

Varicella-Zoster Virus

Virology and Clinical Management

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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 eliminated 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, 1981) 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 acquaiulon; *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,

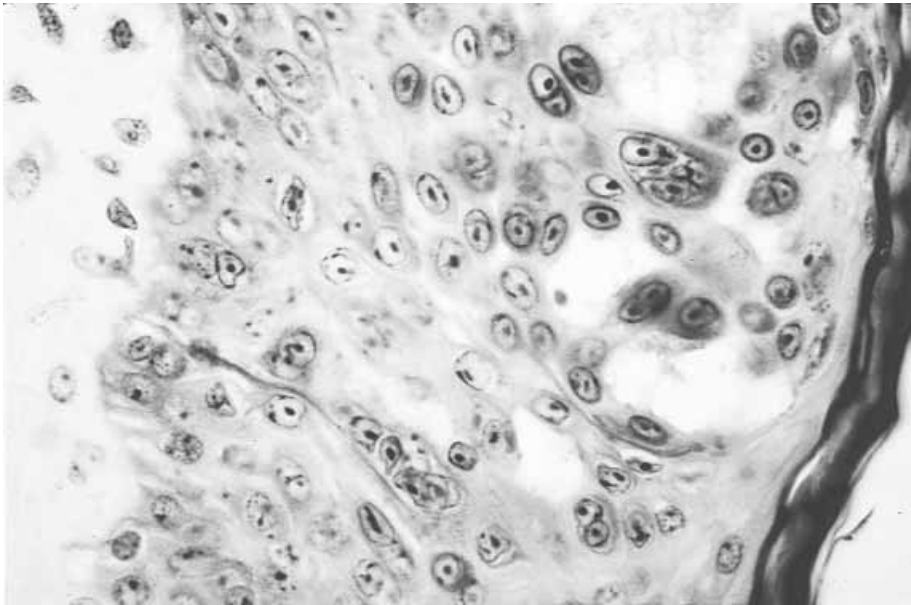


Figure 1.1 Photomicrograph of a day 1 cutaneous varicella lesion prepared by Dr. Tyzzer on June 8, 1904 in the course of his study in the Philippines. Stain: Eosin–methylene blue.

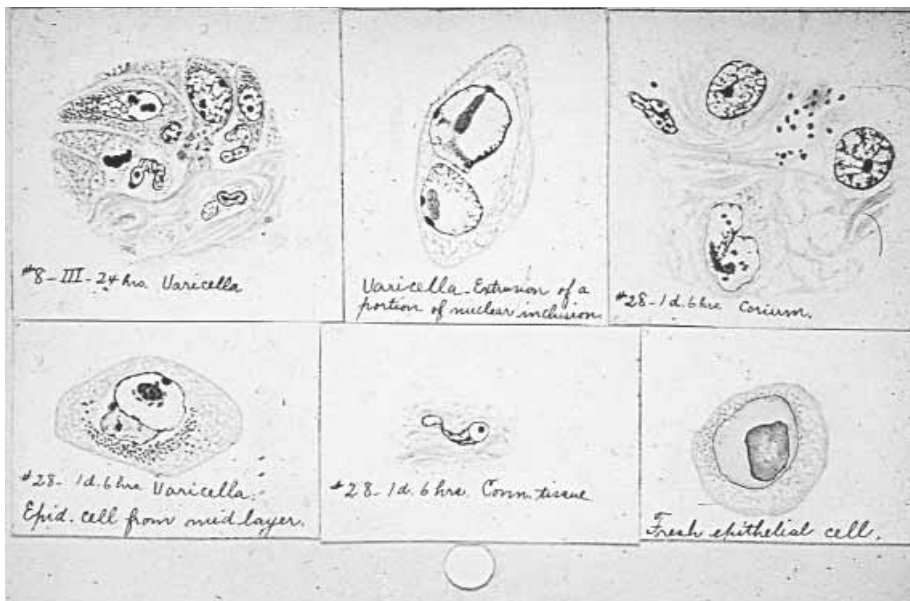


Figure 1.2 Camera lucida drawings made by Dr. Tyzzer of the nuclear changes observed in cells in the cutaneous lesions of varicella.

recorded the presence of intranuclear inclusions in the testicles of monkeys injected with the tissue of human varicella lesions (Rivers, 1926). For many years this was the only report of transmission of the etiologic agent to an experimental animal. However, various workers described what were called elementary bodies seen by light microscopy in samples of vesicle fluid. In a convincing study Amies demonstrated that such bodies were agglutinated by sera from patients convalescing from chickenpox (Amies, 1933). Examination of vesicle fluid by electron microscopy supported the concept that the bodies were viral in nature (Ruska, 1943). Use of a metal shadowing technique improved morphological details and demonstrated that the bodies were different from those of variola virus (Nagler & Rake, 1948).

The relationship of chickenpox and zoster

The question of whether chickenpox and shingles were etiologically distinct or were caused by the same virus remained unanswered for many years. That they were related was first suggested by clinical and epidemiological observations. In 1892 James Bokay, a professor of pediatrics in Budapest, published two reports describing five instances in which chickenpox had developed in individuals who had been in contact with a patient with zoster. With prescience he wrote "All the cases mentioned are very peculiar and I am reluctant to propose an explanation. However, I would like to bring up the question of whether or not the unknown infectious material of chickenpox could under certain circumstances manifest itself, instead of a generalized skin eruption, as a zoster eruption" (Jako & Jako, 1986). (While Bokay's article published in 1909 in German is usually cited, the Jakos published a translation of Bokay's 1892 Hungarian papers and kindly provided a reprint thereof.)

Many years elapsed before experimental and observational data began to accrue that supported Bokay's monistic theory of the etiology of varicella and zoster. In 1921, Lipschutz showed that the histopathology of the skin lesions of zoster was similar to that described by Tyzzer for varicella (Lipschutz, 1921). Kundratitz in 1925 experimentally transmitted the agent of zoster to volunteers with the production of varicelliform lesions, a finding confirmed by Bruusgaard (Kundratitz, 1925; Bruusgaard, 1932). By 1938, the School Epidemics Committee of Great Britain had linked 18 outbreaks of varicella in children to an exposure to zoster (School Epidemics Committee, 1938).

Using varicella and zoster vesicle fluids and crusts as antigen and convalescent phase sera from both entities in a complement fixation test, Netter and Urbain found almost identical reactions in the homologous and heterologous systems (Netter & Urbain, 1926). This finding was confirmed by Brain (1933). Amies found that some convalescent sera cross-agglutinated elementary bodies in vesicle fluid

samples from both entities (Amies, 1934). An electron microscopic study of vesicle fluids from the two entities revealed that the viral particles were morphologically identical (Rake et al., 1948).

By 1940 enough evidence supporting the monistic etiological theory had accrued to cause Zinsser (1940) and Sabin (1941) to comment on a close relationship, perhaps reflecting strains that were either dermatotropic or neurotropic. In 1943, Garland suggested that zoster reflected activation of a latent varicella virus, a situation similar to that observed with herpes simplex virus (Garland, 1943). Garland is credited with first expressing this now accepted view. Hope-Simpson elaborated on this concept, suggesting that after an attack of varicella, the virus persisted as a latent infection in the sensory ganglia (Hope-Simpson, 1965).

Cultivation of the varicella-zoster virus

As first shown by Tyzzer, the varicella-zoster virus could not be propagated in common laboratory animals. In 1944, Goodpasture and Anderson grafted fragments of human skin on the chorio-allantois of 9-day-old chick embryos and inoculated the fragments with zoster vesicle fluid. In a single experiment, histologic examination of fragments removed 4 to 8 days later showed intranuclear inclusions and multinucleated giant cells (Goodpasture & Anderson, 1944). This observation was confirmed by Blank et al. (1948).

In 1941, Dr. L. C. Kingsland and I, while interning at the Children's Hospital in Boston, attempted to grow varicella virus in cultures of human embryonic tissues. The effort was unsuccessful, reflecting the problems of contamination in the pre-antibiotic period, and enforced termination due to calls to active military duty.

In 1947, when I joined Dr. John F. Enders in organizing the Research Division of Infectious Diseases at the Children's Hospital, I returned to the problem of isolating the agent of varicella. Several unproductive months were spent using embryonated chicken eggs. Then, lacking the equipment for roller-tube cultures, but influenced by the obvious advantage of the prolonged maintenance of cultured cells, I altered the customary Maitland flask culture system. The nutrient medium was changed frequently and as a result the tissue fragments were left unchanged and remained viable. The technique proved of value and mumps virus was cultured for the first time (Weller & Enders, 1948). Then, influenced by the concept that varicella virus might be dermatotropic, on March 30, 1948 I prepared a series of cultures containing fragments of human skin-muscle tissue from a 4-month-old fetus. The majority of the cultures were inoculated with throat washings from a case of varicella and the few remaining were inoculated with a suspension of mouse brain containing Lansing poliomyelitis virus. The varicella cultures were negative, a finding that now would be expected, for virus can rarely be isolated from the oral secretions

of children with varicella. The poliomyelitis cultures were positive, thus initiating our collaborative study on the cultivation of the poliomyelitis viruses (Enders et al., 1949).

When I returned to the varicella problem and inoculated flask cultures of human embryonic tissues with varicella vesicle fluid samples from four different patients, there were positive results in six consecutive experiments. On histological examination eosinophilic intranuclear inclusions were demonstrable (see Figure 1.3). However, when we attempted to subculture the inclusion-producing agent by transferring affected tissue fragments to fresh tissue cultures, all attempts at subculture were unsuccessful (Weller & Stoddard, 1952). This frustrating situation reflected the now established fact that varicella-zoster virus remains strongly cell associated in tissue cultures.

In 1952, we began to use roller-tube cultures of human embryonic tissue and of foreskin tissue. In such cultures, the inoculation of vesicle fluid samples from six cases of varicella and from two cases of zoster resulted in slowly enlarging foci of swollen refractile cells that could be seen under low magnification in the living cultures. When stained, the swollen cells characteristically had intranuclear inclusions, and multinucleated giant cells were a common feature (see Figure 1.4). Subculture could be easily accomplished if the inoculum contained living infected cells. The foci appeared to develop as the result of transfer of infectious material from cell to contiguous cell. Similar cytopathic changes were induced by agents from the two clinical entities (Weller, 1953).

These findings initiated a 5-year study of the viruses. Strains of virus from 14 cases of varicella and from eight cases of zoster were propagated serially. Various types of cells of human origin and several of monkey origin were susceptible to infection in cultures. Again, strains of virus from the two clinical entities had similar cultural characteristics (Weller et al., 1958).

The unusual cell-associated behavior of the agents *in vitro* precluded the immediate application of the usual serological approaches to investigate the relationship. The fluorescent antibody technique then under development by Coons was therefore applied. Using preparations of the infected cells as antigen, fixation of antibody from human sera was detected by use of a fluorescent antihuman gamma globulin conjugate. Antibody reacting to the varicella and to the zoster antigens to an almost identical degree appeared during convalescence in serum specimens from the two diseases. This evidence supported the view that the etiological agents of the two diseases had been isolated and that they were closely related immunologically (Weller & Coons, 1954).

Concentration of the fluid phase of infected cultures yielded a workable complement-fixing antigen and by introducing convalescent-phase sera as a component of the medium, a neutralization test was developed. Convalescent-phase

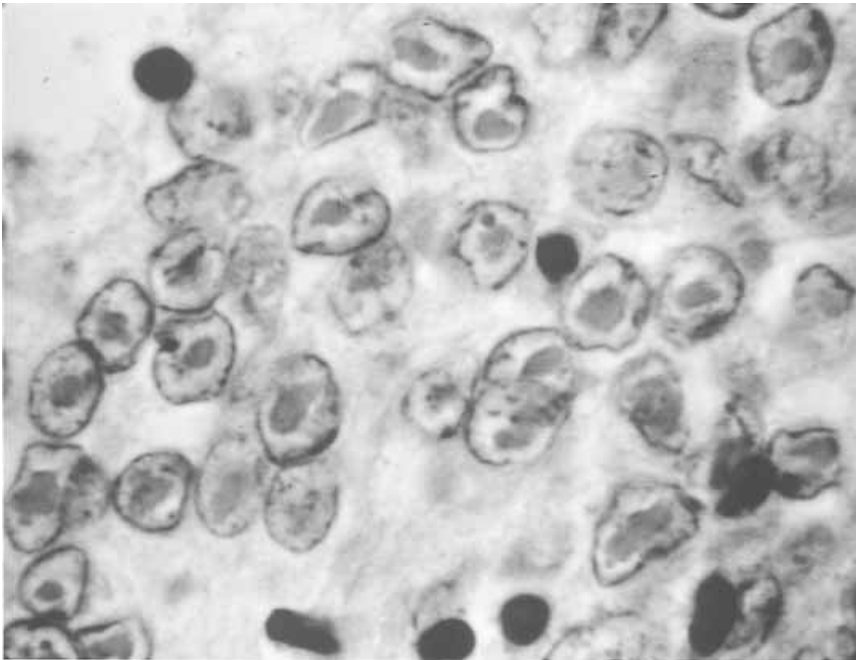


Figure 1.3 Fragment of human embryonic tissue from a Maitland type culture inoculated 14 days earlier with varicella vesicle fluid, showing nuclear inclusion bodies. From the first successful suspended cell culture; prepared March 19, 1949. Stain: hematoxylin–eosin.

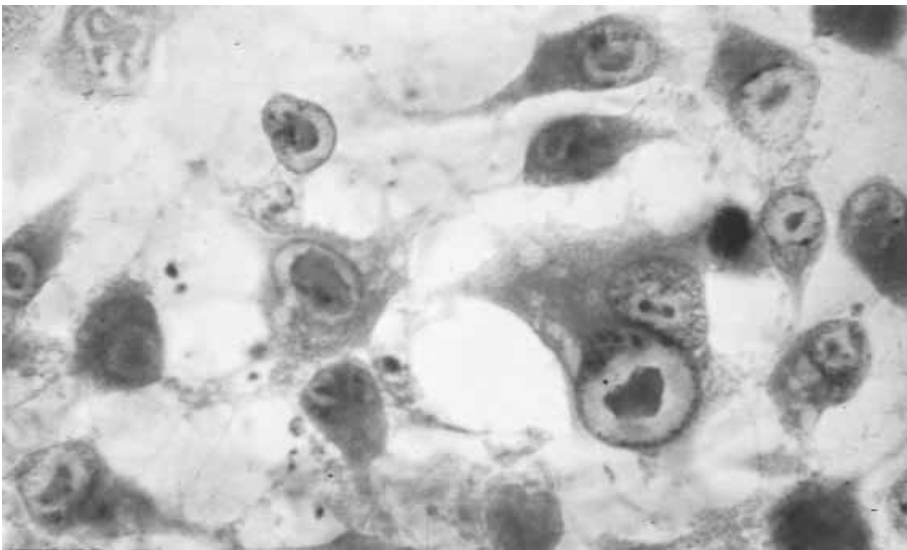


Figure 1.4 Edge of a focal lesion in the first successful roller-tube experiment. Tissue harvested 13 days after inoculation with varicella vesicle fluid (PWel.strain) showing numerous intranuclear inclusion bodies. Prepared November 19, 1952. Stain: hematoxylin–eosin.

sera from cases of varicella and from cases of zoster reacted similarly in both tests with the homologous and the heterologous antigens. We coined the phrase “varicella-zoster virus” and concluded “the accumulation of epidemiological and laboratory evidence in support of the hypothesis that a single etiologic agent is responsible for varicella and herpes zoster appears so impressive that the burden of proof must now shift to those who desire to refute the monistic concept” (Weller & Witton, 1958).

The availability of cultured virus permitted the application of the techniques of molecular biology as they evolved. While there proved to be only one type of varicella-zoster virus, application of restriction-endonuclease techniques revealed genomic differences between epidemiologically unrelated isolates (Straus et al., 1983). Using this approach, Straus and his coworkers provided proof of the co-identity of the etiological agents. Isolates were obtained from a patient with varicella and from the same patient who later developed zoster; on molecular characterization the isolates were identical (Straus et al., 1984).

In 1986, Davison and Scott reported the complete DNA sequence of varicella-zoster virus (Davison & Scott, 1986).

The increasing social significance of varicella-zoster virus

Heberden in his lecture in 1767 stated that illnesses caused by varicella “occasion so little danger or trouble to the patients, that physicians are seldom sent for to them, and have therefore very few opportunities of seeing this distemper. Hence it happens that the name of it is met with in very few books, and hardly any pretend to say a word of its history”. This view of a benign illness persisted for almost 200 years. In medical school my pediatric textbook gave brief mention to varicella, referring to its mild constitutional symptoms and the fact that serious complications and sequelae were very rare (Holt & McIntosh, 1936)

Shortly thereafter increasing knowledge and changes in the human host altered the prevalent concept. Additionally, and paradoxically, medical progress *per se* enhanced the potential lethality of varicella-zoster virus. In 1942, as reviewed by Feldman (1994), it was recognized that varicella in adults was a more serious disease than in children, with viral pneumonia a common presentation. In 1947, Laforet and Lynch described the congenital varicella syndrome (Laforet & Lynch, 1947).

The changing age and nature of the population acquired importance as it was recognized that zoster increased in frequency with advancing age. In Hope-Simpson’s classical study it was observed that in a cohort of 1000 people who lived to be 85 years old, 500 would have had one attack of zoster and ten would have had two attacks (Hope-Simpson, 1965). It is now known that this finding reflects the

gradual decay of cellular immunity in old age. Currently, the indigenous population is aging; one estimate is that in the next 40 years in the United States the number of persons over 85 years of age will increase from 3.5 to 8.8 million (Gilford, 1988).

The nature of the population is also changing due to the immigration of adults from tropical areas, many of whom have not had varicella. The Census Bureau reported that in the United States between 1983 and 1992, the Hispanic population increased by 42% to 22.8 million people (US Census Bureau, 1994). Thus was introduced a large group of adults in whom varicella would be more severe. Of more import is the fact that these individuals may acquire caretaking jobs in hospitals and, if incubating varicella, may expose high risk patients.

In 1956, we described two cases of varicella from which we isolated virus at autopsy; one was a child on steroid therapy and the other a child undergoing treatment for malignancy (Cheatham et al., 1956). As similar cases were observed, a category of high risk patients subject to a severe or fatal varicella-zoster virus infection was recognized. All were immunosuppressed. One form of immunosuppression was biological as in those with reticuloendothelial or hematopoietic cancer, or with a concurrent infection such as the human immunodeficiency viruses (HIV). It was recognized that depression of cellular rather than of humoral immunity was important (Arvin et al., 1978). The other type of immunosuppression was iatrogenic as in the chemotherapeutic immunosuppression procedures essential in the burgeoning organ transplant field. In such individuals, either a primary infection or the reactivation of a latent infection could lead to a severe disseminated lethal process. With recognition of the high risk group, the virus lost its benign characteristics and the search for improved therapeutic and preventive measures was stimulated.

Modification, prevention, and treatment

Passive immunization

In 1962, Ross summarized the then limited literature on cases of severe varicella and conducted a classical study on the use of gamma globulin to modify the illness (Ross, 1962). Counts of pox proved to be a useful index of modification of varicella, and it was concluded that gamma globulin was an effective modifier if given within three days of exposure. A significant advance in providing an increased supply of high potency gamma globulin resulted from the selective use of outdated blood bank lots shown by complement fixation to have significant levels of varicella antibodies (Zaia et al., 1978).

Chemotherapy

Specific therapy for varicella developed in the 1970s. Interferon and transfer factor proved to be of some value in treating infections in high risk patients. Concurrently, compounds that interfered with the synthesis of viral DNA were introduced. Of the early compounds studied, adenine arabinoside, ARA-A, a purine nucleoside, was the most promising; a multi-institutional study demonstrated its value in the treatment of herpes zoster in high risk patients (Whitley et al., 1976).

As reviewed by Whitley & Gnann (1992), the synthesis of acyclovir by Gertrude Elion and her group in 1977 was a striking advance. The virus-encoded thymidine kinases present in infected cells convert acyclovir to its monophosphate derivative, which is subsequently converted to acyclovir triphosphate, a substance that inhibits viral DNA synthesis. This was the first of the currently available highly effective drugs.

Active immunization

In 1974, Takahashi and his co-workers reported that a live virus vaccine developed by them had prevented the spread of varicella in a hospital (Takahashi et al., 1974). The virus, the Oka strain, had been obtained from the vesicles of a typical case of varicella in a 3-year-old boy. Attenuation of the strain followed 11 passages in cultures of human embryonic lung cells at 34°C and 12 passages in guinea pig embryo cells at 37°C (Takahashi et al., 1975).

In retrospect, it is of interest that in spite of innumerable attempts no similar attenuated strain has been developed. Thus, the Oka strain remains the essential element of current vaccines. Takahashi's vaccine produced by the Biken Institute was used extensively in Japan and other far eastern countries. In 1984, Varilrix, a Smith-Kline Beecham product, was first licensed in Europe and is now licensed in about 40 countries (Francis Andre, personal communication). In the 1980s Pasteur Merieux Serums and Vaccins S.A. initiated studies of a vaccine in France. Varivax, produced by Merck and Company, was licensed in the United States in 1995 following 14 years of extensive collaborative studies organized by Dr. Anne Gershon (Gershon et al., 1984, 1989; Hardy et al., 1991). Thus, vaccines are now universally available. While the need to prevent varicella in the expanding population at high risk is obvious, studies by Preblud (1986) indicated that normal children would benefit from vaccination "not by virtue of the severity of the disease but rather because of the inevitability of the disease and its associated expense". Historical reviews of the varicella vaccines have been published (Gershon, 1995; White, 1997).

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The author is indebted to Drs. Henry Balfour, Jr. and Janet A. Englund, who provided photocopies of some early historical papers.

When Dr. Ernest Tyzzer retired at Harvard in 1942 he gave me the microscopic slides and drawings that he had made in 1904–5 during his studies of the outbreak of varicella in Bilibid prison in the Philippines. Representative items have been deposited in the Registry of the Armed Forces Institute of Pathology and in the historical archives of the Countway Library at Harvard.

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