who presents with a bilaterally symmetrical vesicular rash that covers most of the body; the child complains of itch and recovery is usually uneventful. The typical case of shingles (herpes zoster [HZ]) is an elderly adult who presents with a vesicular rash that is limited to a discrete area on one side of the trunk or face; the patient complains of pain, and recovery is sometimes associated with a chronic and intractable pain syndrome – postherpetic neuralgia (PHN). How can such different presentations be due to the same pathogen?

In the present article, we review the history of the search for the answer to this question, and also recent progress on the question of the mechanisms that underlie the pain conditions caused by shingles and postherpetic neuralgia are reviewed. The framework for the current conceptualization is Hope-Simpson’s latency hypothesis. Data from recent work in virology, neuroanatomy and epidemiology are reviewed, as is work using varicella-zoster virus-infected animals. The recent data largely confirm Hope-Simpson’s hypothesis and extend it significantly.

**THE PAST**

Shingles has been recognized as a distinct disease since at least the Middle Ages, and the existence of PHN as a consequence of shingles has been known since the early 19th century (7). In 1900, Head and Campbell (8) published a still-famous paper in the journal Brain that established the concept of the dermatome based on the correlation between the area of skin affected by the HZ rash and the consequent scarring and degeneration in the trigeminal and dorsal root ganglia found at autopsy. Head was a giant of turn-of-the-century neurology. He endorsed the then-popular opinion that HZ was an infectious disease that appears in epidemics, similar to chickenpox and measles, and that it was acquired directly from another person with HZ (9). While popular, this hypothesis did not address a well-known phenomenon – children in contact with an adult with HZ developed an illness that appeared to be identical to varicella. Varicella resulting from exposure to HZ was known as Z-varicella to distinguish it from the ordinary childhood disease, which was designated as O-varicella. Confirmation of this link between varicella and HZ came from an experiment (10) that seems shocking today – healthy children were inoculated with fluid from an HZ vesicle from an adult and shown to develop a condition that appeared to be identical to varicella; also, they could transmit the condition to other children.

By the mid 20th century, some accepted the idea that childhood O-varicella and Z-varicella were the same disease. For example, Abramson (11) reported an outbreak of O-varicella among hospitalized children in which those in contact with the children were protected by inoculation with plasma from adult patients convalescing from HZ. With today’s knowledge of the exquisite specificity of the immune system, this would be evidence that O-varicella and Z-varicella were caused by the same pathogen. However, such confidence in immunospecificity was not widespread in that day and a skeptic may have argued the infection that started it all was Z-varicella. As late as the 1950s, opinion was still divided regarding the relationship between O-varicella and Z-varicella. For example, Barnett (12) proposed that the link between HZ and varicella was indirect – HZ occurred when a person with fading immunity to varicella encountered the agent that caused HZ. Opposition to the proposal that O-varicella and Z-varicella were identical was not mere stubbornness. After all, the causative agent had not been identified conclusively and accepting the identity hypothesis gave rise to an unsolved problem – if O-varicella and Z-varicella in children were the same disease, then what...
was HZ in an adult? The answer came from the observations of a remarkable general practitioner and self-taught epidemiologist named Edgar Hope-Simpson, who practiced in the ancient Cotswolds town of Cirencester (United Kingdom).

**Hope-Simpson and the latency hypothesis**

At the time of Hope-Simpson's work (9), general practitioners in the United Kingdom had a unique opportunity for pursuing observational research. They were serving a relatively stable population of several thousand people of all ages, thus allowing the physician to follow his cases for many years, and patients were easily characterized by their data on the National Health Service List. The general practitioner was probably consulted for every case of HZ in his practice. This opportunity was fleeting. Within just a few decades, general practitioners began to amalgamate into large group practices in which individual doctors lacked a personal list, and long-term follow-up became difficult as the postwar population became increasingly peripatetic.

Hope-Simpson formed an epidemiology research unit in Cirencester that focused on the bionomic features of infectious diseases – for example, the time from infection to illness and the disease's serial interval (ie, the interval between illnesses in the donor and recipient). He found that measles, mumps and O-varicella each had their own highly individual and consistent pattern of bionomic characteristics. Although he had worked out the bionomics of O-varicella, he believed that comparable efforts on Z-varicella would be inconclusive in Cirencester because of potential cross-infections from surrounding large towns. His attention was thus drawn to an article in the British Medical Journal (13) describing an attack of HZ in a teacher that had initiated an outbreak of varicella among the students in her school on the remote Shetland island of Yell (United Kingdom). Hope-Simpson corresponded with the teacher and learned that a similar incident was in progress – a crofter in the nearby hamlet of Herra had developed HZ, and his five school-aged children had developed varicella and infected their schoolmates.

Hope-Simpson and his team went to the island and collected the case histories. Their analysis of the data revealed that the bionomic features of Z-varicella were identical to those of O-varicella in both Yell and Cirencester. His data showed conclusively that HZ did not come in epidemics and was not more abundant in years with varicella epidemics. Furthermore, he found that persons with a history of O-varicella who were at household risk of infection with Z-varicella were completely cross-protected, whereas, had there been no cross-protection, 60% would have developed Z-varicella. Hope-Simpson (14) was thus convinced that varicella and HZ were caused by the same agent. His conclusion was supported by the work of Thomas Weller and his colleagues in Boston (USA) (15-17) who used what were then the most modern methods of virological investigation and had shown that the varicella virus appeared to be identical to the virus isolated from HZ lesions.

Still, if the two diseases were due to the same pathogen, why did chickenpox and shingles look so different?

Hope-Simpson solved the puzzle with the latency hypothesis, a revolutionary proposal that HZ is due to the reactivation of a latent varicella infection in a sensory ganglion (18). He further hypothesized that viral latency is maintained by immunosurveillance, which is boosted by periodic subclinical reactivations and exposure to exogenous virus, and that reactivation (ie, HZ) appears when immunosurveillance falls below a critical threshold. His hypothesis explained the puzzling dermatomal predilection of HZ, which is most often seen in the thoracic and trigeminal dermatomes, as a consequence of those ganglia being seeded with a larger quantity of viral particles during the varicella attack, when the varicella rash is usually heaviest on the trunk and face. His summary diagram of the latency hypothesis is republished in contemporary textbooks (Figure 1).

**Immunosurveillance**

Nearly half a century later, our ideas about varicella and HZ are little changed from Hope-Simpson’s proposal. His idea that latency is boosted by an infected person’s periodic exposure to exogenous virus has been proven repeatedly, with perhaps the nicest example being a study showing that HZ is approximately one-half as common in pediatricians as in psychiatrists (19). However, Hope-Simpson’s belief that the critical parameter of immunosurveillance was the plasma level of B cell-secreted antibodies is now known to be incorrect. The critical parameter is T cell-mediated immunity (20,21).

Hope-Simpson’s proposal that exposure to exogenous virus boosts an adult’s immunocompetency and keeps HZ at bay suggests that it may be possible to vaccinate adults against HZ. This prediction has been confirmed (22). More than 38,000 subjects 60 years of age or older were treated with a vaccine prepared from the live, attenuated Oka/Merck VZV strain (a more potent vaccine than that used in children). After a median period of postvaccination observation of approximately three years, vaccination reduced the incidence of HZ by 51.3% and the incidence of PHN by 66.5%. Vaccinated patients who nevertheless did develop HZ experienced pain that was significantly less intense and of shorter duration than that experienced by nonvaccinated cases. Moreover, vaccinated patients who developed PHN had pain syndromes that were less severe than those of nonvaccinated patients. Thus, the vaccine not only prevented disease but also attenuated it.

**Viral evolution**

Hope-Simpson (18) believed that the VZV virus evolved the latency strategy to perpetuate itself in the small and isolated bands that characterized the population structure of primitive humans. In effect, the virus hid in adults until a new generation of hosts was born. The idea that VZV is an ancient affliction has been confirmed by modern molecular biology. Mapping mutations in the human mitochondrial genome across diverse populations allows for a reconstruction of human migrations and has led to the ‘out of Africa’ hypothesis for the origins of modern man. The same sort of analysis has been performed on the genomes of isolates of VZV strains from around the world. The geographical pattern of mutations in the viral genome matches that of the human genome, thus supporting the idea that the virus has travelled with man for hundreds of thousands of years. Indeed, comparing the VZV genome with the genomes of other viruses in the alpha-herpesvirus family indicates that VZV originated 60 to 70 million years ago in African primates (23,24). It is thus possible that the virus infected our Australopithecus ancestors.

**The Present**

The present
Epidemiology of HZ and PHN in Canada

Our understanding of the epidemiology of HZ and PHN is far better than in Hope-Simpson’s day. For example, the incidence of HZ in Canada has been estimated from studying the billing records of Manitoba physicians during the period from 1979 to 1997 (25,26). The Canadian estimates are very close to those from the United States and the United Kingdom, and are very likely to be close to those of all developed countries in the temperate latitudes. The epidemiology of HZ and PHN in underdeveloped countries will likely differ because of several factors that affect the spread of the virus (eg, the number of children attending primary school).

In the Canadian population (approximately 30 million), 130,000 people will develop HZ each year. Men and women will be affected approximately equally. More than 46,000 of these people will be 65 years of age or older. Over 5000 cases will occur in people who are at particular risk because of an immunosuppressive condition. Over 4000 individuals will be admitted to hospital and approximately 30 will die from complications. In each yearly cohort of 130,000 HZ patients, approximately 17,000 will develop PHN and join the population of PHN sufferers from previous years. The majority of the new PHN patients will be older than 60 years of age; men and women will be affected equally (27).

The estimated Canadian health care cost for HZ and PHN is more than $67 million. This estimate does not capture the full impact of PHN pain, which is rarely eliminated by available therapies and often completely refractory to treatment. Nearly one-half of PHN patients will report daily pain of moderate intensity (3 to 7 on a 0 to 10 scale, in which 10 is the ‘worst pain imaginable’). Approximately 20% of PHN patients will report severe daily pain (greater than 7). As is expected from such a severe burden, the patients experience significant decreases in their daily activities, significantly impaired sleep and clinically significant depression (27).

Zoster-associated pain

A child with varicella complains of itch, but an adult with HZ complains of pain, and in the case of PHN, the pain remains after the virus re-enters dormancy. Research has begun to shed light on the source of the pain.

It is possible that there are at least some pain mechanisms that contribute to both the pain of shingles and the pain of PHN. The concept of zoster-associated pain reflects this possibility. It is difficult to make a precise determination of when pain ceases to be due to the attack of shingles and begins to be due to PHN. For most shingles patients, the pain resolves in a few weeks, at approximately the time when the rash begins to heal, but for the PHN patient, the pain persists long after the disappearance of signs of active viral replication. There is often no pain-free interval between the pain of shingles and the PHN pain. In clinical trials, PHN has usually been defined somewhat arbitrarily as pain lasting for more than three or four months after the appearance of the rash.

Pain mechanisms in acute HZ

In shingles, viral particles originating in the trigeminal or dorsal root ganglion (DRG) neuron travel antidromically (ie, down the cell’s axon) to the sensory terminals in the skin. The rash begins when the virus escapes the nerve terminals and invades the skin. The resulting rash is accompanied by an obvious inflammatory response and it is possible that this inflammation sensitizes pain-specific sensory fibres (nociceptors). Sensitized nociceptors have a lowered activation threshold, such that they are excited by normally innocuous stimuli such as gentle touching (alldynia), and an increased response to stimuli that are more intense than the normal threshold, such that normally painful stimulation causes greater than
normal pain (hyperalgesia). Sensitized nociceptors also have an abnormal spontaneous discharge that is likely to cause spontaneous pain sensations (28).

However, the pain of shingles has causes that are distinct from those arising from the skin, as shown clearly by the common presence of pain occurring days or even months before the rash appears (prodromal pain) and the rare cases in which there is pain but the rash never appears (zoster sine herpete). Replicating virus in heavily infected neurons is likely to cause direct neurolytic lesions to the cell bodies or their axons, and indirect injury via the endoneurial inflammatory response and hemorrhage that occur as virus particles escape from damaged neurons and axons. Thus, potential mechanisms for neuropathic pain exist at the same time – and may even come before – the rash appears (prodromal pain) and the rare cases in which there is pain but the rash never appears (zoster sine herpete). Reproduced from reference 59 with permission.

CNS pathology
For many years, the standard concept of the anatomical damage caused by an attack of shingles was based on the postmortem studies that Head and Campbell reported in 1900 (8). They showed that, at the onset of HZ, a violent hemorrhagic inflammation occurs in the ganglion and adjacent nerve (Figure 3) and, over time, results in extensive fibrosis and loss of nerve cells and fibres in the ganglion, root and peripheral nerve (Figure 3). It is not known whether any of the patients autopsied by Head and Campbell had PHN. More than eight decades passed before it was shown that DRG scarring and nerve cell loss are also present in PHN patients (31,37,41). These studies also found that PHN is associated with severe atrophy of the dorsal horn (Figure 3) of the spinal cord at the level of the damaged DRG, and at spinal levels above and below. These data show that PHN is associated with severe irreversible damage to both the peripheral nervous system and the CNS, and suggest that the CNS damage may be of particular importance to the genesis of PHN pain.
HZ and PHN in laboratory animals

VZV is exquisitely tailored to the human host and it is thus very difficult to cause an active VZV infection in laboratory animals. Limited success can be achieved when VZV is grown for a long time in cultures of guinea pig cells. This yields a 'conditioned' virus that can successfully infect guinea pigs. The use of a mutant strain of guinea pig that does not grow fur allows the rash to be monitored (42). The problem with the guinea pig model is, of course, that one does not know what changes have been induced in the human virus by the conditioning process.

It was thus a landmark discovery when Sadzot-Delvaux et al (43,44) found that a latent infection in the rat’s DRG could be established by a simple subcutaneous injection of cultured cells that bore a human VZV infection. The latent infection occurs without an active infection (i.e., the virus does not replicate in the animal) and no cutaneous rash is formed. No one has succeeded in reactivating such a latent infection in the live animal, which would be a true model of shingles. However, it is possible to induce viral reactivation in cultured DRG neurons removed from a rat with this type of latent infection, showing that the infection is truly latent, rather than abortive. The latent infection lasts for at least nine months, which is a long time relative to a rat’s life span of approximately 2.5 years. The latent virus is found almost exclusively in the lumbar DRG corresponding to the dermatome that received the injection.
showing that the virus enters the neuron via retrograde transport along the neuron's axon – the same path used to establish a clinical latent infection.

Remarkably, rats with this latent infection develop clear signs of neuropathic pain on the hind paw that received the inoculation (45-48). There are well-established methods for determining pain sensitivity in laboratory rodents (49). For example, successively stiffer von Frey ‘hairs’ (actually, nylon monofilaments of different diameters that exert defined levels of force when pressed against a surface to the point at which they bend) can be applied to the sole of the hind paw. The threshold force that evokes the protective withdrawal reflex defines the animal's pain threshold. Heat hypersensitivity can be inferred from the latency of the withdrawal reflex evoked by shining a hot light through a glass pane that the animal stands on. Normal rats respond with a latency that corresponds to a skin temperature of approximately 45°C; this is also the normal human heat-pain threshold (it is the temperature at which protein degradation, and hence tissue damage, begins). Following the induction of the latent VZV infection, stimulation of the ipsilateral hind paw evokes a withdrawal reflex to weak von Frey hairs that rarely, if ever, evoke a withdrawal reflex in the normal case. As well, heat evokes a withdrawal reflex at latencies corresponding to temperatures that do not ordinarily evoke pain. Such hypersensitivity to touch (alldynia) and heat is often present in PHN patients. Some, but not all, PHN patients also have hypersensitivity to cold, such that even gentle cooling produces pain (50). This abnormal cold-evoked pain does not appear to be present in the rats. PHN patients also report spontaneous pain, ie, pain that does not appear to be related to any stimulus. There are no validated methods to measure spontaneous pain in animals and it is thus unknown whether the latently infected rats have spontaneous pain.

The pain hypersensitivity begins as early as three days after the inoculation and lasts for 60 to 100 days. Some studies (46,48) have noted an additional, relatively mild and brief period of pain hypersensitivity on the hind paw contralateral to the inoculation. The reason for this contralateral pain is unknown. Clinically, bilateral PHN is very rare. However, as noted above, PHN is associated with symptomatically silent lesions to sensory neurons that innervate skin contralateral to the rash (34).

Control inoculation with uninfected cells has no effect on pain sensitivity. Moreover, control infections of cells infected with human herpes simplex virus type 1 produce only a few days of modest pain hypersensitivity (46). The herpes simplex virus type 1 pain hypersensitivity is prevented by valacyclovir treatment, while the pain hypersensitivity produced by VZV injection is not (46,48). One can thus conclude that the long-lasting pain hypersensitivity seen with the latent VZV infection is not secondary to an inflammatory response to the presence of virus per se, or to a reaction to the cells that the virus is grown in, and that it is not associated with viral replication.

The incidence of rats developing the pain syndrome and the severity and duration of the syndrome are roughly correlated with the amount of virus inoculated (47,48). This may be related to the clinical observation that PHN is more likely when the acute attack of shingles is severe or untreated (51). In the rat, comparable pain syndromes have been found with VZV from different viral strains, including clinical isolates from patients who did, and who did not, develop PHN (48). This suggests that the development of the pain is likely to be a function of the host's response to the virus, rather than a mechanism intrinsic to the virus itself.

The pain syndrome seen in rats with a latent VZV infection seems to have a pharmacological response profile that is similar to that of PHN pain (47,48,52). The rats’ pain is relieved by antidepressants, sodium channel blockers (mexiletine), and antiepileptics (gabapentin and lamotrigine). There is evidence that WIN 55,212-2 (a cannabinoid receptor agonist) is also effective in these animals. Whether the pain syndrome in rats responds to opioid and anti-inflammatory analgesics (ibuprofen and diclofenac) is controversial.

THE FUTURE

Epidemiology

Increasing childhood vaccination against varicella, increasing awareness of the need for instituting aggressive antiviral therapy within the first three days of the attack (53), and the introduction of the adult vaccine will surely decrease the incidence of shingles and PHN, but to an extent that is not yet clear and on a timeline that is very difficult to predict. On the other hand, the number of patients with particular susceptibility to HZ will increase steadily as the percentage of the elderly in the population and the number of immunocompromised patients increase (eg, transplant recipients, HIV patients, cancer patients receiving radiation and chemotherapy, etc).

Mathematical modelling indicates that increasing rates of childhood varicella vaccination may have the paradoxical effect of increasing the rate of HZ infection because adults from the prevaccine era will be exposed to less exogenous virus and thus will not receive the periodic boosting of immunosurveillance that keeps the disease in check (34,55). This could be a very significant effect, with an anticipated increase in the incidence of HZ of up to 40% to 50% during the next 20 to 50 years. It is still too early in the vaccine era to be certain that this increase will occur. Childhood varicella vaccination was approved by the United States Food and Drug Administration in 1995, and by Health Canada in 2006; the adult HZ vaccine entered the American market in 2006 and was approved for use in Canada in September 2008.

Pain mechanisms

The historical picture of PHN as being associated with a unilateral, one-level, sensory ganglionopathy with axonal degeneration extending peripherally is incomplete. It is now clear that the pathological features associated with PHN include particularly severe peripheral axonal loss, degeneration of the sensory neuron's centrally directed axon, multisegmental dorsal horn atrophy and the presence of clinically nonsymptomatic contralateral changes in the innervation of the skin. How this pathology produces PHN pain is not yet understood. There is also the possibility of CNS abnormalities not visible by light microscopy, or abnormalities at higher levels of the neuroaxis that have not yet been characterized. Excessive discharge in injured peripheral axons may cause secondary damage to neurons in the spinal cord dorsal horn (56,57). For research purposes, it is now clear that the contralateral mirror-image site
Neuronal injury occurs in every patient with shingles; however, only some experience PHN, and nerve fibre loss is documented contralaterally where there is no pain. It is thus clear that neuronal injury is not a sufficient explanation for the development of PHN pain. The rat data suggest that neuronal damage may be neither sufficient nor necessary for the development of PHN pain.

VZV has been with us for many thousands of years – it probably has more surprises in store for us.

STATEMENT OF INTERESTS: Preparation of this article was supported in part by Merck Frosst Canada, Ltd. Within the past year, GJB accepted consulting fees and/or speaker's honoraria from Aillon Therapeutics (Canada), Endo Pharmaceuticals (USA), Johnson & Johnson (USA), KAI Pharmaceuticals (USA), WEX Pharmaceuticals (Canada) and Xanodyne Pharmaceuticals (USA), and has a research contract with Trophos SA (France). CPNW accepted speaker's honoraria from Merck (USA), Pfizer (USA) and Purdue (USA), and has a research contract with Purdue. Neither author is a major shareholder or has any significant financial relationship with any relevant commercial interest.

REFERENCES