Varicella: Historical Perspective and Clinical Overview

Thomas H. Weller

In immunocompetent children in Europe and the United States, varicella is usually a benign disease. However, infants born to women who acquire varicella during or shortly after pregnancy are at high risk of infection. For unknown reasons, the disease is more severe in adolescents and adults, with pneumonia the most common cause of death. Varicella may also be lethal in patients of any age in the presence of biologic or iatrogenic immunosuppression. It is now well documented that varicella-zoster virus remains latent in the dorsal root and cranial ganglia following an attack of varicella. Viral reactivation appears with advancing age as cellular immunity wanes. The contemporary relative aging of the population will enhance the social significance of zoster. The immigration of nonimmune adults in temperate climates poses a major problem in terms of protection of high-risk children. A vaccination program is indicated.

This review focuses on two aspects of varicella: first, the scientific findings leading to the conclusion that the two clinical entities, varicella and herpes zoster, were caused by a single virus [1], and second, the evolving environmental, ecologic, and biologic factors affecting the human host that convert a virus that produces a relatively benign illness in children to a socially significant pathogen with a lethal potentiality.

Classical Observations on the Varicella-Zoster Virus (VZV)

The classical observations on the histopathologic changes produced by VZV were made by two pathologists, E. E. Tyzzer and E. Goodpasture. In 1901, Tyzzer, then a senior medical student at Harvard, studied an outbreak of smallpox in Boston under the direction of W. T. Councilman; smallpox was considered by Councilman to be caused by a protozoan parasite [2]. In 1904, Tyzzer was sent to the Philippines to study the susceptibility of monkeys to smallpox. However, an outbreak of varicella in Bilibid Prison diverted his attention. In 38 subjects, the evolution of cutaneous lesions was followed by histopathologic examination of serial biopsies [3].

After his retirement in 1942, Tyzzer gave me the technically beautiful preparations that he had made in 1904. Tyzzer’s classical report contains many scientific gems. He noted inclusion bodies in the endothelium of blood vessels and hypothesized that the dermal lesions were preceded by a viremic phase. He stated, “seems quite reliable and may be applied at the bedside.”

Ernest Goodpasture was an assistant professor of pathology at Harvard when, in 1921, he published the first of several papers that were to establish the viral etiology of the intranuclear inclusion bodies characteristic of herpes group agents [4]. In 1931, Goodpasture introduced the embryonated hen’s egg as an experimental host for a variety of viral pathogens; this was a major technologic contribution. Convinced that the common laboratory animals could not be infected with varicella virus, Goodpasture grafted fragments of human skin on the chorioallantois membrane of 9-day-old chick embryos and then inoculated the fragments with zoster vesicle fluid. Typical eosinophilic intranuclear inclusions were seen on histopathologic examination of the skin samples 4–8 days later [5].

The classical studies of Tyzzer and of Goodpasture were also unique in the nature of the patients they studied. Tyzzer commented on the unexpected occurrence of an outbreak of varicella in adult prisoners—a situation very different from the childhood disease he had observed in Boston. This was the first notice of an epidemiologic characteristic of varicella only recently recognized, namely that, in tropical countries, varicella is often a disease of adults. For example, a recent investigation of an epidemic of varicella in soldiers from Puerto Rico revealed that 42% were negative for varicella [6], and a serologic survey in St. Lucia, an island in the West Indies, indicated that <10% of the population had experienced a VZV infection before the age of 15 years [7].

In 1944, when Goodpasture inoculated human skin fragments grown in eggs, the inoculum consisted of zoster vesicle fluid obtained from a typical segmental lesion in a 30-month-old child. He noted that the child had experienced a typical attack of varicella 1 year earlier. Terada et al. [8] more recently summarized data from their clinic on 31 cases of zoster in immunocompetent children and concluded that chickenpox in the first year of life is a risk factor for zoster occurring before 7 years of age. Terada et al. [9] also demonstrated that varicella in infants <1 year old induced a lower level of specific cellular and humoral immunity than did varicella in older children, thus...
explaining the reactivation of VZV with the occurrence of zoster at an early age.

In healthy individuals, there is an age-related increase in the severity of varicella. For example, varicella pneumonia is a common complication in adults [10]. As pointed out by Nader et al. [10], little is known of the differences in the immunologic response of adults to varicella compared with that of children; however, they demonstrated that children are more responsive immunologically to varicella vaccine than are adults.

The relationship between varicella and zoster is now accepted, although in 1940 it was taught at Harvard that the two clinical entities were distinct and unrelated. Epidemiologic evidence of a relationship dates from Bokai's (also known as von Bokay) published account in 1892. Grose [11] has published an excellent summary of Bokai's observations. In 1921, Lipschutz [12] described the cutaneous histopathology changes in zoster, and the findings were identical with those described by Tyzzer in varicella. A logical capstone was the explanatory hypothesis posed by Garland, a pediatrician, in 1943 [13]. Drawing an analogy to the situation with recurrent herpes simplex infections, Garland suggested that zoster reflected activation of a latent varicella virus. However, definitive conclusions awaited isolation and comparison of the etiologic viruses.

In 1947, when I joined John Enders in setting up a laboratory at Children’s Hospital in Boston, the varicella problem was tackled. Goodpasture’s observations and the evidence of host specificity suggested the use of cultures of human tissues. Influenced by earlier work with roller cultures, the customary Maitland flask culture technique was modified by changing the nutrient fluid phase at 3–4 days, thus maintaining the tissue fragments for long periods.

In March 1948, I prepared a set of flask cultures of human embryonic skin-muscle tissue and inoculated them with throat washings from a case of varicella; a few extra cultures were inoculated with Lansing strain poliovirus. The varicella cultures were negative, a finding that would now be expected. (While VZV can be demonstrated in throat washings by polymerase chain reaction, standard culture systems are relatively insensitive indicators of the virus, and VZV has rarely been isolated from active-phase throat washings.) However, to my surprise, fluid from the cultures of poliovirus produced paralysis in mice if inoculated intracerebrally, and polio became the focus of research by the group.

I returned 8 months later to the varicella problem, using vesicle fluid as the inoculum. Histologic examination of tissue fragments from the cultures revealed foci of cells with intranuclear inclusions [14]. It was frustrating that repeated attempts to subculture an agent and to replicate this finding were negative. The use of roller cultures of human tissues was then studied. In such cultures, inoculated with varicella or with zoster vesicle fluid, a slowly spreading collection of swollen cells that contained intranuclear inclusions developed. Infectious virus rarely appeared in the fluid phase; subculture was accomplished by the transfer of infected cells. Isolates from the two clinical entities produced identical cytopathic changes [15]. Immunologic evidence of the etiologic roles and the co-identity of the viruses was obtained by the fluorescent antibody technique of Weller and Coons [16], by complement fixation, and by an in vitro neutralization test. When my group’s definitive papers were published in 1958 [17, 18], we concluded that the evidence that varicella and zoster were caused by the same virus was irrefutable; the agent was named “VZ” virus.

Host Relationships of VZV

During the 40 years since the isolation of the virus, knowledge of the host relationships of VZV has expanded. A selective summary of the findings of many investigators follows.

Classically, varicella was considered a benign childhood disease that produced a solid immunity. However, the concept of a static host-virus relationship is now unacceptable. The relationship is dynamic with temporal fluctuations in humoral antibody levels reflecting subclinical or even clinical activity by superinfection with VZV from an external source or by the reactivation of endogenous strains.

Concepts of the pathogenic potential of varicella have changed. In 1947, Laforet and Lynch [19] recognized the congenital varicella syndrome. Affected infants present with a zoster-like distribution of lesions, often with limb hypoplasia, cicatricial scars, and central nervous system damage. In a recent study in the United States and Canada [20], the risk of embryopathy after a maternal varicella infection in the first 20 weeks of pregnancy was estimated to be ~2%. In a joint prospective study in Germany and the United Kingdom [21], 1373 women who had varicella and 366 women who had herpes zoster during the first 36 weeks of gestation were followed. The overall risk of the congenital syndrome during the first 20 weeks of gestation was ~1%, with the highest risk, 2%, observed between weeks 13 and 20. Ten cases of infantile zoster later developed in babies who were asymptomatic at birth; in this group, the maternal infection occurred between weeks 14 and 33 of gestation. No cases of the congenital syndrome occurred in the offspring of women who had zoster while pregnant.

Recognition that VZV could produce a life-threatening illness slowly developed. Varicella pneumonia, a subject recently reviewed by Feldman [22], was not described until 1942, when it was recognized in healthy adults. Other complications may occur in immunocompetent adults including hepatitis, glomerulonephritis, encephalitis, and meningitis. Thrombotic complications have been reported in adults [23] and in children; 6 cases with thromboses were associated with deficient levels of protein coagulation inhibitors [24]. However, in contrast to the relatively benign illness VZV produces in immunocompetent subjects, that occurring in immunodeficient persons is often serious. In 1956, 2 fatal cases with virus isolated at autopsy were described [25]. One patient was a 4-year-old boy undergoing treatment for a neuro-
blastoma; he developed progressive varicella, and death occurred 17 days after the appearance of the first vesicle. The other case was a 7-year-old girl who developed varicella while receiving steroid therapy for rheumatic fever. These patients were categorized as high-risk iatrogenically immunosuppressed individuals, a group that is increasing rapidly as medicine advances. A second major category of high-risk persons consists of those biologically immunosuppressed, either by reticuloendothelial or hematopoietic cancer or by a concurrent infection, such as human immunodeficiency virus (HIV).

In the transplantation field alone, the social and economic consequences of VZV are catastrophic. The number of transplantations done annually increases rapidly; in the United States in 1992, more than 2000 marrow and stem cell transplantations and more than 9000 kidney transplantations were done [26]. Immunosuppressed individuals who have had zoster may experience a severe generalized recurrent infection, while a primary infection may be progressive and lethal. Even with optimal use of VZIG (varicella immune globulin) and of acyclovir therapy, VZV infections occurred in 216 patients receiving marrow transplantation, with 2 deaths [27]; 8 of 13 children receiving renal transplants developed varicella, again with 2 deaths [28]. Paralleling the increasing number of iatrogenically immunosuppressed individuals is the increasing number of those biologically immunosuppressed by HIV infection. Quinn [29] estimates that worldwide some 14 million people are now infected with HIV and that as many as 40 million may be infected by the year 2000. VZV activity in such infected persons may present a progressive infection with extremely bizarre features.

Changes in the human population are enhancing the social significance of VZV. One change is that the average life span is increasing, thus increasing both the risk of zoster and of developing a malignancy. It is estimated that in the next 40 years in the United States the number of persons ≥65 years will increase from 32 to 64 million, and the number ≥85 years will increase from 3.5 to 8.8 million [30]. Hope-Simpson [31] estimated that in a cohort of 1000 people who lived to be 85 years old in the United Kingdom, 500 would have had one attack of zoster and 10 of them would have had two attacks.

A second alteration in the nature of the population is the increasing presence of adults who have not had varicella. As mentioned earlier, varicella is an adult disease in the tropics. In the United States, the Census Bureau reports that in the 10 years preceding 1993, the Hispanic population increased by 65% to 85%. Of these, two-thirds claimed Mexican origin, 13% came from Central and South America, and 11% came from Puerto Rico [32]. This immigration of nonimmune adults leads to increased severity of the disease in adults and the risk of the congenital varicella syndrome. Of even more importance is the fact that such unskilled immigrants frequently obtain janitorial or caretaking positions in hospitals. If incubating varicella, they may expose groups of high-risk subjects hospitalized in cancer therapy or transplantation units.

Conclusion

VZV can no longer be classified as producing a benign disease. As we discuss indications and the need for varicella vaccine, the increasing importance of the illnesses produced by this reclusive virus per se constitute a persuasive argument for its use.

References