Zoster, a recrudescence of VZ virus infection

HARVEY BLANK
M.D.

WILLIAM H. EAGLSTEIN
M.D.

GARY L. GOLDFADEN
M.D.

*Department of Dermatology,
University of Miami School of Medicine, Miami, Florida*

Pathogenesis

Varicella and zoster are different clinical manifestations caused by the same (VZ) virus. Infection of a previously uninfected person produces varicella or in some cases an inapparent infection. Zoster is believed to result from the activation of VZ virus which has been present, but inactive, in the patient's dorsal root ganglion cells and/or his skin cells. Most are 'immune' to a second exogenous VZ virus infection but during recovery from varicella the VZ virus presumably assumes a latent state within the patient's cells. Opinion varies on the route by which the infectious virus reaches the ganglion cells. Zoster tends to involve skin served by one or two adjacent ganglia, suggesting that the virus does not reach the ganglion via the blood stream for if it did it would be expected to infect all ganglia. Nonetheless haematogenous spread has not been ruled out. Evidence of cerebrospinal fluid passage along spinal nerves in pigs and sheep has provided support for the theory that VZ virus could reach the ganglion cells by centripetal passage along a nerve from a skin lesion of varicella (Steer & Horne, 1968).

Virus has not been isolated during the hypothesized latent state assumed by the VZ virus in the ganglion cells of man. However, the prophage state of lambda bacteriophage in *Escherichia coli* offers biologic precedent for the latency concept (Lwoff, 1961). Lambda can enter a latent or prophage state in the bacteria during which the bacteriophage genetic material associates and multiplies in synchrony with the bacterial nucleoprotein. Certain stimuli will cause rapid multiplication of the phage and consequent destruction of the host cell. In the human, herpes simplex is also considered an example of viral latency but like zoster has not been proved.

Varicella-zoster virus

The association between varicella and zoster was first noted by von Bokay in 1909 (Blank & Rake, 1955). By 1925, Kundratiz (quoted by Blank & Rake, 1955) had demonstrated that children inoculated with zoster vesicle fluid would develop and transmit varicella; children with a history of varicella did not develop disease. Electron microscopic and immunologic investigations have confirmed the impression that varicella and zoster are caused by the same virus and have substantially increased our knowledge of the VZ virus. The zoster virus was first seen with the electron microscope in 1948 by Rake and his collaborators. It was found to be morphologically indistinguishable from the varicella virus. More sophisticated electron micrographs of negatively stained specimens have shown the VZ virus to consist of a central capsid covered by hollow identically sized capsomeres (Almeida, Howatson & Williams, 1962) (Fig. 1).

Antibodies and immunity

Using fluorescent antibody techniques, Weller & Coons (1954) first provided serologic proof that the agents of zoster and varicella had been successfully isolated and propagated. Complement-fixation tests showed the agents causing varicella and zoster to be indistinguishable (Taylor-Robinson & Downie, 1959). Further evidence that the same agent is responsible for varicella and zoster is the observation that patients with zoster produce only IgG complement-fixing antibody, a molecular class of antibodies usually produced as a secondary or booster response. In contrast, patients with varicella produce IgM complement-fixing antibody which is then succeeded by IgG (Gold, 1966) (Gold & Godek, 1965). Convalescent sera from zoster patients have

FIG. 1. Electron micrographs of virus (kindly prepared by Mrs Carol Collins). The bar is 100 nanometers. (a) Phosphotungstate stained vesicle fluid containing zoster virus typical of herpesvirus group. (b) PTA stained vaccinia virus showing how easily these true pox viruses can be distinguished from VZ virus. (c) Thin section of biopsy of cutaneous vesicle of zoster showing fine internal structure of the virus.

a higher antibody titre than convalescent varicella serum, also suggesting a secondary antigenic stimulus (Gold, 1966) (Gold & Godek, 1965).

Because zoster is caused by activation of endogenous virus acquired during an earlier infection, the incidence of zoster in children is low. However, zoster does occur in children and has even been reported in an infant three-and-a-half months old whose mother suffered varicella during pregnancy. The incidence and severity of zoster increases with age (Burgoon, Burgoon & Baldrige, 1957). This has led to the suggestion that zoster develops when humoral immunity to the VZ virus has waned. Rifkind (1966) has shown that zoster can occur in patients with a high titre of complement-fixing antibody in their pre-zoster sera. A loss of complement-fixing antibody titre, however, does not result in apparent increased susceptibility to clinical disease (Gold 1966) (Gold & Godek, 1965). It is known that complement-fixing antibody titres to the viruses of mumps, measles and poliomyelitis fall more rapidly than neutralizing antibody titres. A similar situation could account for Gold's findings and investigations of neutralizing antibody should be done. Unfortunately, measurements of virus-neutralizing activity are technically difficult as free infections VZ virus needed for such determinations is not easily available from the usual tissue culture systems. The exact cellular and immune mechanisms by which antibody protects against varicella but not zoster remain to be elucidated.

Relationship to underlying disease

Humoral factors do appear to be important in preventing varicelliform dissemination of zoster. The increased incidence of dissemination in certain haematologic neoplasms seems related to the breakdown of host resistance in these patients. Dissemination of a localized zoster infection may indicate a serious underlying disease, and even be a prognostic sign of impending death (See Fig. 2). The ominous course of patients with Hodgkin's disease or leukemia who get disseminated zoster is well summarized

FIG. 2. Severe thoracic zoster with localized areas of gangrene and disseminated vesicles in a patient with Hodgkin's disease.

by Merselis, Kaye & Hook (1964). They demonstrated that once dissemination takes place, the chances are one in four that the patient will die during that episode. Sokal & Firal (1965) confirmed the grave significance of generalized spread of zoster compared with ordinary zoster. The hypogammaglobulinaemia in patients with chronic lymphatic leukaemia and the deficiency in antibody production in patients with multiple myeloma and Hodgkin's disease apparently predispose to disseminated zoster. In these patients immunosuppressive drugs such as adrenal corticosteroids, antimetabolites, and alkylating agents are alleged to have contributed to the dissemination of zoster. Immunosuppressive agents reduce or prevent the production of antibodies to unfamiliar antigens but have almost no effect on the antibody response to antigens to which the patient has already responded. As zoster is caused by activation of the VZ virus in a patient recovered from varicella, immunosuppressive agents would be expected to have little effect on the antibody response. Indeed, a study of patients with kidney transplants but with no haematologic neoplasm who received a combination of X-rays, azathioprine, actinomycin C or prednisone showed no depression or delay in VZ antibody response when they developed zoster (Rifkind, 1966). It is notable that in over 100 closely observed, otherwise healthy patients treated with systemic corticosteroids for early zoster no generalization occurred (Eaglstien, Katz & Brown, 1970; Elliott, 1964; Elliott, 1968; Breen & Talinledar, 1965). Nor were corticosteroids found hazardous in a large series of patients with Hodgkin's disease and zoster. The response is more likely to be attributable to the stage of the disease than to the treatment being given (Sokal & Firal, 1965).

Although the incidence of zoster in the general population is not accurately known, the disease occurs more commonly in patients with malignant diseases and the reticuloses (Williams *et al.*, 1959; Dayan *et al.*, 1964; McSweeney, 1953). The relationship between this increased incidence and the corticosteroids, antimetabolites, alkylating agents and X-rays often used to treat malignant diseases has been the subject of much speculation and lively controversy. Only X-irradiation has been clearly implicated in causing zoster. Instances of exogenous VZ virus causing zoster are rare but well documented especially in patients with diseases which are associated with impaired immunologic mechanisms. There is strong circumstantial evidence that neoplasms near a ganglion may cause zoster. However, the majority of patients with zoster are healthy and no precipitating factors are apparent.

Evidence for X-ray treatment causing zoster to become manifest comes from a number of clinical

observations. Ellis & Stoll's studies (1949) seemed to provide clinical proof of the relationship. In their study, over sixty patients developed zoster related to X-irradiation rather than malignant involvement of the posterior nerve root. A group of twelve women with breast carcinoma is included, all of whom were treated with radical mastectomy followed in 2-4 months by prophylactic deep X-ray therapy. All developed zoster in the irradiated area and none had signs or symptoms of malignancy when the eruption occurred. Because these patients did have a malignancy the study could not completely exclude the neoplasm as an important factor in the development of zoster. Pendergrass & Kirsh (1948) reported two comparable groups of women: one treated with surgery alone and the other with surgery plus X-ray therapy for carcinoma of the breast. The group that got the X-ray had a clearly higher incidence of zoster. Further clear cut evidence was provided by Rifkind (1966) who found a close temporal relationship between local X-irradiation at the site of a transplanted kidney and the development of zoster in the same location in five of six patients. These patients had no malignancy. It is ironic that X-ray therapy was formerly widely used to treat zoster, but definitive studies such as the one by Rhys-Lewis (1965) clearly showed it to be useless for this purpose.

Neuralgia

Pain is a regular accompaniment of zoster and when it precedes the skin eruption may present a temporary diagnostic dilemma. Pain which persists long after the skin lesions have healed is one of the most annoying of medical problems. The incidence of persistent neuralgia increases with age and 40% of people over 60 years old will suffer this complication (Burgoon *et al.*, 1957). The early neuralgia is presumably due to inflammation of ganglia and peripheral nerves. Some investigators believe subsequent nerve and ganglion fibrosis accounts for persistent neuralgia. However, light and electron microscopy have failed to demonstrate any correlation between the degree of fibrosis and persistence of neuralgia (Zacks, Elliott & Langfitt, 1964). Even such extreme measures as posterior rhizotomy and cordotomy (Crikelair & Minervini, 1960) have failed to relieve zoster neuralgia, raising doubts as to the location of the changes which cause the persistent pain.

The severe complications of zoster involve the central nervous system and may present as encephalitis, encephalomyelitis, encephalomyelitis, or myelitis (Appelbaum, Kreps & Sunshine, 1962). Although zoster of any area may be followed by such central nervous system involvement, it occurs most commonly with zoster of the trigeminal nerve and because it occurs 2-4 weeks after the skin eruption, an auto-immune mechanism has been suggested.

Death from zoster encephalomyelitis is rare but there are some necropsied cases (Rose, Brett & Burstn, 1964). These showed a preponderance of lesions near the involved ganglion with or without thrombosis of large vessels and suggested a direct spread of virus in the neuroaxis. Cerebrospinal fluid examinations show large numbers of leucocytes, elevated protein, and lowered glucose concentrations. Neither bacteria nor virus has been cultured.

Eye involvement

Ocular complications occur in 50% of cases involving the ophthalmic division of the trigeminal nerve. The process varies from superficial conjunctival erosions with mild conjunctivitis to keratitis, corneal scarring, panophthalmitis, and even loss of the eye. In most patients, however, even with corneal involvement, the process subsides with little if any residual reduction in vision. Vesicles on the side of the nose, served by the nasal branch of the nasociliary nerve, in early ophthalmic zoster may forewarn of ocular involvement because the nasociliary also gives origin to the long ciliary which innervates the iris, ciliary body and cornea. Ophthalmic zoster

FIG. 3. Palsy of right upper eyelid following ophthalmic zoster. It is controversial whether it is due to involvement of the III nerve or reflex guarding.

often causes extra-orbital muscle palsies (Fig. 3) and when the ciliary ganglion is involved a temporary or even permanent Argyll–Robertson pupillary response may be produced.

The Ramsey–Hunt syndrome results from geniculate ganglion involvement and zoster without skin lesions is considered by some as a cause of Bell's palsy. Hyperacusis presumably due to zoster-induced stapedius muscle paralysis has been reported (McSweeney, 1953).

Visceral involvement

Hemidiaphragmatic paralysis may occur when cervical zoster involves the phrenic nerve (Brostoff, 1966). Patients with zoster of the neck should have an X-ray examination of the chest to record the disorder. Recovery may take months. Pleural friction rubs are often present near an area of thoracic zoster. However, pneumonia caused by zoster is very rare. It does occur in patients with haematopoietic neoplasms and haematogenous varicelliform dissemination of zoster (Pek & Gikas, 1965). At necropsy such patients may have characteristic inclusion bodies in cells in their lungs. Pastinszky & Kenedi (1962) reported electrocardiographic changes in twenty-six young, healthy patients with thoracic zoster. Most of these changes reverted to normal after 5–14 days but chronically depressed Q-waves were reported. There were no cardiac symptoms associated with the pathologic electrocardiograms. Confirmation of these findings has not been published by others.

Urinary retention associated with zoster of the lumbar and sacral regions has been reported (Gernert, Bischoff & Bors, 1967) (Gibbon, 1926). Retention may last for 1 month and knowledge of this association may prevent unnecessary surgical procedures.

Laboratory diagnosis

Multinucleated epithelial giant cells are seen in Wright's stained smears of cells scraped from the base of vesicles caused by any of the herpes group of viruses, including VZ virus (Fig. 4). If electron microscopy is available the virus can be seen in phosphotungstate stained preparations of vesicle fluid. Both of these techniques take only a few minutes and provide laboratory confirmation of the diagnosis. Unfortunately they cannot distinguish between herpes simplex virus and VZ virus. For this, more specialized techniques of tissue culture isolation of virus and/or serologic studies of the patients' sera are necessary. Because of the fastidious nature of VZ virus in the laboratory, as compared with herpes simplex or vaccinia, studies of VZ virus usually are done only in specialized research laboratories.

FIG. 4. Multinucleate giant epithelial cells typical of herpes group virus infections. Prepared by scraping the lining of a vesicle of zoster and staining the cells spread on a slide with Wright's stain.

Treatment

Specific chemotherapy is not known at this time. The newly studied zoster immune globulin (Brunell *et al.*, 1969) prepared from patients convalescing from zoster may prove to be useful in patients with life-threatening disseminated zoster. Systemic corticosteroids appear to be useful in reducing persistent neuralgia for those over the age of 60 (Elliott, 1968; Eaglstein *et al.*, 1970). The drug should be given for 3 weeks, 12 tablets a day the first week, 6 tablets a day the second week, and 3 tablets a day for the third week. The tablets could be either prednisone, 5 mg, or triamcinolone, 4 mg.

Symptomatic treatment while the process runs its course is helpful. The most useful drugs are aspirin, 1.0 g every 4 hr, with codeine, 30 mg or 60 mg, added at night or other times when the pain is severe. Reassurance that the pain will abate in a few weeks is useful.

Healing of the skin lesions is not usually a problem and in our experience the less topical treatment the better. Vesicles can be left undisturbed. Unopened pustules usually result from the virus, not secondary bacterial infection, and are unaffected by antibacterial antibiotics. During the crusted stages an emollient or wet dressings followed by an emollient may be soothing but often are unnecessary.

If the eye is involved in ophthalmic zoster, an ophthalmologist should be consulted. Treatment usually includes a topical mydriatic and often topical corticosteroids (Scheie & Alper, 1955). In contrast with herpes simplex, zoster does not seem to be made worse by corticosteroids. Lubricating or emollient preparations are often helpful.

Acknowledgment

This study was supported in part by Public Health Service Grant No. CA 40436 from the National Cancer Institute, National Institutes of Health.

References

- ALMEIDA, J.D., HOWATSON, A.F. & WILLIAMS, M.G. (1962) Morphology of varicella. *Virology*, **16**, 354.
- APPELBAUM, E., KREPS, S.F. & SUNSHINE, A. (1962) Herpes zoster encephalitis. *American Journal of Medicine*, **32**, 25.
- BLANK, H. & RAKE, G. (1955) *Virus and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man*. Little Brown, Boston.
- BREEN, G.E. & TALINLEDAR, P.K. (1965) Corticosteroids in acute infections. *Lancet*, **i**, 158.
- BROSTOFF, J. (1966) Diaphragmatic paralysis after herpes zoster. *British Medical Journal*, **2**, 1571.
- BRUNELL, P.A., MILLER, L.H. & LOVEJOY, F. (1968) Zoster in children. *American Journal of Diseases of Children*, **115**, 432.
- BRUNELL, P.A., ROSS, A., MILLER, L.H. & KUO, B. (1969) Prevention of varicella by zoster immune globulin. *New England Journal of Medicine*, **280**, 1191.
- BURGOON, C.F., BURGOON, J.S. & BALDRIDGE, D.G. (1957) The natural history of herpes zoster. *Journal of the American Medical Association*, **164**, 265.
- CRICELAIR, G.F. & MINERVINI, F. (1960) Postherpetic pain. *Journal of Chronic Diseases*, **11**, 69.
- DAYAN, A.D., MORGAN, H.G., HOPE-STONE, H.F. and BOUCHER, B.J. (1964) Disseminated herpes zoster in the reticuloses. *American Journal of Roentgenology*, **92**, 116.
- EAGLSTEIN, W.H., KATZ, R. & BROWN, J.A. (1970) The effects of early corticosteroid therapy on the skin eruption and pain of herpes zoster. *Journal of the American Medical Association*, **211**, 1681.
- ELLIOTT, F.A. (1964) Treatment of herpes zoster with high doses of prednisone. *Lancet*, **ii**, 610.
- ELLIOTT, F.A. (1968) Shingles. *Lancet*, **ii**, 170.
- ELLIS, F. & STOLL, B.A. (1949) Herpes zoster after irradiation. *British Medical Journal*, **2**, 1323.
- GERNERT, J.E., BISCHOFF, A.J. & BORS, E. (1967) Herpes zoster as a cause of urinary retention. *Urology International*, **22**, 222.
- GIBBON, N. (1926) A case of herpes zoster of the bladder. *Journal of Urology*, **15**, 583.
- GOLD, E. (1966) Serologic and virus isolation studies of patients with varicella or herpes-zoster infection. *New England Journal of Medicine*, **274**, 181.
- GOLD, E. & GODEK, G. (1965) Complement fixation studies with V-Z antigen. *Journal of Immunology*, **95**, 692.
- HOPE-SIMPSON, R.E. (1965) The nature of herpes zoster: A long-term study and a new hypothesis. *Proceedings of the Royal Society of Medicine*, **58**, 9.
- LWOFF, A. (1961) The dynamics of viral functions. *Proceedings of the Royal Society of Biology*, **154**, 1.
- MC SWEENEY, A.J. (1953) A case of Bell's palsy followed by herpes zoster oticus. *New York State Journal of Medicine*, **53**, 1118.
- MERSELIS, J.G., KAYE, D. & HOOK, E.W. (1964) Disseminated herpes zoster. *Archives of Internal Medicine*, **113**, 679.

- PASTINSZKY, I. & KENEDI, I. (1962) Electrocardiographic changes associated with herpes zoster. *Acta Medica Hungarica*, **19**, 23.
- PEK, S. & GIKAS, P.W. (1965) Pneumonia due to herpes zoster: Report of a case and review of the literature. *Annals of Internal Medicine*, **62**, 350.
- PENDERGRASS, E.P. & KIRSH, D. (1948) The role of irradiation in the management of carcinoma of the breast. *Radiology*, **51**, 767.
- RAKE, G., BLANK, H., CORRIELL, L.L., NAGLER, F.P.O. & SCOTT, T.F. (1948) Relationship of varicella and herpes zoster: Electronmicroscope studies. *Journal of Bacteriology*, **56**, 293.
- RHYS-LEWIS, R.D.S. (1965) Radio therapy in herpes zoster. *Lancet*, **i**, 102.
- RIFKIND, D. (1966) The activation of varicella-zoster virus infections by immuno-suppressive therapy. *Journal of Laboratory and Clinical Medicine*, **68**, 463.
- ROSE, F.C., BRETT, E.M. & BURSTON, I. (1964) Zoster encephalomyelitis. *Archives of Neurology*, **11**, 155.
- SCHEIE, H.G. & ALPER, M.C. (1955) Treatment of herpes zoster ophthalmicus with cortisone or corticotropin. *American Medical Association, Archives of Ophthalmology*, **53**, 38.
- SOKAL, J.E. & FIRAL, D. (1965) Varicella-zoster infection in Hodgkin's disease. *American Journal of Medicine*, **39**, 452.
- STEER, J.F. & HORNE, D. (1968) Evidence for passage of CSF along spinal nerves. *Canadian Medical Association Journal*, **98**, 71.
- TAYLOR-ROBINSON, D. & DOWNIE, A.W. (1959) Chickenpox and herpes zoster. I. Complement-fixation studies. *British Journal of Experimental Pathology*, **40**, 398.
- WELLER, T.H. & COONS, A.H. (1954) Fluorescent antibody studies with agents of varicella and herpes zoster propagated *in vitro*. *Proceedings of the Society for Experimental Biology and Medicine*, **86**, 89.
- WILLIAMS, H.M., DIAMOND, H.D., CRANER, L.F. & PARSONS, H. (1959) *Neurological Complications of Leukemias*, p. 134. Charles C. Thomas, Springfield, Illinois.
- WRIGHT, E.T. & WINER, L.H. (1961) Herpes zoster and malignancy. *American Medical Association, Archives of Dermatology*, **84**, 242.
- ZACKS, S.I., ELLIOTT, F.A. & LANGFITT, T. (1964) Herpetic neuritis. *Neurology*, **14**, 744.