Varicella-Zoster Virus

Published in association with the VZV Research Foundation, this is a comprehensive account of the biology and clinical features of the varicella-zoster virus. The successful development of a vaccine reflects intense research interest in this virus over recent years, and this book surveys current knowledge of the molecular biology, pathogenesis and clinical features of VZV as the causative agent of chickenpox and zoster (shingles).

Topics covered include viral replication, latency, immune mechanisms, epidemiology and disease manifestations, and complications of varicella and zoster. There is detailed information on live attenuated varicella vaccine, treatment strategies and the management of postherpetic pain in zoster patients. As the most authoritative review and guide to the virus and its diseases, this book will appeal to a wide range of clinicians and investigators, including pediatricians, geriatricians, neurologists, dermatologists and infectious diseases specialists as well as virologists interested in the herpes viruses.

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The VZV Research Foundation was founded by Richard T. Perkin in 1991 as a nonprofit organization dedicated to research and education on VZV. It has awarded numerous research grants, bestowed four Scientific Achievement Awards and sponsored four major international conferences and a public information campaign about the problems caused by VZV and current knowledge about varicella and zoster.

The editors and authors dedicate this volume to Richard T. Perkin, President of the VZV Research Foundation. His unfailing support of scientific research on VZV has been an inspiration to all of us and we are truly grateful for his many efforts on our behalf.

Varicella-Zoster Virus

Virology and Clinical Management

Edited by

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Preface

Major milestones in the understanding of varicella-zoster virus (VZV) occurred in the eighteenth century when varicella was recognized to be distinct from smallpox, and in the mid-twentieth century Weller and colleagues first succeeded in isolating the virus in cell culture. Nevertheless, as recently as 30 years ago only a handful of virologists were pursuing research on VZV, mainly because the diseases it caused were perceived as minor and it proved to be extremely difficult to propagate the virus in the laboratory. There were several achievements, however, that resulted in a veritable explosion in research on this pathogen, beginning in the early 1970s. First was development of a live attenuated varicella vaccine by Takahashi and colleagues. Other significant new interventions were introduced almost simultaneously, including passive immunization and antiviral therapy, along with the realization that diseases caused by VZV are not necessarily benign, especially in developed nations with aging populations and increasing numbers of immunocompromised patients. Next came the availability of molecular techniques, permitting bypass of propagation of the virus for its study, and allowing mutation of viral genes within the virus, leading to elucidation of the processes of VZV gene expression, latency, viral pathogenesis and immune responses. Finally the organization of the Varicella-Zoster Research Foundation by Richard Perkin led to improved communication between basic and clinical investigators studying VZV. In the brief period of about 10 years, this Foundation has hosted four international meetings on VZV, produced three volumes of Proceedings, presented four awards to premier senior scientists involved with VZV, and supported seven research fellowships for young investigators interested in VZV. Thirty years ago, there were about 100 publications on VZV annually; now there are ten times that many. At this time of great progress and success on our understanding of molecular events, natural history, prevention, and treatment of VZV, it seemed appropriate to develop a consensus of where this field stands today. Therefore this volume was conceived and executed, and the editors are extremely grateful for the efforts of all the outstanding contributors. Hopefully the

comprehensive chapters contributed by current international experts in the various aspects of VZV will inspire young scientists to continue to explore and develop this exciting field even further.

Ann M. Arvin
Anne A. Gershon
January 2000

Introduction

Ann M. Arvin and Anne Gershon

Throughout the years, there have been many scientists who have contributed to our knowledge of the varicella zoster virus and the prevention, diagnosis and management of VZV-related diseases. In recent years, four of them, including two Nobel Laureates, have had the distinction of receiving the VZV Research Foundation (VZVRF) Scientific Achievement Award, which recognizes lifetime achievements in VZV research. Established in 1991, the Foundation is the first and only nonprofit organization in the world dedicated to VZV research and education.

Thomas H. Weller, M.D.

Thomas H. Weller, M.D., professor emeritus of the Harvard School of Public Health, Boston, and a Nobel Laureate, was the recipient of the first VZVRF Scientific Achievement Award in 1993. He remarked that his VZVRF award was in a way more gratifying than his Nobel Prize.

According to Dr. Weller, "Although my work in isolating and growing the poliomyelitis virus in tissue cultures was the most significant contribution I have made to medical science in terms of global impact, I am most proud of my work with the varicella-zoster virus. It's something I planned to do and worked for years to do."

It was the work that Dr. Weller and his colleagues did on the poliomyelitis virus that garnered them the Nobel Prize in 1954, and led to the Sabin and Salk vaccines. Likewise, Dr. Weller's work on the varicella-zoster virus led to many important discoveries in VZV research, including Dr. Michiaki Takahashi's development of the varicella vaccine. In 1953, in addition to isolating VZV from cases of chickenpox and zoster, Dr. Weller was able to show that the same virus is responsible for both illnesses.

Dr. Weller's research – conducted alone or in collaboration – also helped pave the way for vaccines against mumps and rubella. He was co-discoverer of the rubella virus, the cause of German measles, and the cytomegalovirus, which he named. He was one of the first to grow the mumps virus in tissue culture.

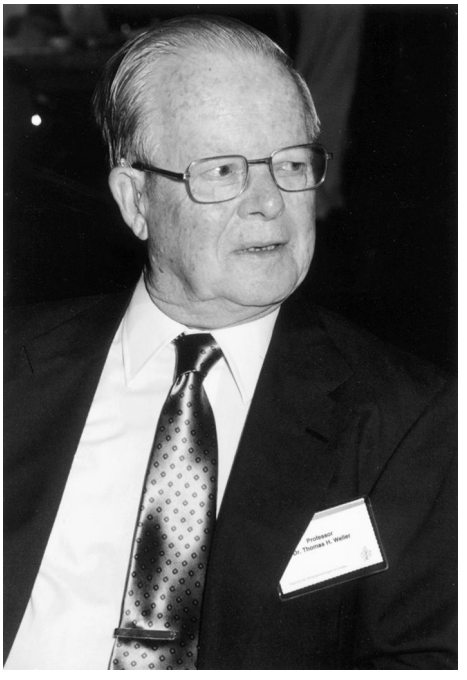

Figure I.1 Thomas H. Weller, M.D.

Figure I.2 Gertrude B. Elion, D.Sc.

Trained as a pediatrician, Dr. Weller is also a recognized expert in the field of tropical medicine and is a past president of the American Society of Tropical Medicine and Hygiene. In addition to the Nobel Prize, he is the recipient of many awards, including the George Ledlie Prize from Harvard University, the Bristol Award from the Infectious Diseases Society of America and the Walter Reed Medal from the American Society of Tropical Medicine and Hygiene. Dr. Weller graduated from Harvard Medical School, Boston, in 1940.

Gertrude B. Elion, D.Sc.

In 1995, the late Gertrude B. Elion, D.Sc., another Nobel Laureate, became the second recipient of the VZVRF Scientific Achievement Award. The award recognized Dr. Elion's "pioneering work in antiviral therapy," specifically, VZV research. Dr. Elion was instrumental in the development of antiviral therapy for herpes zoster.

Dr. Elion died in February of 1999 at the age of 81. In 1988 she and colleague George Hitchings, Ph.D., whom she worked with for 40 years, along with Sir James

Black, were awarded the Nobel Prize for their research leading to drugs for leukemia, gout, malaria, zoster and other diseases of the immune system, in addition to drugs that eventually made organ transplants possible. Their scientific collaboration also led to the development of AZT for AIDS.

In a February 22, 1999 Associated Press story that reported on her death, Dr. Elion was remembered as "blazing new trails as a woman scientist in what was then a man's world."

Dr. Elion was a scientist emeritus at Glaxo Wellcome Inc., where she had served as head of the Department of Experimental Therapy. She was the recipient of more than 35 honors and awards, including the National Medal of Science, the Medal of Honor from the American Cancer Society and election to the Institute of Medicine of the National Academy of Science.

She received her master's degree in chemistry from New York University in 1941 and held honorary doctorates from 20 universities.

Michiaki Takahashi, M.D., D.M.Sc.

In 1964, during his research fellowship at Baylor Medical College in Houston, Dr. Michiaki Takahashi's 3-year-old son was suffering from a severe case of varicella. He remembers asking himself, "What if varicella could be prevented by a vaccine?" Eight years later, Dr. Takahashi, the VZVRF's third Scientific Achievement Award winner, began development of a live varicella vaccine.

Dr. Takahashi's involvement with vaccines began at Osaka University's Institute for Microbial Diseases, where he worked on a measles vaccine. He later studied adenovirus and herpes simplex virus from the viewpoint of cellular transformation by these viruses. In conjunction with these studies, he collaborated on the development of a live mumps and rubella vaccine. He then commenced work on the varicella vaccine.

According to Dr. Takahashi, "The varicella-zoster virus was one of the most difficult viruses to study because of its poor cell-free virus yield and heat-labile property." Nevertheless, he overcame these difficulties and developed the varicella vaccine in 1974. Twenty-one years later, in March 1995, the US Food and Drug Administration approved the country's first varicella vaccine for use in children and adults who have not had varicella.

Dr. Takahashi received the VZVRF Award in 1997, calling it "the highest honor in my career." He currently is professor emeritus at Osaka University, Japan, and director of The Foundation for Microbial Diseases of Osaka. Dr. Takahashi earned his M.D. degree from Osaka University Medical School.

Figure I.3 Michiaki Takahashi, M.D., D.M.Sc.

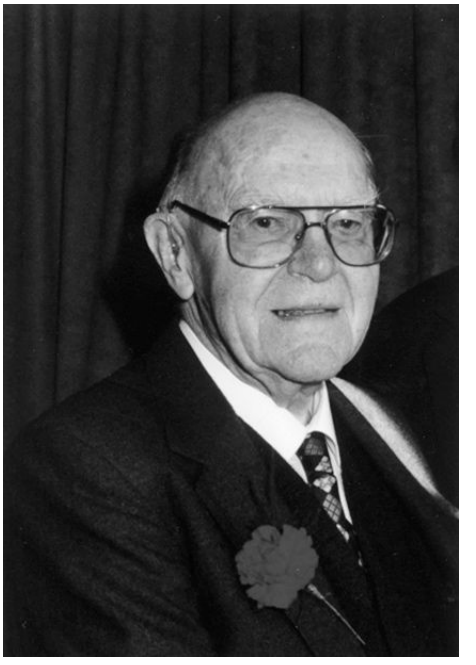

Figure I.4 Robert Edgar Hope-Simpson, O.B.E., F.R.C.P.

Robert Edgar Hope-Simpson, O.B.E., F.R.C.P.

The most recent recipient of the VZVRF Scientific Achievement Award is Robert Edgar Hope-Simpson, O.B.E., F.R.C.P., a British general practitioner who wrote, in 1965, a definitive paper on which future VZV research would be based. His 18-year study of zoster and chickenpox among his patients led him to the conclusion that zoster is due to reactivation of latent VZV. That same year, he also hypothesized that the increased incidence and severity of zoster in older people is the result of declining immunity.

With no formal training in research or epidemiology, Dr. Hope-Simpson used the 3400-patient base of his Cirencester practice to conduct his life's work of epidemiological field studies of infectious diseases. In total, he authored more than 80 papers on infectious disease and epidemiology, including his 26-year experience with postherpetic neuralgia.

Dr. Hope-Simpson was the first chairman and founding member of the College of General Practitioners. He is the recipient of many awards, including the Stewart Prize and the Ekke von Kuennsberg Prize from the Royal College of General Practitioners. Dr. Hope-Simpson was honored by Queen Elizabeth with an O.B.E. (Officer of the Order of the British Empire) for his services in Public Health Medicine. He graduated from St. Thomas Hospital, London, in 1932.

Figure I.5 Richard T. Perkin, Chairman and President, VZV Research Foundation.

Richard T. Perkin, Chairman and President, VZV Research Foundation

Richard T. Perkin founded the VZV Research Foundation in 1991, as a result of his then 82-year-old mother's struggle with zoster and postherpetic neuralgia. In an attempt to help his mother cope with her excruciating pain, he searched for information and assistance from several medical specialists. Mr. Perkin soon learned that while scientists had collected a great deal of knowledge on these afflictions, more research and education was needed to better understand and fight the virus that causes them. Yet there was no single organization championing this effort.

He soon began the work of forming the VZV Research Foundation, a nonprofit organization dedicated to research and education on VZV, and in October 1991, held the Foundation's first scientific and organizational meeting in Harriman, NY.

Since then, under his leadership, the Foundation has amassed more than 30 of the leading international scientists in VZV research to serve on its Scientific Advisory Board. The Foundation has awarded ten research grants (totaling more than $1 million by the year 2001), bestowed four Scientific Achievement Awards, and sponsored four major international conferences, CME programs, and a public information campaign including an 800 number (1–800–472–VIRUS), web site (www.vzvfoundation.org), newsletter (VZV FOCUS) and educational literature on chickenpox and zoster.

Mr. Perkin is chairman emeritus of The Perkin Fund, a family foundation that supports scientific research. He is also a trustee of The Juilliard School and the Wildlife Conservation Society, and a member of the Executive Committee of the Rockefeller University Council. He also serves on the Committee for Planetarium Policy at the American Museum of Natural History and the Advisory Board of New York Presbyterian Hospital. He formerly served on the Visiting Committee of Harvard University's Department of Astronomy.

Earlier in his career, Mr. Perkin was active in public media, including television documentary syndication. He is a graduate of Harvard College.

Part I

History

1

Historical perspective

Thomas H. Weller

Introduction

The development of our knowledge of the ubiquitous varicella-zoster virus has been fascinating, illustrating as it does the interplay of different scientific disciplines and the changing nature of the human host. Initially, clinicians differentiated varicella from variola. Then, epidemiologists provided evidence in support of the view that chickenpox and shingles had a common etiology, a thesis supported by pathologists who studied the lesions. Additional evidence of co-identity was provided on cultivation of the viruses in the laboratory. Yet proof of this fact awaited the application of molecular biological techniques.

Concurrently, and paradoxically in large part due to the advances of curative medicine, varicella lost its benign label as an ever-increasing number of high risk subjects in whom varicella might be lethal was recognized. Also concurrently in the developed countries the prevalence of zoster increased in parallel with the increasing longevity of the human population. As varicella emerged as a lethal disease, the need for therapeutic drugs and vaccines became obvious and the efforts of pharmacologists and immunologists yielded effective antiviral drugs and vaccines.

The differentiation of varicella from variola

Whereas zoster was recognized and described in medieval times, varicella was considered to be a mild form of smallpox until 1767 when Heberden read a paper entitled "On the Chickenpox" before the College of Physicians in London (Heberden, 1768). He indicated that chickenpox, then also called swinepox, was a mild disease, but said "yet it is of importance on account of the small-pox, with which it may otherwise be confounded, and so deceive the persons, who may have had it, into a false security, which may prevent them either from keeping out of the way of small-pox or from being inoculated". He described the evolution of the pox and listed criteria by which the cutaneous lesions of the two diseases could be distinguished.

In spite of Heberden's description of varicella, the possible relationship of the

disease to smallpox continued to be considered for many years. In 1892, Osler wrote "there can be no question that varicella is an affection quite distinct from variola and without at present any relation whatsoever to it". He described a case "documenting that an attack of one does not confer immunity from an attack of the other" (Osler, 1892). Yet Tyzzer in 1904 found it necessary to explore the possible relationship and experimentally elminated variola as a causative agent in his study of a varicella outbreak.

Origin of nomenclature

The origin of the term chickenpox is not clear. One opinion (Lerman, !981) credits Richard Morton with the first use of the word in the literature when in 1694 he described chickenpox as a mild form of smallpox. In his text of 1886 Fagge attributed the term to the phrase "chickpease" derived from the French "chiche" and Latin "cicer" (Fagge, 1886). Lerman notes that the surface texture and cream color of one kind of chickpea is similar to the early pustular chickenpox vesicle.

Christie (1969) offered an alternative explanation of the derivation, noting that in old English the term "cicen" refers to a barnyard fowl. A third suggested derivation is that the term may be derived from the old-English word "gican" meaning to itch (Englund & Balfour, 1989).

The origin of the term varicella likewise has variable interpretations. Taylor-Robinson & Caunt (1972) state that the term 'is an irregular diminutive of variola (smallpox) from the Latin "varius", various or mottled'. Another author, in an early pediatrics textbook, indicated that the term, which was introduced by Vogel in 1764, is a derivative of "varus", a pimple (Jennings, 1890).

Juel-Jensen & MacCallum (1972) summarized the terms commonly used for varicella. *French:* Varicelle; *Scandinavian:* Skaalkopper, Skoldkopper, Vandkopper, Vattenkopper; *German:* Windpocken, Wasserpocken, Spitzblattern. Varizellen; *Italian:* Varicella, Vaiuolo acquaiuolon; *Spanish:* Varicela, Viruelas locas.

The derivation of the terminology relating to zoster is less obscure. Christie (1969) noted that nomenclature relating to the segmental nature of the lesions in zoster derives from the classical Greek, where a warrior used a zoster – a belt-like binding – to secure his armor. The term shingles derives from the medieval Latin word "cingulus", a girdle.

Nature of the varicella-zoster agent

That varicella is caused by an infectious agent was demonstrated in 1875 by Steiner, who transmitted the disease to children by inoculation of vesicle fluid samples from patients with chickenpox (Steiner, 1875). However, the nature of the agent

remained unknown. Thus when Tyzzer in 1904 initiated his studies on an epidemic of varicella in Bilibid prison in the Philippines, since some physicians still maintained that the disease was a mild form of smallpox, his first task was to rule out smallpox. He noted that most of his patients with varicella either bore the scars of a past attack of smallpox or else had smallpox vaccination scars. He wrote "If the two diseases are identical as asserted by Hebra, it is difficult to explain why the severe form as seen in variola vera, as well as the oft-repeated vaccinations, should not protect against so slight a form as varicella". Further, aware that the agent of variola would produce lesions in monkeys and on the corneas of rabbits, Tyzzer inoculated monkeys and the corneas of rabbits with both clear vesicle fluid and crusts from lesions of his cases. He concluded "the negative character of these inoculations indicates clearly that the disease is distinct from smallpox" (Tyzzer, 1906).

Tyzzer noted that whereas varicella was considered to be a childhood disease, in the Philippines he was dealing with an epidemic in adults. This observation, the first report of the now well-recognized occurrence of chickenpox in adults in tropical climates, might be explained by "race, climate, and confinement in a crowded prison".

Tyzzer took serial biopsies of the cutaneous lesions of 11 cases of varicella. His eosin–methylene blue stained sections still retain their color. He published camera lucida drawings and photomicrographs of typical cellular changes. These he summarized as "the initial change consists in the appearance of peculiar eosin-staining inclusions within the nuclei and cytoplasm of epithelial and various other cells. Direct division of nuclei without subsequent division of the cytoplasm is associated with these inclusions. Cells undergoing these changes often attain relatively enormous dimensions . . .". (Figure 1.1 is a photomicrograph of a slide prepared by Tyzzer and Figure 1.2 depicts one of his camera lucida drawings).

Based on his studies, Tyzzer recommended that the differential diagnosis of cases of varicella and of smallpox could be made rapidly by microscopic examination of the cutaneous lesions. He wrote "The contents of early clear vesicles . . . may be examined under the microscope. The presence of large multinucleated cells is consistent with varicella and against smallpox. This test seems quite reliable and may be applied at the bedside". Thus, the procedure now referred to as the Tzanck test was described in 1906.

In 1921, Ernest Goodpasture studied the enlarged cells of cytomegalic inclusion disease and noted similarities with the histopathology of varicella as described by Tyzzer (Goodpasture & Talbot, 1921). Then Goodpasture initiated a series of animal experiments that demonstrated that intranuclear inclusions were a characteristic of an infection with herpes virus (Goodpasture & Teague, 1923). By analogy it was assumed that varicella was caused by a virus. Rivers, in 1926,