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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Combating Varicella Through Drugs and Vaccination

Prager D, Bruder M, Sawitsky A. Disseminated varicella in a patient with acute myelogenous leukemia: treatment with cytosine arabinoside. J Pediatr 1971;78:321-3.

Prager et al described a 6-year old girl with newly diagnosed leukemia who then contracted disseminated chickenpox, the disease caused by primary varicella zoster virus (VZV) infection. She improved with a 7-day course of cytosine arabinoside, a pyrimidine analog with putative antiviral and antineoplastic properties. Subsequent trials demonstrated that cytosine arabinoside impairs host response to infection, thus prolonging VZV dissemination, without reaching adequate antiviral concentrations in vivo. In the mid-1970s, the introduction of acyclovir, another nucleoside analog but with selective activity against herpes simplex and VZV polymerase, opened the era of efficacious and safe antiherpetic drugs. Valacyclovir, the prodrug of acyclovir, and famciclovir, the prodrug of penciclovir, were approved by the Food and Drug Administration in the 1990s; both have antiviral activity similar to that of acyclovir but much improved bioavailability, completing an array of treatment options for herpetic infections regardless of immune status.

The control of VZV infection in children was ultimately addressed by the development of the attenuated VZV vaccine by Japanese investigators in the 1970s. Small trials in Japan indicated that immunization safely reduced infection among chickenpox contacts. Subsequent trials tested vaccine safety and effectiveness among children with leukemia, a courageous step because it involved deliberately injecting a live herpesvirus into a compromised host. The proposal to apply the VZV vaccine to American children generated several concerns, however, including the unknown rate of vaccine failure and the potential of the vaccine strain to cause early zoster. VZV vaccine champions won the day, however, and the product was incorporated into the American childhood vaccine schedule as a single dose in 1995. The concern about early zoster ultimately proved unwarranted; the potential for zoster requires dermal lesions though which the organism can enter the neuron, and because vaccinated children rarely acquired rash, immunization likely reduced, not promoted, the incidence of zoster. The issue of faulty immunity proved more troublesome. School outbreaks among immunized children continued, presumably due to primary vaccine failure. This phenomenon was largely addressed by the incorporation of a booster dose starting in 2006, completing a success story in which a ubiquitous respiratory virus was controlled through careful, scientifically sound development of therapeutics and vaccines.

Peter Paul Lim, MD
Philip Toltzis, MD
Department of Pediatrics
Rainbow Babies and Children's Hospital
Cleveland, Ohio