Infections

MEDICAL GRAND ROUNDS

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VARICELLA-ZOSTER VIRUS

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INTRODUCTION

A review of our current understanding of varicella-zoster virus (VZV) seems pertinent for the following reasons: 1) Chickenpox or varicella persists as a childhood disease essentially unmodified by any preventive measures. This is unusual in an era where marked progress has been made in reducing the incidence of other childhood exanthems (rubeola, rubella) by potent vaccines. 2) Herpes zoster, a common disease of later life, is frequently encountered in the course of certain lymphoreticular malignancies and stands as a troublesome complication of immunosuppressive therapy. Present methods of dealing with some of the problems presented by zoster, for example, post-herpetic neuralgia, are debated but must be considered imperfect. 3) Means now exist [zoster immune globulin (ZIG)] for the prevention of varicella in compromised hosts if applied during a suitable period after exposure. 4) Antiviral chemotherapeutic agents, currently undergoing clinical evaluation, have been demonstrated in vitro to inhibit VZV replication. We shall consider the most promising of these agents, i.e., cytosine arabinoside (Ara-C) and adenine arabinoside (Ara-A).

ETIOLOGY

It has now been incontestably proven that a single virus, VZV, causes both varicella and herpes zoster (24,143,144). VZV has a central core containing DNA, its genetic material, which is enclosed in a capsid possessing icosahedral symmetry. Viral replication takes place in the cell nucleus, often within discrete centers of virus synthesis or "factories". The viral nucleocapsid acquires one or more envelopes in its passage to the cell surface. Current evidence indicates that the initial envelope applied to the virus particle is derived from the inner nuclear membrane. Subsequent envelopment may take place within the cytoplasm of the cell. It is thought that the cytoplasmic membrane does not contribute significantly to the envelope system of the virus. During VZV replication and assembly, many immature particles are produced. These particles are nonviable but conceivably could contribute to the pathological process by the formation of immune complexes.

In tissue culture, viable virus particles are usually cell associated. This accounts for the focal nature of the cytopathic effect. In human fibroblast cultures, the cytopathic effect progresses along the linear axis of the cells. The

virus is cytocidal in this system with the resultant formation of small, rounded refractile cells and giant cells containing multiple nuclei. On H&E stain, Cowdry Type A inclusion bodies can be seen. These inclusions are eosinophilic, separated from the nuclear membrane by a clear zone and correspond to the most active sites of virus replication (8). The formation of giant cells infers that VZV may have a direct effect on cytoplasmic membranes by virtue of its capacity to fuse adjacent cells. Viable, cell-free VZV particles have been produced from sonicated human fibroblast cultures and from human thyroid tissue cultures (15,22). This development has made neutralization tests possible. A soluble antigen, derived from infected human fibroblast tissue cultures, is available for complement fixation antibody testing (16).

VZV is a member of the herpesvirus group of animal viruses. Other viruses of this group infecting man are herpes simplex virus, types 1 and 2, cytomegalovirus, Epstein-Barr virus and herpesvirus B (herpesvirus simiae). All these viruses are capable of undergoing latency and periodic reactivation. It has been shown by complement fixation, neutralization and fluorescent antibody tests that VZV and herpes simplex virus contain certain common antigens. In persons previously exposed to VZV who then undergo infection with herpes simplex virus, a heterologous increase in VZV antibody titers can be demonstrated. This increase was present in some, but not all persons with prior VZV experience and was most marked if the preceding VZV infection was recent. The converse (herpes simplex virus antibody titer rise with VZV infection) could also be shown but to a lesser extent, and then only with complement fixation antibody testing and not with the more specific neutralization test (125). That VZV and herpes simplex virus may share some common antigens should be considered in the interpretation of diagnostic serological tests. Herpes simplex virus infections may also serve to boost immunity to VZV.

EPIDEMIOLOGY

It is now generally agreed that the initial encounter of the non-immune human host with VZV results in varicella whereas herpes zoster represents a reactivation of a latent infection originating in dorsal root or cranial nerve ganglion cells. Although this generalization is probably true for the most part, certain exceptions may exist. A zosteriform eruption may occasionally complicate varicella (152). There have now been several epidemics in immunosuppressed patients where the data support but do not unequivocally prove the concept that zoster may occasionally occur as a result of exogenous reinfection (10,112,126).

Varicella is an acute communicable disease of childhood with an incubation period of 14-17 days and extremes of 10-20 days. The child is considered infectious during the prodrome and through the fifth day of the rash. The disease is highly contagious with a secondary attack rate in susceptible contacts approximating 75%. Transmission of the virus occurs by direct contact and through droplet nuclei. Involvement of the respiratory tract promotes the efficient dissemination of the virus. The disease has its peak incidence in the spring. Case rates fluctuate by year; high rates may be maintained for 1-5 years and are followed by periods of decreased incidence. There has been an apparent decrease in the number of varicella cases in recent years but the decline may be coming to an end as, in Dallas, Texas, for example, where there has been an increased number of cases in 1971-1972 and 1972-1973 (Figure 1) (69).

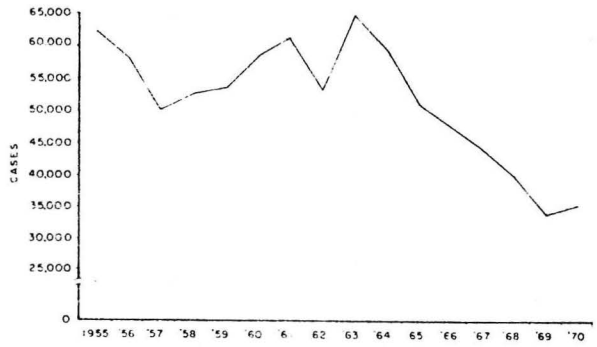

Figure 1. Reported cases of varicella in eight states (Alabama, Arkansas, Arizona, Florida, Iowa, Massachusetts, Michigan, and Washington) 1955–1970.

As a result largely of a varicella → varicella transmission sequence, the cumulative percentage of persons with a history of varicella increases by age. Over 80% of young adults give a history of having had varicella (Figure 2) (69).

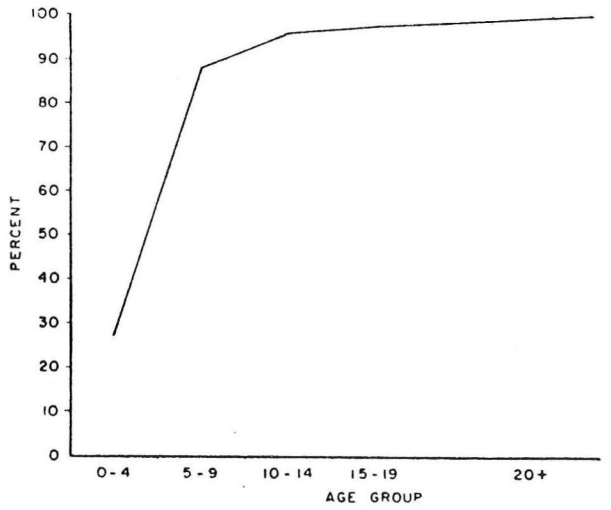

Figure 2. Cumulative percentage of varicella cases by age group (from Illinois, Massachusetts, and New York City) 1967–1969.

The prevalence of VZV complement fixing antibody increases with age up to 50 years. It then decreases with age for several decades and shows an apparent upturn in elderly persons. Complement fixation antibody titers $\geq$ 1:16 are noticeably less frequent in middle aged persons than in younger or older groups (Table 1) (137).

TABLE 1

TITERS OF ANTIBODY TO VARICELLA-ZOSTER VIRUS IN SERA FROM 308 PATIENTS

Age Group	No. of Patients	Number of Sera With Titers Equal to or Greater Than			
		1/4	1/8	1/16	1/32
0-10	19	9 (47)	6 (32)	5 (26)	5 (26)
11-20	59	43 (73)	32 (54)	26 (44)	20 (34)
21-30	98	69 (70)	57 (58)	47 (48)	27 (28)
31-40	35	25 (71)	19 (54)	14 (40)	6 (17)
41-50	23	18 (78)	9 (39)	9 (39)	4 (17)
51-60	26	18 (69)	12 (46)	11 (42)	5 (19)
61-70	19	11 (58)	10 (53)	9 (47)	4 (21)
71-80	20	12 (60)	11 (55)	8 (40)	6 (30)
81-90	9	6 (67)	6 (67)	5 (56)	4 (44)

Figures in parentheses indicate percentage of the total number in each group

Herpes zoster is a sporadic disease and does not have a seasonal peak. Varicella epidemic years are not accompanied by an increased incidence of zoster. Although zoster is known to give rise to varicella, documented examples of varicella → zoster or zoster → zoster in normal persons are rare and usually thought coincidental. Teleologically, zoster may be looked upon as a means of maintaining VZV in the community in the absence of a continued occurrence of varicella cases. Attack rates for zoster increase linearly with age after 50 years (Table 2) (62).

TABLE 2

ZOSTER AGE-SPECIFIC ATTACK RATES
(Cirencester, England, 1947-1962)

Age Groups (years)	Population	No. of Cases	Rate per 1000	Rate per 1000 per Annum
0-9	510	6	11.8	0.74
10-19	455	10	22.0	1.38
20-29	412	17	41.3	2.58
30-39	491	18	36.6	2.29
40-49	492	23	46.7	2.92
50-59	454	37	81.5	5.09
60-69	350	38	108.6	6.79
70-79	263	27	102.7	6.42
80-89	99	16	161.6	10.10
90-99	8	-	-	-
Total	3.534	192	54.3	3.39

The increase in incidence of zoster with age has been postulated to coincide with waning immunity to VZV, one reflection of which is found in declining complement fixation antibody titer levels (62,137).

In addition to age, other factors have been suggested to precipitate herpes zoster. Among these factors are trauma, arsenic therapy, syphilis, tumor intrapping dorsal root ganglion cells, lymphoreticular malignancies, irradiation therapy and corticosteroid or other immunosuppressive chemotherapy (150). Proof that these events influence the occurrence of zoster is at times not rigorous and it is often difficult to dissect the quantitative importance of individual factors when these are combined in a single patient (Table 3).

TABLE 3

OCCURRENCE OF HERPES ZOSTER IN VARIOUS DISEASE CATEGORIES

Disease Category	Per Cent of Patients With Herpes Zoster								
Hodgkin's disease									
Rx unspecified	9.4	8.2		19.0		25.0			
Irradiation					15.4				
Irradiation + chemotherapy					29.1				
Irradiation + splenectomy					22.9				
Irradiation + chemotherapy + splenectomy					28.6				
Other lymphomas	0.9				7.1	8.7			
Leukemias									
Acute						1.2			
Chronic									
Lymphocytic						8.3			
Granulocytic						0			
Solid tissue neoplasms	0.9					1.8			
Renal transplant recipients									
Prednisone + azathioprine							6.7		
Prednisone + azathioprine + irradiation			8.2						
Corticosteroid therapy								5.0	
Hospitalized patients	0.3								
Non-hospitalized persons (all ages)									5.4
Years encompassed by study	5	43	2-3	4	11	2	2	4	15
Reference	147	132	151	146	48	126	PMH Data	112	62

In Table 3, it should be noted that it was not possible to calculate a case rate for zoster by year in most of the reported series. In most of these reports, the ages of the patients and those at risk are not given and it is impossible to estimate the effect of age on the occurrence of zoster. The data on non-hospitalized cases is from an extremely complete study done in a single general practice in England and does demonstrate the real frequency of zoster in the population. It is generally accepted that Hodgkin's disease, other lymphomas ± therapy, chronic lymphocytic leukemia, intensive immunosuppressive therapy (irradiation, corticosteroids, azathioprine) predispose to zoster. The effect of trauma and solid tissue neoplasms without irradiation or immunosuppressive therapy may be real but is difficult to prove with the available data. Although nerve entrapment by tumor may play a predisposing role, it is also difficult to prove this since the patients may be irradiated and nerve involvement, for example, in Hodgkin's disease usually implies advanced disease and the concomitant development of impaired delayed hypersensitivity responses.

The effect of irradiation therapy appears to decline with time (Figure 3) (48).

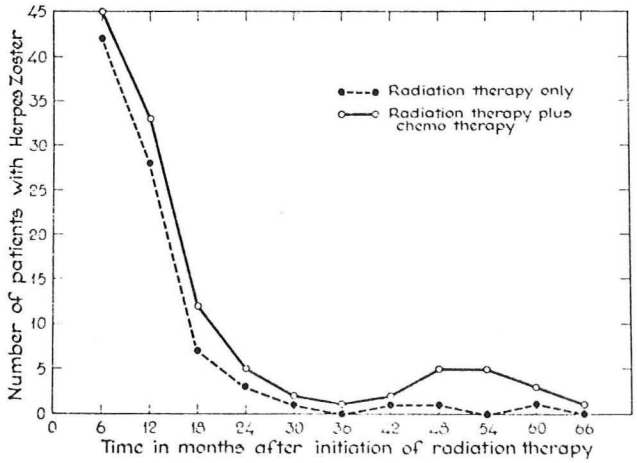

FIGURE 3. Number of infections occurring at various time intervals after initiation of radiation therapy

It has been suggested that the radiation port might determine the site of the subsequent zoster. Of six patients developing herpes zoster after renal transplantation, 5 did so in temporal relation to irradiation therapy and in all these, the lesions arose in proximity to the area irradiated. Contralateral involvement was noted in one patient (151).

By analogy with other acute viral exanthems, it seems probable that exogenous reinfection with VZV should occur if the challenge is sufficient. Data on this point are sparse but suggestive in two personnel who developed complement fixation antibody titer rises ($< 1:4 \rightarrow 1:8$; $\leftarrow 1:4 \rightarrow 1:16$) without symptoms in association with intensive exposure in an epidemic of VZV infections on a ward with cancer patients (126). At present, it is an open question whether such exogenous reinfection in compromised hosts can given rise to overt clinical manifestations (varicella, zoster, disseminated zoster or atypical forms of disease). Several epidemics have recently been reported which are consistent with but do not

absolutely prove this possibility. Histograms depicting the course of two of these epidemics are shown (Figures 4 and 5) (126, MMWR).

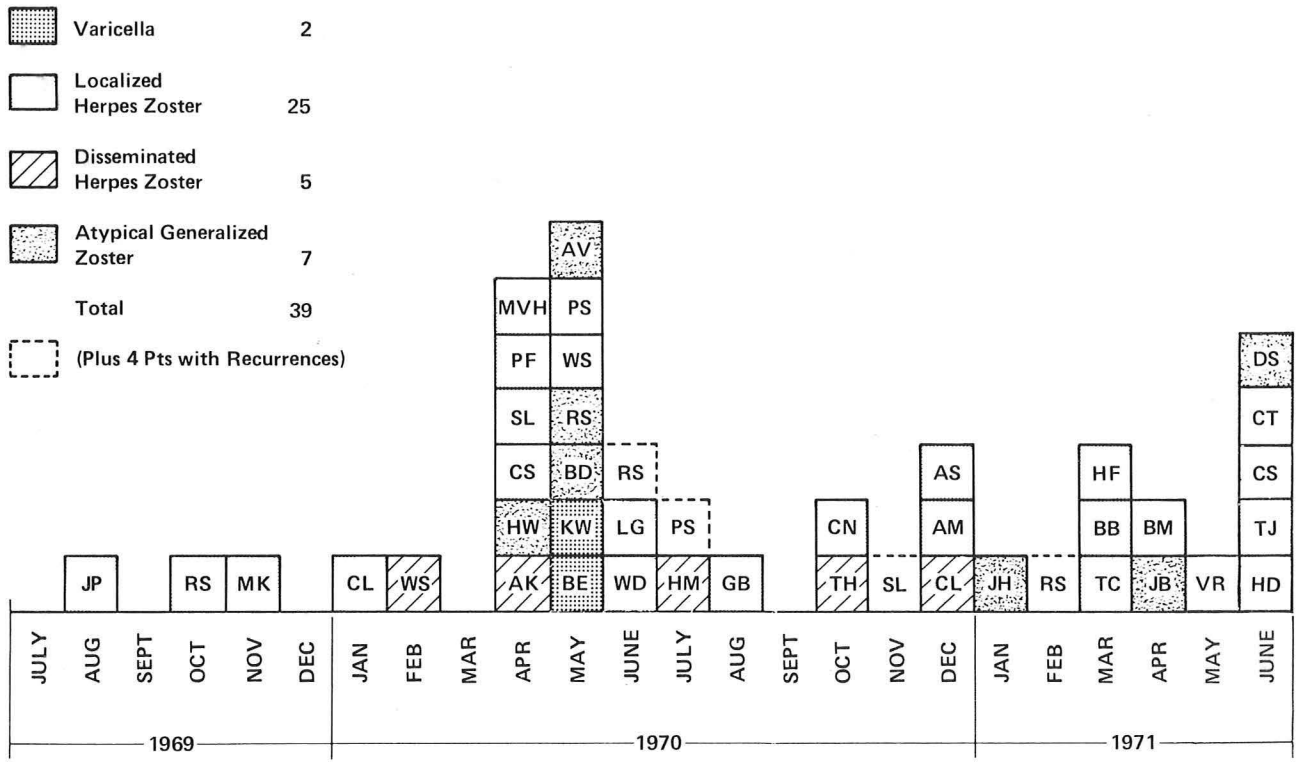

FIGURE 4. Occurrence of varicella-zoster at the Baltimore Cancer Research Center from 1 July 1969 to 30 June 1971

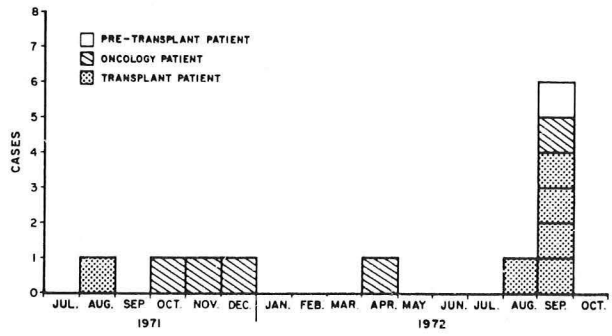

FIGURE 5. Cases of herpes zoster by month of onset - Leukemia Research Center - July 1971-September 1972

It is difficult to exclude the possibility that the clusters of cases that developed in these epidemics may be related to chance circumstances. Further observations are needed. In the Baltimore Cancer Research Center experience, an incubation period for zoster was estimated and may have been slightly longer than generally considered for VZV primary infections, i.e., 20-30 days instead of ~ 14 days for varicella (126).

PATHOLOGY

The typical lesion resulting after VZV infection begins as a macule and then progresses through papular, vesicular, pustular and crusting stages. The vesicle is usually entirely within the epidermis with the base being formed by the deeper prickle cell layer. Healing of varicella is almost always without scarring unless there is secondary bacterial infection. Zoster has a greater tendency to scar, implying more destruction of the germinal epithelial layer. Within the vesicle, ballooning degenerated epithelial cells are seen along with multinucleated giant cells. Type A intranuclear inclusions can be seen. As the vesicle progresses, polymorphonuclear cells enter and a pustular lesion develops. In progressive VZV infections, similar focal areas of necrosis develop in other organs, particularly in lung, liver, spleen, adrenal glands, gastrointestinal tract and pancreas. A pathologic change not usually emphasized is the occurrence of endothelial damage with intranuclear inclusions in vascular endothelial cells (152).

Head and Campbell's classical description of the nervous system changes in zoster cites the occurrence of acute inflammatory changes in the dorsal root or cranial nerve ganglia, with hemorrhage and round cell infiltration (154). Later, fibrosis eventuates in areas where the inflammation has been most marked. Nerve cell degeneration and demyelination occur in peripheral nerves and nerve roots served by the involved ganglion. Electron microscopy has revealed virus particles in the cytoplasm of perineural cells and in the cytoplasm and nuclei of Schwann cells. Ganglion cells and satellite cells also contained virus particles in both the nucleus and cytoplasm (38). A localized lymphocytic meningitis can occur at the entry of the affected root into the spinal cord. Infrequently, anterior horn cells are affected and this accounts for the motor paralysis that may be seen rarely in zoster. Dorsal column demyelinating changes may also be seen.

IMMUNOLOGY

During primary infection with VZV, IgM and IgG antibodies develop. These antibodies are detectable by neutralization, complement fixation and immunofluorescence testing. The antibody response following zoster is anamnestic and consists mainly of IgG. It has been demonstrated that human IgG can be divided into four subclasses, these being differentiated by antigenic determinants on the heavy chain of the immunoglobulin molecule. Electrophoretic mobility studies have shown that human IgG can be separated into two major fractions, a "slow" and a "fast" component. Primary infection with VZV results in antibody mainly detected in the "slow" IgG component. After zoster, antibody is found in both component fractions. Since in experimental animals, the "fast" component of IgG has been shown to confer greater protection against challenge with herpes simplex virus, this may mean that the antibody response in varicella may be incomplete and only partially protective (84). In tissue culture, incorporation of specific antibody into the culture media reduces plaque number although virus, in this system, must be considered almost entirely cell associated.

The T cell response (delayed hypersensitivity) following VZV infections has been incompletely studied. Increased DNA synthesis as measured by incorporation of labelled thymidine occurs in lymphocyte cultures prepared from sensitized individuals when exposed to non-viable VZV antigen. Interferon has been found in vesicle fluid in patients with zoster. In this situation, interferon has been postulated to result predominantly from synthesis by sensitized lymphocytes (134).

VZV has been found in tissue culture to be sensitive to human interferon (6). The relative importance of antibody vs delayed hypersensitivity mechanisms in preventing zoster can be argued. The increased incidence of zoster in patients with Hodgkin's disease, particularly with advanced involvement and known T cell dysfunction as opposed to a normal or slightly increased attack rate in patients with multiple myeloma and predominant B cell abnormalities implies that delayed hypersensitivity responses are quantitatively more significant.

Two major defects have been identified in patients who undergo dissemination during the course of zoster: 1) A few patients have delayed and quantitatively diminished antibody responses, as measured by complement fixation tests (95). 2) Other patients have deficient vesicular fluid interferon responses, as shown by slower rises and decreased quantities of this viral inhibitor in zoster vesicles (134). The lack of an appropriate interferon response may be a measurable index of a broader dysfunction in T cells, as evidenced by an apparent correlation of dissemination with inability of some of these patients to become sensitized after treatment with dinitrochlorobenzene (126). The relationship of vesicular fluid interferon levels to dissemination is shown in Figure 6 (134).

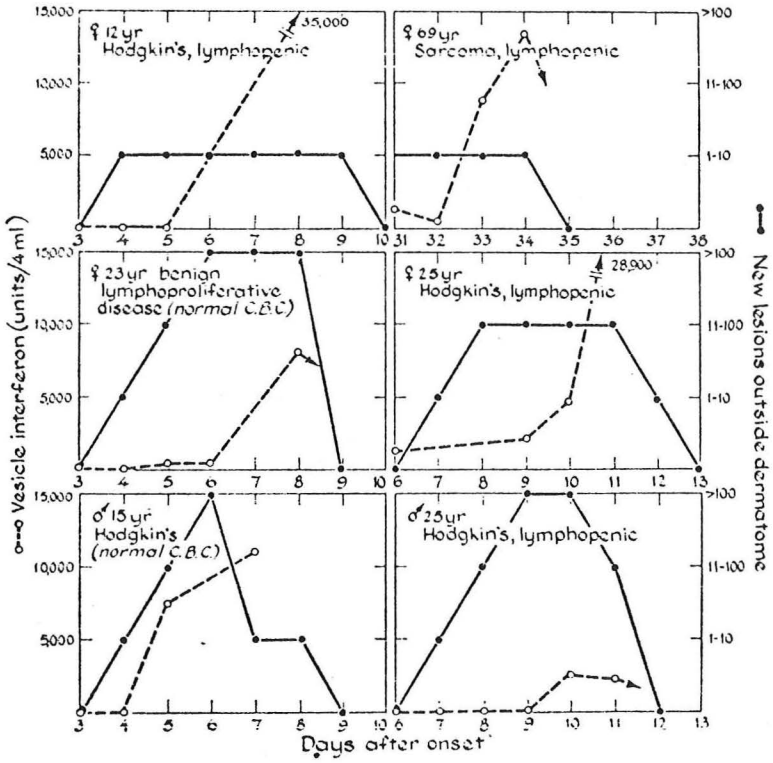

FIGURE 6. Relationship of dissemination of herpes zoster to V-IF. Dissemination phase of illness in six representative patients is shown. V-IF curve shown to development of peak titer; in some cases beginning of decline during crusting phase is shown (descending arrow).

Certain non-specific responses must be mentioned as they probably influence the course of VZV infections. Among these are temperature and influence of pH. As the vesicles pustulate, polymorphonuclear leucocytes enter into the lesion. Presumably these cells have increased metabolic activity and the pH of the fluid should decrease. By analogy with other herpesviruses, an acid pH (< 5.5) might be presumed with time to inactivate some VZV particles. The influence of lysosomal enzymes liberated by the leucocytes is not known for certain, but conceivably could also influence virus viability.

During varicella, a transient impairment of delayed hypersensitivity with respect to other antigens may develop. This is manifested by anergy to a variety of skin test antigens.

PATHOGENESIS

In varicella, virus is probably initially implanted on the mucosa of the upper respiratory tract. Viral replication occurs here; a subsequent viremia ensues with a postulated seeding of cells of the reticuloendothelial system. After maturation in these cells, another episode of viremia occurs, this time resulting in the typical skin lesions. The crops of vesicles are probably best related to the asynchronous maturation of virus particles in the reticuloendothelial system.

Involvement of the tracheobronchial tree by VZV lesions may pave the way for superinfection and the consequent development of bacterial pneumonia. True viral pneumonia occurs almost exclusively in adults and reflects tracheobronchial involvement and probable hematogenous dissemination diffusely to lung parenchyma. Vascular endothelial cells may contain virus particles and surface damage may result. In some cases, this may eventuate in disseminated intravascular coagulation. Rarely this may become clinically manifest as hemorrhagic varicella. Documented instances of gangrene of digits and other areas of the body have been reported and are probably best related to disseminated intravascular coagulation and vascular thromboses (56,59). Rare cases of thrombocytopenic purpura have been reported without significant depression of other clotting factors (86). Presumably, this represents immunological peripheral destruction of platelets. Mild degrees of thrombocytopenia may commonly develop during varicella. The relative contribution of disseminated intravascular coagulation, accelerated peripheral destruction of platelets and direct megakaryocyte damage in the genesis of this thrombocytopenia is not known.

Circulating immune complexes have been demonstrated in one patient with hemorrhagic varicella (100). It can be postulated that these immune complexes may be etiologic in the production of the mild, transient glomerulonephritis that may occasionally complicate varicella.

With the development of skin lesions in varicella, virus is transported to cranial nerve and dorsal root ganglion cells by centripetal movement along sensory nerve fibers. Virus particles are transported in Schwann cells and in perineural cells. Axon cylinders are probably not involved in this transfer. A state of viral latency supervenes. It is not known if reactivation occurs commonly and is successfully contained by immunological surveillance mechanisms. Zoster results with reactivation of VZV and movement of virus along sensory nerve fibers to skin with the subsequent development of the typical vesicles. VZV may also be transported toward the spinal cord with the development of a localized leptomeningitis.

This meningitis may become generalized. Occasionally, anterior horn cells may be involved and paralysis may ensue. Transverse myelitis has been reported as a complication of zoster. VZV has been isolated from cerebrospinal fluid in patients with zoster.

Since neural interconnections exist, it is not unusual to see zoster affecting adjacent dermatomes. Dissemination of zoster to skin removed from the site of primary localization may occur in normal persons but is more common in compromised hosts. This dissemination reflects episodes of viremia that may also involve important viscera, particularly the lungs.

The mechanisms underlying central and peripheral nervous system dysfunction in VZV infections have been debated. Previous concepts of the pathogenesis of "post-infectious" encephalitis complicating common childhood exanthems (rubeola, rubella, varicella) need revision in view of the recent isolation of rubeola virus from brain in a child with measles encephalitis by newer cocultivation techniques. VZV has also been isolated from brain for the first time in a leukemic child dying with varicella (91). At issue in the debate on mechanisms is the relative importance of the direct effect of virus on cells (cell lysis, neuronal functional impairment, oligodendrocyte dysfunction and resultant effect on myelin production, action on myelin per se, and vascular endothelial involvement with thromboses) vs the damage related to immunological injury (immune complex formation with complement activation and delayed hypersensitivity responses to either viral or damaged cell antigenic components) (Table 4) (54,58).

TABLE 4

MECHANISMS UNDERLYING CENTRAL NERVOUS SYSTEM DYSFUNCTION IN VZV INFECTIONS

Direct Viral Effect	Immunological Injury
Cell lysis	Immune complex formation with complement activation
Functional neuronal impairment	Delayed hypersensitivity responses
Oligodendrocyte dysfunction → impaired myelin formation	Viral and/or cellular constituent antigens
Action on myelin per se	
Vascular endothelial involvement with thromboses	

The argument cannot be settled at the present time. Both mechanisms may be operative. At polar ends of the spectrum may be seen the ganglionitis, leptomeningitis and localized anterior horn cell injury that may occur in zoster and which is probably best related to a direct effect of the virus as opposed to the occasional instances of the Landry-Guillain-Barré syndrome that may complicate VZV infections and which presumably indicate immunological injury as the major mechanism. The debate has more than academic

significance in that it bears on the potential therapy of central nervous disease in the course of VZV infections, i.e., the use of corticosteroids or other immunosuppressive drugs.

In infrequent instances, Reye's syndrome (cerebral edema, visceral fatty metamorphosis, hypoglycemia, ↑ SGOT, ↑ NH_3) may follow varicella (47,66). Since this syndrome has also been documented to occur after influenza B infection, it may signal an unusual host response to a variety of viral infections. Alternately, these infections might potentiate the effect of certain environmental toxins to which the child has been exposed. Solution to the enigma of Reye's syndrome may have important implications for pathogenetic mechanisms of viral diseases, in general, and hence needs to be vigorously pursued.

CLINICAL MANIFESTATIONS

VARICELLA

In developed countries, during childhood, varicella is usually a mild illness with a short prodrome and a 3-4 day period of active vesicle development. Fever, headache, malaise and anorexia are non-specific accompaniments of the acute illness. The vesicles are seen in varying stages of development primarily on the trunk. Mucous membranes may also be involved. After 6-8 days, most of the lesions are observed to be crusting and they soon heal without scar formation.

Complications following varicella occur more commonly in underdeveloped countries, in adults and in children on immunosuppressive therapy. Secondary skin infection is the most common complication. Other much less frequent complications include hemorrhagic varicella (this may occasionally progress to gangrenous varicella or purpura fulminans), bullous varicella (bullae 1-3 cm in diameter), bacterial otitis media, eye involvement (conjunctivitis, keratitis, iritis), hepatitis, myocarditis, polyarthritis, orchitis and glomerulonephritis.

The incidence of pulmonary involvement in varicella is shown in Table 5.

TABLE 5

PULMONARY INVOLVEMENT IN VARICELLA

Type of Involvement	Per Cent of Hospitalized Patients											
	≤ 6 years				7-18 years				> 18 years			
Bacterial Pneumonia	6.8											
Viral												
Laryngotracheobronchitis	2.2											
Pneumonia	0	0	-	-	0	0	-	-	16.5	33.3	16.3	14.3
Reference	142	79	141	138	142	79	141	138	142	79	141	138

Bacterial pneumonia complicating varicella occurs almost entirely in children $\leq$ 6 years of age. The bacteria implicated in the causation of the pneumonia include the ordinary pyogenic cocci (pneumococci, Group A streptococci and the staphylococci) and Hemophilus influenzae. In contrast, true viral pneumonia occurs primarily in adults (> 18 years) in from 14.3 to 33.3% of such persons hospitalized with varicella. The case-fatality ratio of true varicella pneumonia varies between series and according to criteria used for the diagnosis. Different series have found the case-fatality ratio to be 0/110, 0/7, 1/10, 4/29 and 6/20 (Total 11/176, or 6.3%) (141,138,79,142,123). The clinical manifestations of 10 cases of primary varicella pneumonia are listed (Table 6) (79). Pleural effusions may be present as a result of vesicles on the pleural surface. The x-ray apperance may indicate localized abnormalities; more typically in the severe case bilateral diffuse nodular densities appear. These nodules may increase in size and coalesce. Recurrent pulmonary infarction and bacterial bronchopneumonia may complicate primary varicella pneumonia (46). Residual lung function abnormalities may result after varicella pneumonia. Occasionally, miliary diffuse calcifications may occur as a sequel (113).

During 1969, 48 cases of varicella encephalitis including 12 deaths were reported to the Neurotropic Viral Diseases Unit of the Center for Disease Control. This represented 2.5% of the total of 1,917 cases of encephalitis reported to this unit during 1969 as a result of nationwide surveillance. The central nervous system manifestations of varicella can be subdivided into the following categories (Table 7) (67).

Cerebrospinal fluid findings in central nervous system involvement in varicella reveal from 0-260 cells/mm^3, predominantly mononuclear cells. The protein may be as high as 75 mg.%. The glucose usually is normal but rarely has been reported as low (67).

Maternal VZV infection near parturition may result in congenital or neonatal varicella (19). The disease in neonates may be mild, but occasionally death from overwhelming infection can result. If infection occurs during the first trimester, documented instances of congenital abnormalities have been reported (81).

TABLE 6

CLINICAL MANIFESTATIONS IN 10 CASES OF PRIMARY VARICELLA PNEUMONIA*

Age	Sex	Day of Onset of Cough	Cough	Dyspnea	Cyanosis	Hemoptysis	Rales	Pulmonary Consolidation on X-Ray Study	White Cell Count	Complications
26	F	2	+++	+++	+++	+++	++	+++	12,800	Pulmonary edema; death
27	M	5	+++	+++	+++	+++	+++	+++	10,700	Subcutaneous emphysema; pleural effusion
24	M	3	+++	+++	+++	++	++	+++	12,600	None
29	M	5	+++	+++	+	+	++	++	15,500	Hepatitis
38	M	2	++	++	0	0	+	++	9,600	None
34	F	2	++	++	0	0	+	++	7,800	None
56	M	2	+	+	0	0	+	+++	8,900	Pleural effusion
42	M	2	++	0	0	0	+	++	5,400	None
29	M	3	+	0	0	+	0	+	8,600	None
36	M	2	+	0	0	0	0	+	-	None

* +++ = severe; ++ = moderate; + = mild

TABLE 7

CLINICAL MANIFESTATIONS OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN VARICELLA

Category	Per Cent of Persons in Each Category	Case-Fatality Ratio (%)	Significant Sequelae (%)
Predominant cerebellar involvement	51	0	0
Diffuse cerebral involvement including Reye's syndrome	40	35*	9
Aseptic meningitis	7	0	0
Transverse myelitis	2	0	0

* Case histories of 5 of the 8 deaths are given. On review, 3 of the 5 deaths for which there is adequate pathological information are compatible with Reye's syndrome.

HERPES ZOSTER

Uncomplicated zoster is characterized by pain and by clusters of vesicles in a dermatomal distribution. The pain may be intense and often antedates the appearance of the rash. The vesicles can coalesce and tend to be deeper than those in varicella so that residual scarring is not unusual. Crops of vesicles may continue to occur and isolations of VZV can be made for a longer period of time in zoster after the appearance of the rash than in varicella (Figure 7) (20).

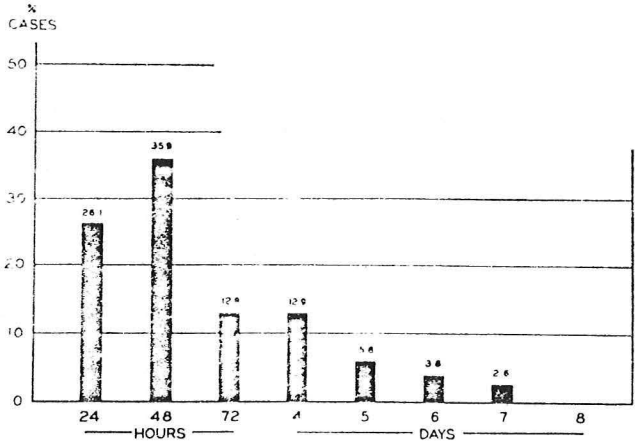

FIGURE 7. Periods of time and percentage of cases (156) in each period within which all vesicles appeared

The duration of symptoms is, in part, a function of age, but the majority of patients (163/183 or 89.1%) have healed their skin lesions and are free of pain within 5 weeks (Figure 8) (20).

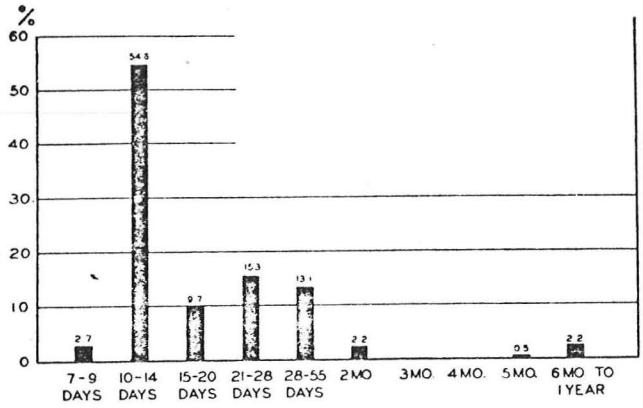

FIGURE 8. Duration in days and months from onset to clearing of all symptoms of herpes zoster and percentage (of 183 cases) in each duration period

The distribution of herpes zoster has been related to the localization of the rash in varicella and tends predominantly to involve the thoracic, lumbar, cervical dermatomes and the facial area innervated by the 5th cranial nerve. Post-herpetic neuralgia (pain after healing of vesicles) is poorly understood, but has been related to scarring in the ganglion and the afferent portion of the nerve. It is much more commonly seen in aged persons, may be prolonged but generally slowly resolves within 6 months (Figure 9) (20).

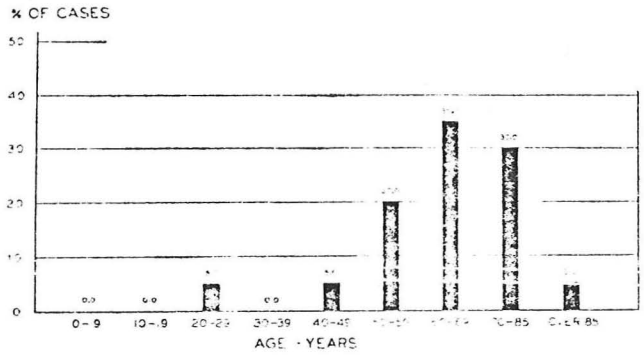

FIGURE 9. Distribution, percentagewise, in various age groups of 20 cases of postherpetic neuralgia

Pain may occur without a rash (zoster sine herpete) and be diagnostically puzzling. It is segmental in distribution and may be either "deep and boring" or "superficial, burning and accompanied with hyperesthesia" or both. A documented case of trigeminal neuralgia without a rash and with rising VZV antibody titers has been reported and indicates the type of clinical situation that may develop (36).

After zoster, the involved segment may be hypesthetic. Motor paralysis occurs in zoster but is uncommon and usually has a good prognosis. Its cause seems best related to involvement of the contiguous motor nerve nuclei, anterior horns or a mononeuritis in peripheral mixed motor and sensory nerves. Facial nerve paralysis is most common, but the oculomotor, glossopharyngeal and vagus nerves also can be affected. Paralytic disease of the extremities and unilateral diaphragmatic paralysis have been described in the course of zoster (2,13). Two cases of urinary retention during sacral zoster have been reported (94).

Specific zoster syndromes are recognized. With involvement of the ophthalmic division of the trigeminal nerve and particularly its nasociliary branch, the eye may become affected. Conjunctivitis, keratitis and iritis can ensue. The cornea may show discrete subepithelial white opacities (nasociliary nerve involvement). The cornea may also be hypesthetic and this predisposes to traumatic injury and secondary bacterial infection. Glaucoma can be seen as a late end result. Rarely external and internal ophthalmoplegia (oculomotor nerve) complicate ophthalmic zoster.

The so-called Ramsay Hunt syndrome refers to zoster involving the external ear and an associated ipsilateral facial paralysis. Taste on the anterior two-thirds of the tongue may be affected. These abnormalities were attributable by Hunt to geniculate (7th cranial nerve) ganglionitis. However, in one case of this syndrome studied at postmortem, the geniculate ganglion was found to be normal. In clinical practice, the actual areas affected on the ear have their innervation derived widely [2nd division of the trigeminal nerve (auriculo-temporal branch), tympanic branch of the glossopharyngeal nerve, auricular branch of the vagus, great auricular and lesser occipital branches of the cervical plexus] (106). Most cases of this syndrome are better related to multiple cranial and cervical nerve involvement including the vestibular and auditory branches of the 8th cranial nerve (106,109). On occasion, isolated 7th cranial nerve paralysis (Bell's palsy) may be linked to zoster but the quantitative contribution of VZV to the etiology of this syndrome is probably limited (76,110,136).

The incidence of zoster disseminating in normal persons is low. Of 206 persons with zoster seen in one series, 4/206 (2%) disseminated (20). These persons were mostly elderly but had no known underlying disease. In contrast, when underlying disease is present, the incidence of dissemination increases markedly. In Hodgkin's disease, dissemination has been found to occur in two series in 10/39, 25.7%, and 21/129, 16.3%, of persons who first developed localized zoster (132,48). The influence of steroid therapy probably increases the likelihood of dissemination, but there are only limited data on this point. In one series of 17 patients with disseminated zoster, 6 persons had no underlying disease process. Two of the 6 had received ACTH immediately before developing generalized zoster. When untreated, disseminated zoster may have a mortality approximating 25% (93). Dissemination also implies advanced underlying disease and even with recovery the long-term prognosis for these patients must be regarded as less good than their counterparts with localized zoster (48). Death in disseminated zoster usually results from complicating bacterial superinfection or VZV pneumonia.

Encephalitis in the course of herpes zoster is an infrequent complication. It may occur with or without other evidence of dissemination. The clinical picture consists of fever, disturbed sensorium, signs of meningeal irritation, convulsions and a variable incidence of ataxia (5,103). The prognosis generally is good but sequelae may be present. The cerebrospinal fluid findings in 14 cases of

zoster encephalitis have been detailed (Table 8) (5).

TABLE 8

SPINAL FLUID FINDINGS IN FOURTEEN CASES OF ZOSTER ENCEPHALITIS

Case No.	Cell Count	Protein (mg/100 cc)	Sugar (mg/100 cc)	Chlorides (mg/100 cc)	Colloidal Gold
1	16	80	65	-	-
2	165	58	64	-	1222211000
3	500	110	84	-	-
4	35	35	50	-	-
5	446	129	53	679	3222210000
6	15	35	50	-	-
7	390	140	61	692	0001110000
8	35	35	55	-	-
9	15	48	67	693	-
10	40	76	75	702	3322100000
11	0	84	-	-	-
12	75	40	56	-	-
13	222	140	61	-	-
14	0	21	102	625	-

DIAGNOSIS

Laboratory confirmation of VZV infections is not generally needed, since the clinical picture is usually diagnostic. Two types of tests are available if specific etiologic diagnosis is desired. The first involves demonstration of the virus or its effects on cells and the second necessitates obtaining a rising titer of complement fixing antibody in serially spaced serum specimens. VZV or its effects on cells can be demonstrated by the following methods: 1) Direct viral culture, 2) gel diffusion studies with vesicular fluid and known specific antibody, 3) electron microscopy of vesicular fluid, and 4) more practically, a Wright's or Giemsa stain of an imprint made from the base of a skin lesion. With the last method, if multinucleated giant cells and characteristic intranuclear inclusions are seen, diagnosis of infection with a herpesvirus can be made. This procedure, however, does not separate VZV from herpes simplex virus types 1 and 2, which can also cause skin lesions which are similar in appearance (11).

It is of interest that herpes simplex virus type 2 was recently isolated from a case that was clinically diagnosed as neonatal herpes zoster. This illustrates that under certain circumstances VZV and herpes simplex virus may produce clinical manifestations which are indistinguishable (99).

The clinical differentiation of varicella from smallpox, particularly when this latter disease is modified by vaccination, may be extremely difficult. If such a situation should arise, consultative services from the Center for Disease Control, Atlanta, Georgia, are available. With this assistance, appropriate specimens for laboratory diagnosis may be obtained and expeditiously processed.

THERAPY

In tissue culture three drugs have been demonstrated to have an inhibitory action on VZV and yet have an acceptable therapeutic ratio in man. These three drugs are 5-iodo-2'-deoxyuridine (IDUR), cytosine arabinoside (Ara-C), and adenine arabinoside (Ara-A). Although topical solutions of IDUR in dimethylsulfoxide have been shown in double-blind studies to influence favorably the course of localized zoster, dimethylsulfoxide is not available for use in the United States and hence this therapeutic modality will not be considered (70).

Enthusiasm for the use of Ara-C in the treatment of severe VZV infections stems from the report in which 6/8 children, all compromised hosts, with progressive viral disease appeared to respond to Ara-C therapy (153). Five of the children had pulmonary involvement and the two deaths were in these individuals. Since that time, there has been further experience with Ara-C in the treatment of these infections but no controlled studies evaluating its efficiency. Recent reports have questioned the value of Ara-C, however, and have called attention to the inherent toxicity of the drug. These reports point out that with conventional dosage regimens (100 mg/M^2/day by constant intravenous infusion x 4-5 days), marrow toxicity is common, with thrombocytopenia and leucopenia (Figure 10) (135).

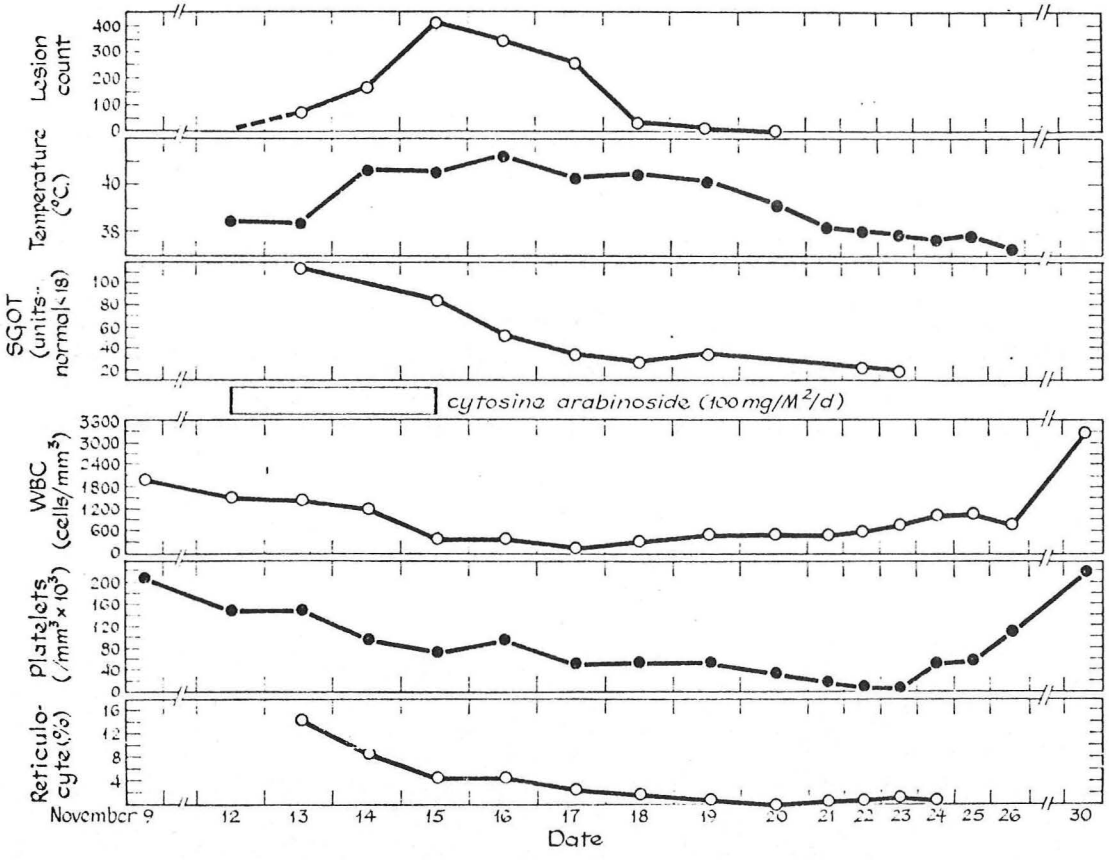

FIGURE 10. Clinical and laboratory parameters of leukemic patient with varicella, treated with cytosine arabinoside

In view of the lack of controlled studies with conventional dosage regimens, studies reporting success with low dose Ara-C (30-40 mg/kg/day) are of interest but must be subjected to rigorous critical evaluation.

A promising new drug, Ara-A, is presently undergoing evaluation. Ara-A is deaminated in the body to hypoxanthine arabinoside (Ara-Hx), a compound that also has antiviral properties which are, however, on a weight basis, less than Ara-A. Ara-A seems especially promising, because of its apparent lack of hematological toxicity at dosages which achieve concentrations which are inhibitory to VZV in tissue culture. At 10 mg/kg/day as a 6-hour infusion x 5 days, marrow toxicity is rarely encountered. The drug does produce nausea and vomiting during the initial days of infusion in about 10-20% of patients. The compound also is sparingly soluble so that the IV fluid used as a vehicle must be warmed. Initial clinical studies in the therapy of VZV infections have been encouraging and double-blind studies are now in progress.

Although Ara-A or another similar compound may eventually prove to be the optimal therapy in VZV infections, it is not presently available for clinical use. At present, Ara-C should be used in progressive VZV disease where there is a reasonable chance of mortality or a significant residual complication, e.g., ophthalmic zoster, Ramsay Hunt syndrome. Its rational use in localized zoster awaits double-blind confirmation.

Corticosteroids have been used in the therapy of VZV pneumonia and encephalitis due to this virus. It is unproven that their use is beneficial. A recent study has evaluated short-term steroid therapy in the treatment of localized zoster. The study was double-blind and appeared well controlled. The patients received triamcinolone 48 mg/day for 7 days, 24 mg/day for the following 7 days, and 16 mg/day for the last 7 days. No patients with "hypertension, tuberculosis, lymphomas, leukemia, bleeding ulcers, diabetes, cardiac disease, or bacterial infections" were included in the study group. The results indicated no difference in the healing of the lesions between control and steroid treated patients, but did show that the duration of post-herpetic neuralgia was shortened by treatment with the corticosteroid (Figure 11) (35).

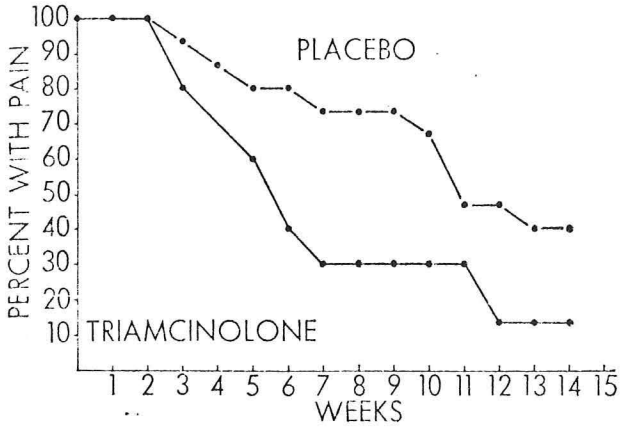

FIGURE 11. In patients more than 60 years old, pain does resolve spontaneously but resolves more rapidly with corticosteroid therapy. Treatment did not affect pain until after two weeks.

Although none of the 15 steroid treated patients developed dissemination, this study does not exclude the possibility that such an event could happen. The sample size in the steroid treated group (15 patients) is insufficient to exclude a possible enhancement of dissemination of zoster that might be significant, e.g., 1% → 5%. This possibility should be kept in mind when contemplating steroid therapy in elderly patients in an attempt to prevent post-herpetic neuralgia. Under no circumstances should systemic steroids be administered to hosts with compromised defenses. Steroid cream should also never be utilized.

In patients on immunosuppressive drugs who develop VZV infections, an attempt should be made to decrease the dose of these agents. Care should be taken in tapering the steroid dose to avoid precipitating adrenal insufficiency.

The therapy of established post-herpetic neuralgia is by and large unsuccessful. Narcotics may be needed. In severe intractable cases injection of the dorsal nerve root with alcohol may be tried but still is only rarely of value.

PREVENTION

Zoster immune globulin (ZIG) when given within 72 hours of exposure has been found to prevent clinical varicella in susceptible contacts (18). It probably prevents infection as assessed by the lack of the development of specific antibody. The ZIG dose is weight related (Table 9), and can be obtained from regional consultants to the Center for Disease Control (MMWR). Since ZIG is in short supply, patients convalescing from zoster and in otherwise good health can donate blood through the American Red Cross for eventual processing to ZIG. This preparation is especially pertinent in the prevention of varicella in compromised hosts. Reliable evidence that ZIG modifies established disease has not been presented.

TABLE 9

ZOSTER IMMUNE GLOBULIN DOSAGE SCHEDULE, BY WEIGHT OF RECIPIENT

Body Weight		ZIG Dose	
Pounds	Kilograms	Milliliters	Vials
0.0-14	0.0- 6.2	1.25	1
14.1-28	6.3-12.5	2.50	2
28.1-41	12.6-18.7	3.75	3
Over 41	Over 18.7	5.00	4

No vaccine is available. The prospects for making an attenuated live vaccine appear limited because of the capacity of this class of viruses to enter a latent state and become reactivated at a later time.

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