

Viral Infections of the Skin

Causative Agents

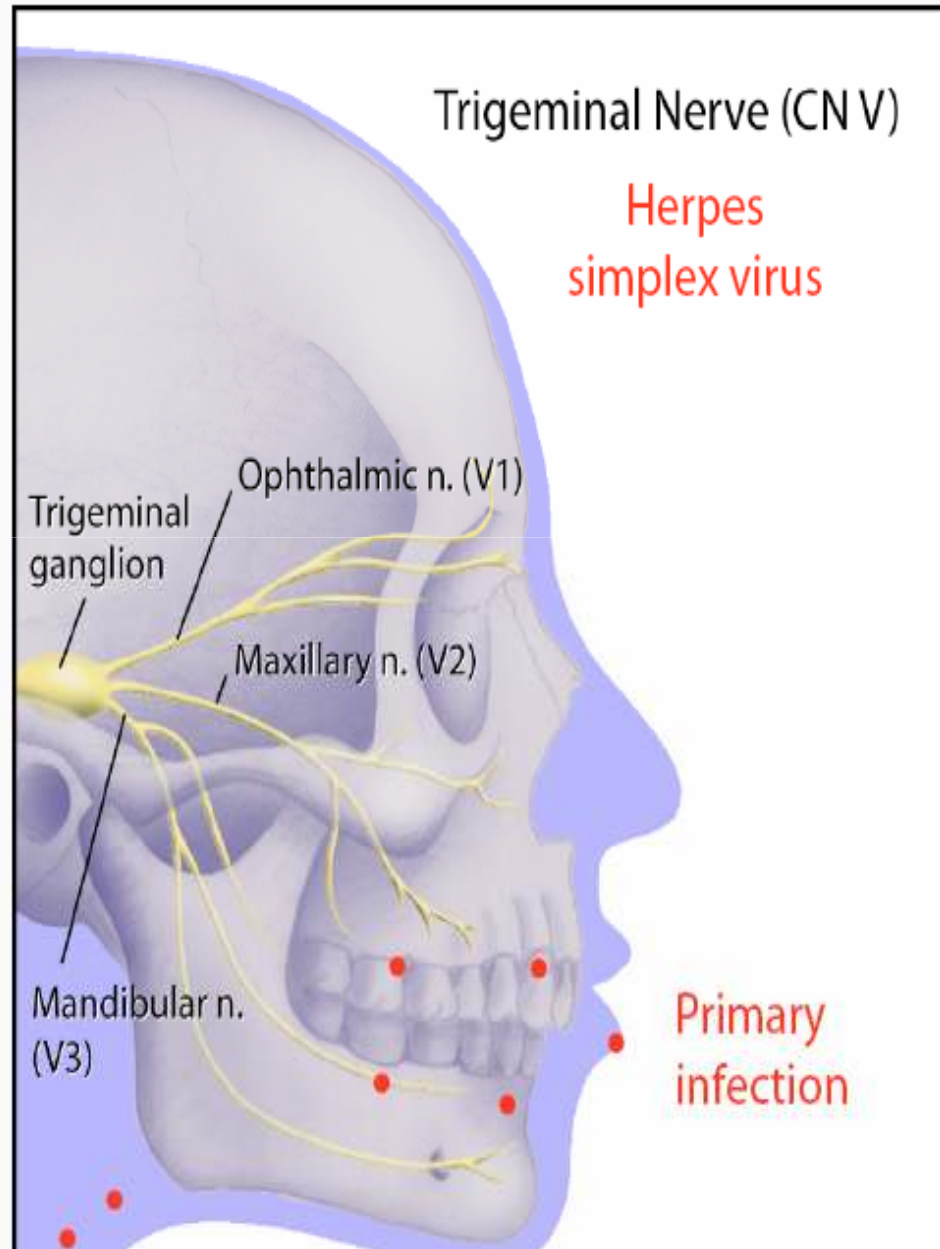
- Herpesviruses (HSV-1&2, VZV, and HHV-6)
- Poxviruses
- Papilloma viruses
- Parvovirus B19
- Measles virus
- Rubella virus

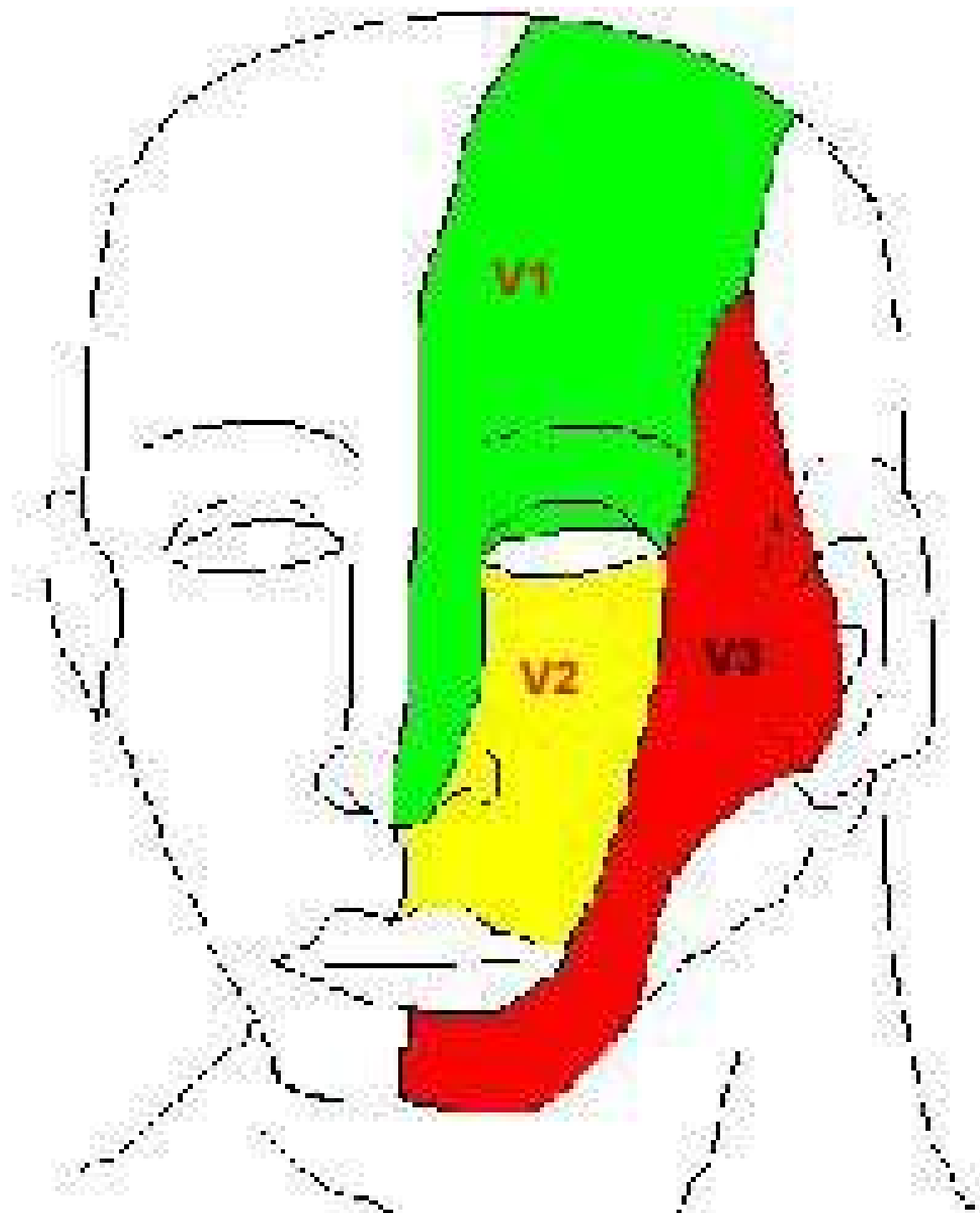
Herpes Simplex Viruses

Pathogenesis and Pathology

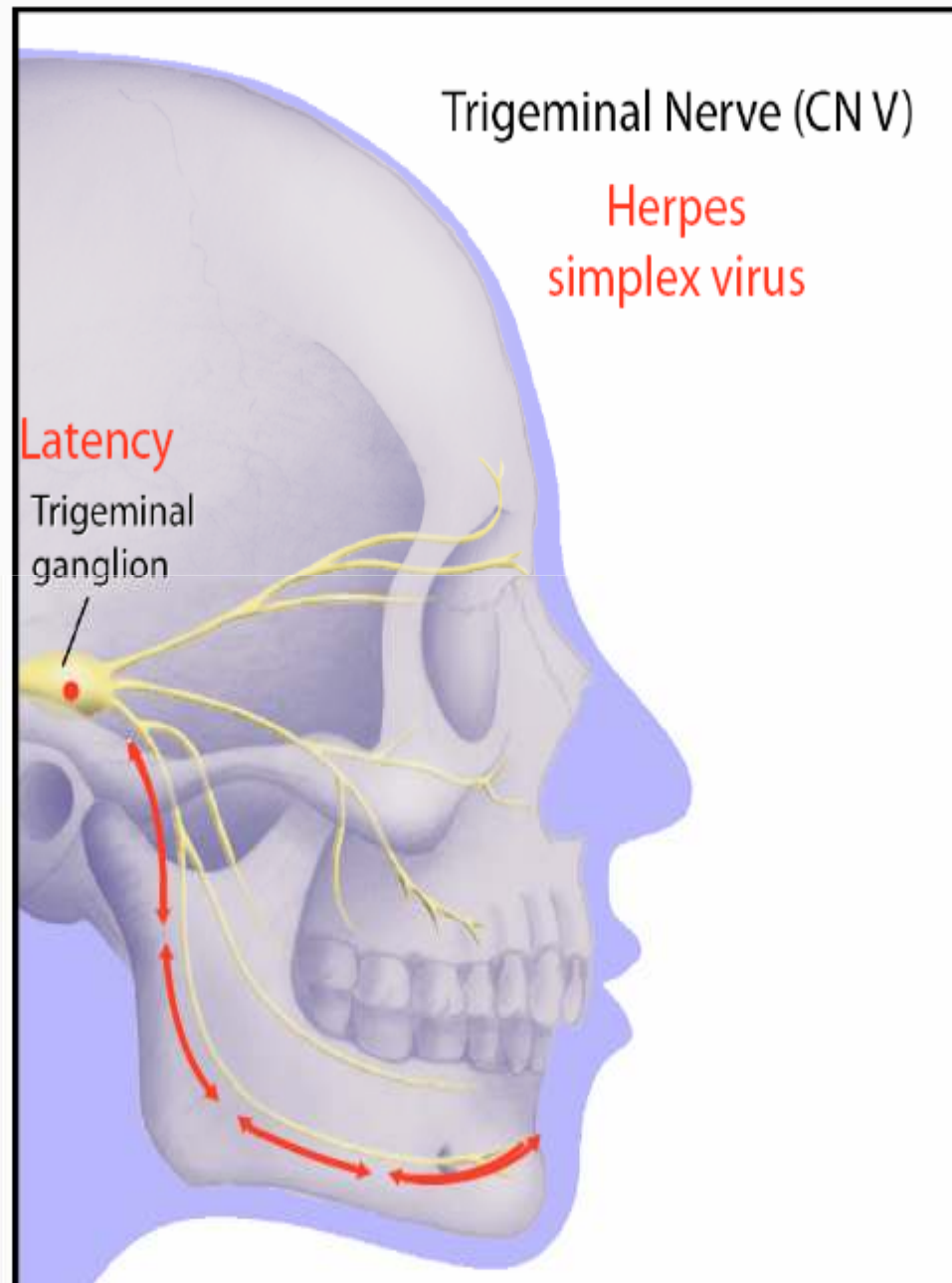
- Virus must come in contact with mucosal surfaces or abraded skin for infection to be initiated.
- Latency is established in sensory nerve ganglia.
- After latency is established, a proper stimulus will cause reactivation to occur.
- Widespread organ involvement is the consequence of viremia in a host incapable of limiting replication to mucosal surfaces

Herpes Simplex Virus

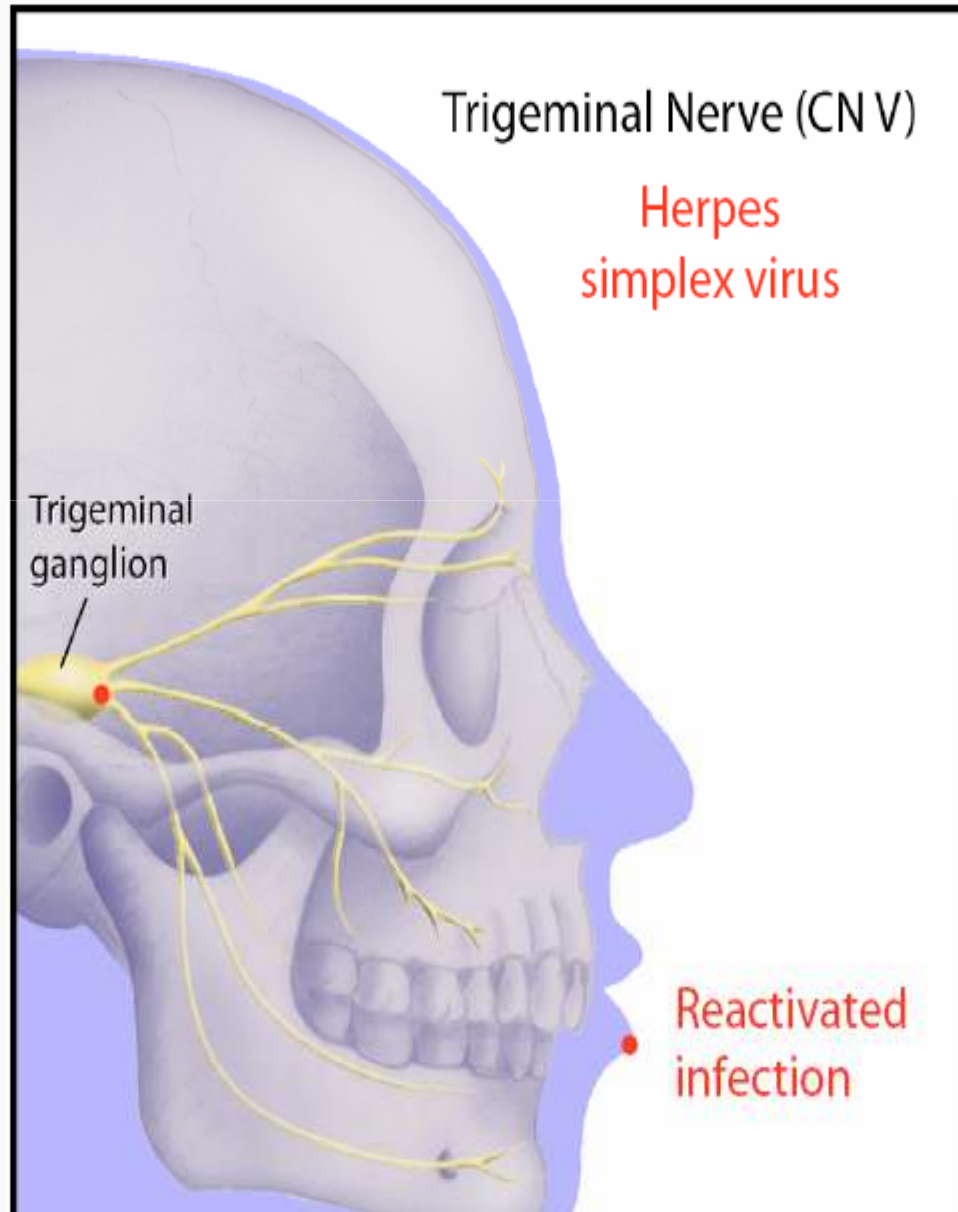




Herpes Simplex Virus



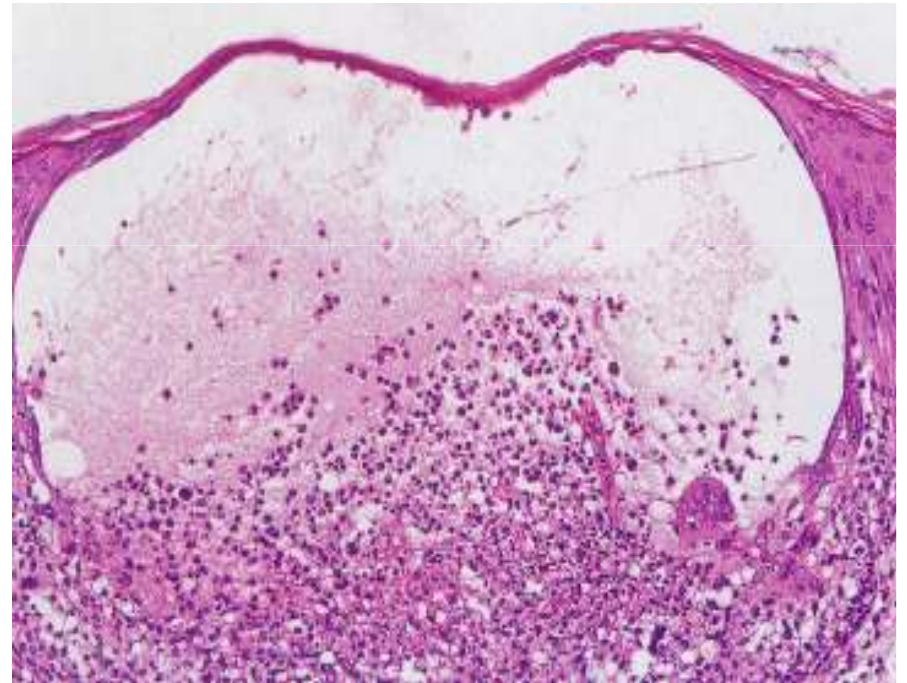
Herpes Simplex Virus



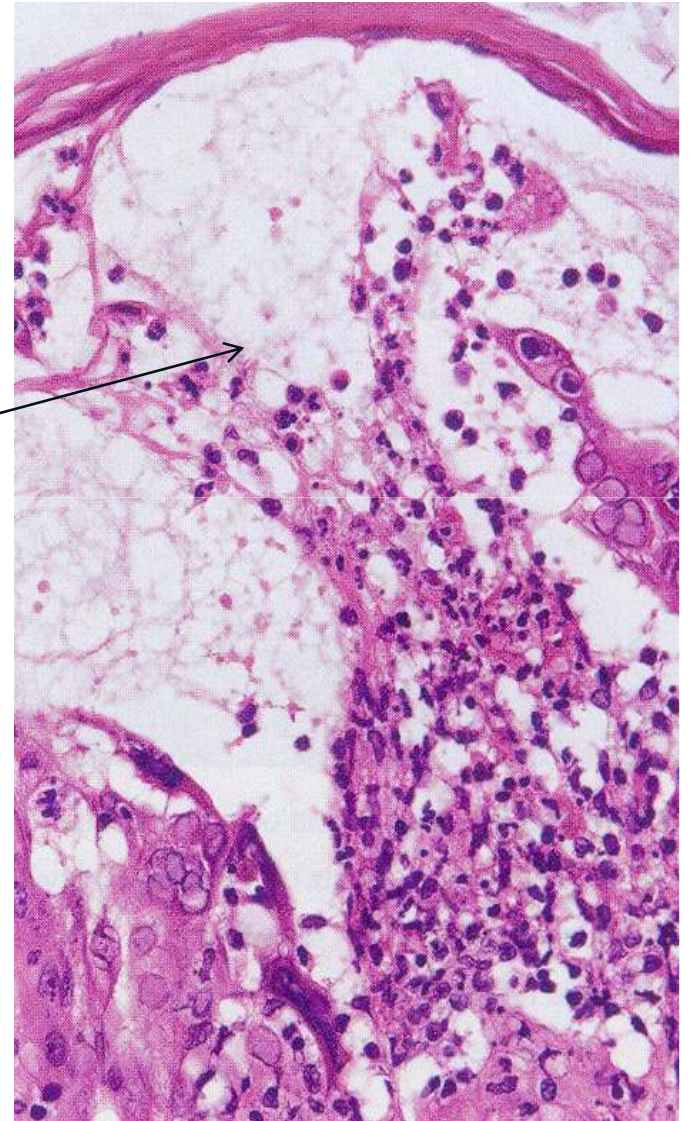
- Ballooning and the appearance of condensed chromatin within nuclei of infected cells.
- Degeneration of nuclei generally within parabasal and intermediate cells of the epithelium.
- Formation of multinucleated giant cells.
- Vesicles appear between the epidermis and dermal layer.

Histopathology

- Intraepidermal vesicle produced by profound degeneration (Ballooning) of epidermal cells → marked 2^{ry} acantholysis.
- Ballooning degeneration occurs mainly at the base of viral vesicles.



- Eosinophilic intranuclear bodies, surrounded by a clear halo, are usually seen in balloon cells.



- The vesicle has the appearance of a **dew drop on a rose petal**.
- An intense inflammatory response usually develops in the corium of the skin.
- Lesions on the mucous membranes are shallow (very thin cornified epithelium).
- Hemorrhagic necrosis is seen in other organs such as the brain.



Clinical Syndromes

- **Gingivostomatitis and cold sores**
- **Keratoconjunctivitis**
- **Eczema herpeticum**
- **Herpetic whitlow**
- **Herpetic Gladiatorum**
- **Erythema multiform**

Herpetic gingivostomatitis

- Affects gums, tongue, pharynx, palate and buccal m.m.







Herpes Facialis (Labialis):

- Lips, nose & cheeks.
- Recurrence at the same site usually.



- ❖ Regional LNs are not enlarged unless 2^{ry} infection of vesicles occurs.
- ❖ No fever & malaise.





Predisposing factors

- Minor trauma.
- UV.
- Immunodeficiency.
- Emotional stress.
- Menstruation.
- Infections (e.g. FLU).

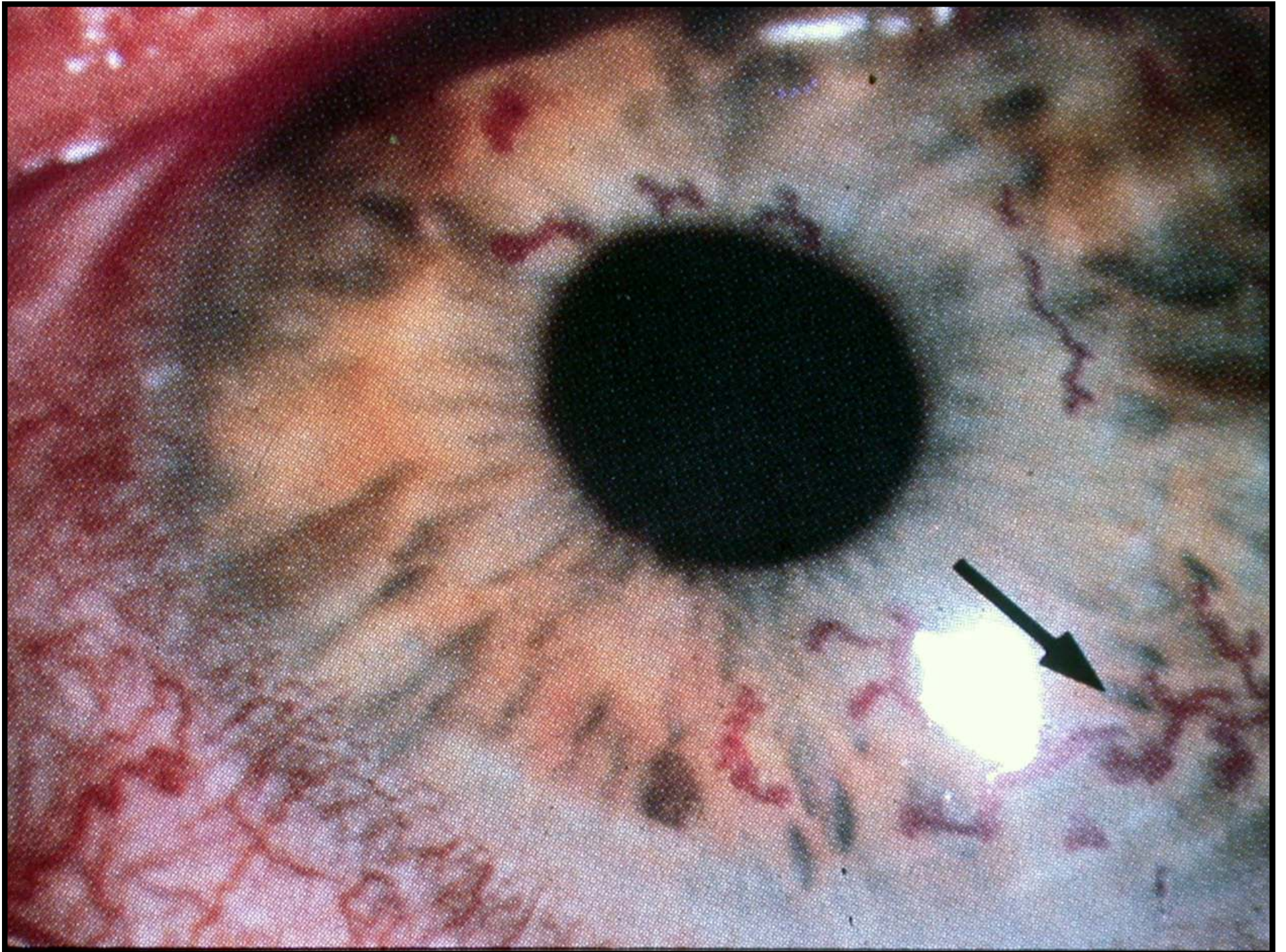
Keratoconjunctivitis

- Keratitis, conjunctivitis and edema of eyelids.
- Punctate or marginal keratitis.
- Dendritic corneal ulcer.

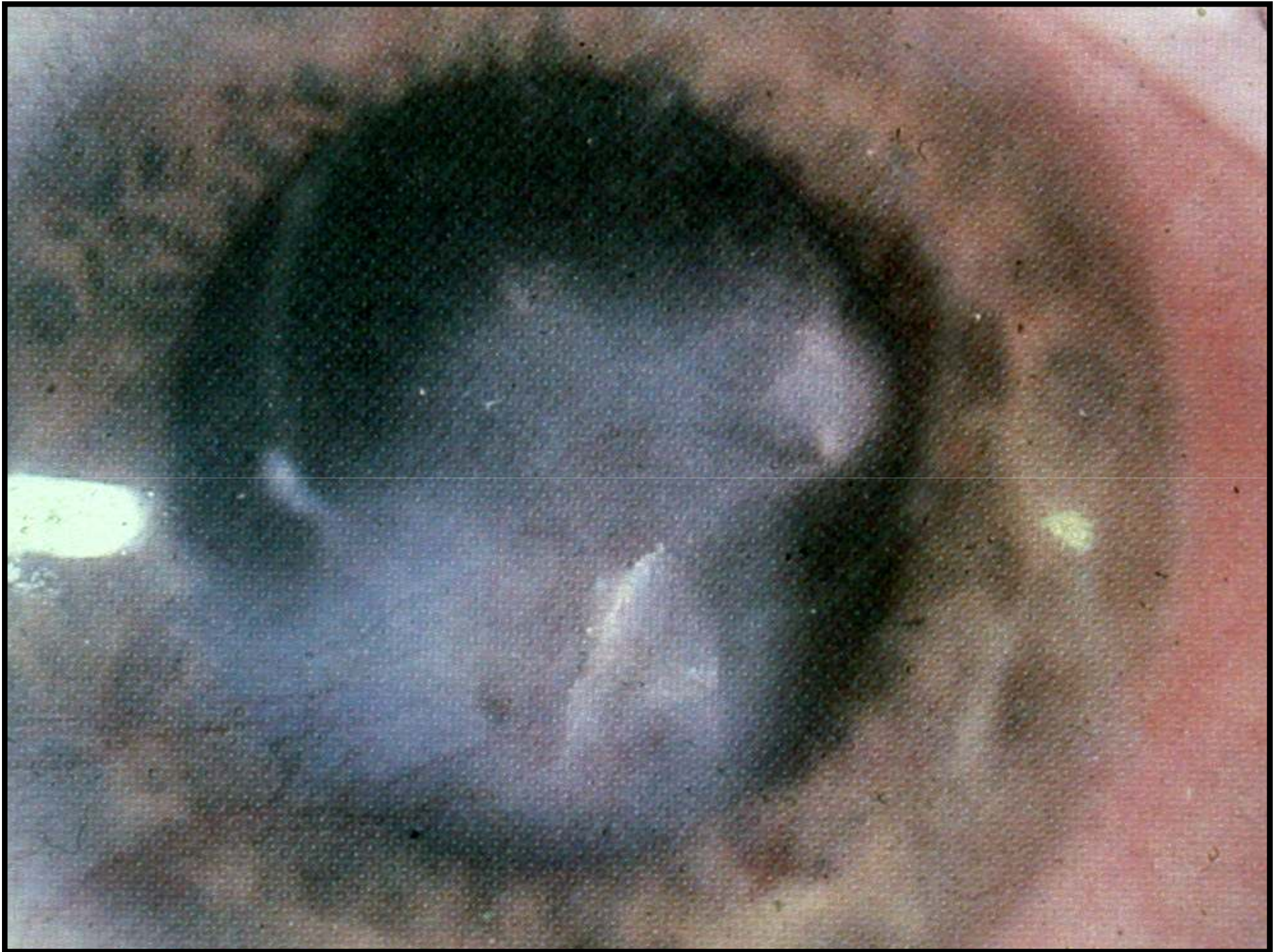












Eczema Herpeticum

(Kaposi's varicelliform eruption)

- Extensive eruption of vesicles & pustules that may be umbilicated occurring mainly on areas of pre-existing dermatosis with fever & prostration.
- The face is usually severely infected with marked edema.





Eczema herpeticum (ulcers are of similar shape and size)





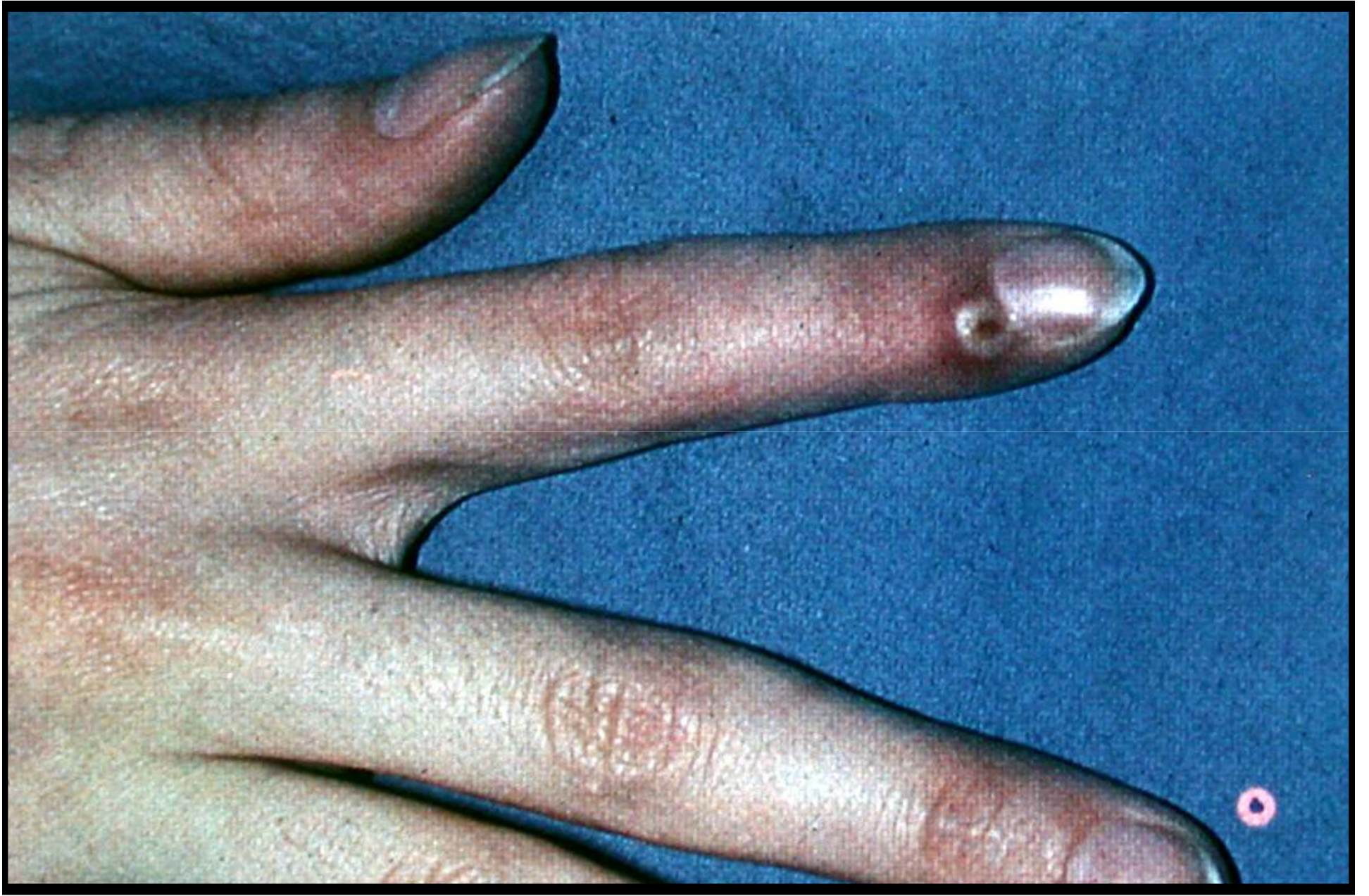


Inoculation H.S. (Herpetic whitlow)

- HSV infection of the digits in dental and medical personnel who do not routinely use gloves.











Varicella- Zoster Virus (VZV)

- Like HSV, VZV replicates in epithelial cells and establishes latency in sensory nerve ganglia.
- Primary varicella-zoster virus infection causes varicella (chicken pox).
- Reactivation of latent virus causes zoster (shingles), manifesting as vesicular rash with a dermatomal distribution and acute neuritis.

Entry and Spread

- VZV enters via the respiratory tract and replicates primarily in local lymph nodes.
- Primary viremia seeds the virus in the liver and other organs of the RES and secondary viremia disseminates the virus (skin, lungs, etc).
- Secondary viremia coincides with the last 4-5 days of the incubation period and first 24-48 hours of acute varicella.
- Cell-associated viremia continue after the initial skin lesions appear, but the infected PBMC are cleared within 24-72 hours after the appearance of the rash.

Cell and Tissue Tropism

- Cells of the epidermis are the major targets for VZV replication and first changes consist of vasculitis.
- Progressive “ballooning” degeneration of epithelial cells, coalescence of fluid-filled vacoules between cells, and increased numbers of infected cells at the base of the lesion are noted as the maculopapular lesions evolve into vesicles.
- Destruction of the germinal layer of the epithelium is observed in larger lesions.

- Early events occur with little or no exposure of the host immune system to viral antigens.
- Infiltration of the involved skin sites by inflammatory cells is minimal in the early vesicular phase.
- Cutaneous lesions that progress to ulceration are characterized by necrosis through the whole dermis.

Clinical Features- Varicella

- Incubation period of 10-21 days, exanthema begins on the scalp, face or trunk where crops of lesions appear progressively on the skin.
- Duration of varicella in otherwise healthy individuals ranges from 1 to 7 days.
- Hypopigmentation of the skin often persists for several weeks but scarring is unusual.
- A single shallow scar of the forehead is very common.

- In young children, prodromal symptoms of chickenpox are uncommon, but in older children and adults, the manifestation of the rash may be preceded by two or three days of fever and chills, malaise, headache, backache, sore throat, and dry cough.
- The rash begins on the face and scalp and spreads rapidly to the trunk, with relative sparing of the extremities.
- New lesions arise in crops, usually appearing centrally. Each crop proceeds through a developmental phase, so that at any given time, a patient can have macules, papules, vesicles, pustules, and crusts.

- The first sign of chickenpox is rose-colored macules that rapidly progress to papules then to vesicles, then to pustules, and finally to scabbing over with crusts.
- The typical wall of the vesicle is so thin that it often resembles a drop of water on the reddened surface of the skin (the "dew drop on a rose petal" appearance).
- As the lesion dries and changes from a vesicle to a pustule, it umbilicates and then crusts over. The crusts fall off in one to two weeks.
- Scarring is rare unless the lesions become secondarily infected. Vesicles can occur on the mucous membranes, most commonly on the palate; they can also occur in the nose, pharynx, larynx, trachea, gastrointestinal tract, conjunctiva, and vagina.



Varicella (Chickenpox)



Chickenpox vesicle behind the ear. Notice the translucent quality of the vesicle on the skin, the classic "dew drop on a rose petal"



Chickenpox on the palate. Notice the glistening, water-drop characteristic of the chickenpox vesicle on the palate.

Varicella (Chickenpox)



Chickenpox on the hand. Notice the simultaneous occurrence of lesions in different stages of development.

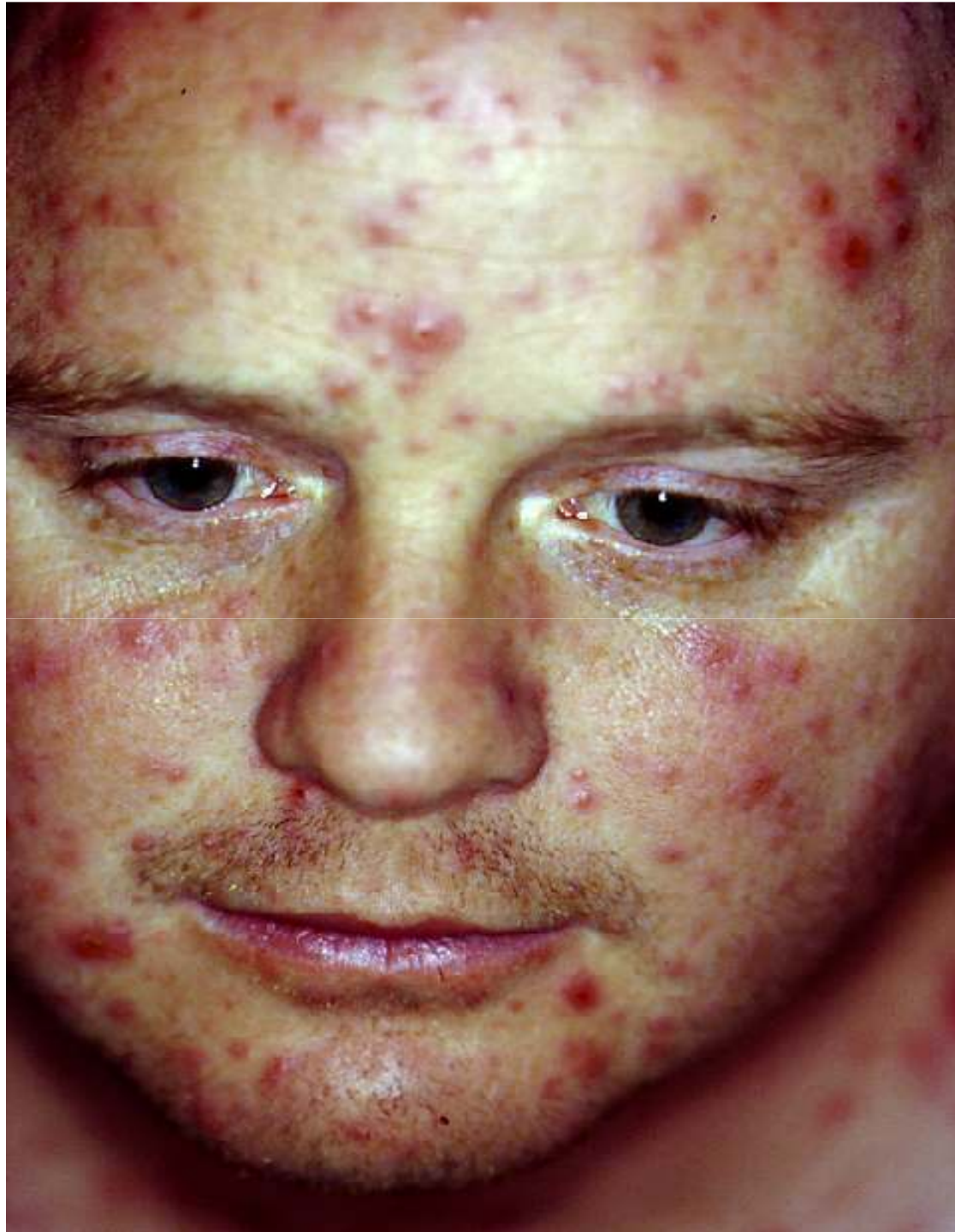


Chickenpox in an infant. Notice the rose-colored macules, papules, vesicles, pustules, necrotic pustules, and crusted lesions occurring simultaneously.











Herpes Zoster

- Vesicular lesions in the dermatomal distribution of one or more adjacent sensory nerves.
- Lesions are preceded or accompanied by pain, hyperesthesia, and pruritis.
- Thoracic (T5 –T 12) in > 50%, cranial nerves in 14 to 20 % and lumbosacral (L1-L2) in 16%.
- Zoster sine herpete is a form of the disease with no rash.

- Herpes zoster is characterized by unilateral radicular pain and a vesicular eruption that is typically limited to one or two dermatomes innervated by a spinal or cranial nerve.
- The most distinctive characteristics of herpes zoster are its localization and its distribution, which is almost always unilateral.
- The individual lesions of varicella (chickenpox) and of zoster are identical, but the lesions of zoster evolve more slowly and are characterized by grouped vesicles.
- The lesions of varicella, by contrast, are more widely distributed. As in varicella, zoster vesicles evolve into pustules, then dry and crust.







Groups of vesicles arranged along the distribution of a cranial or spinal nerve

Cutaneous and visceral dissemination from the original dermatome develops in some individuals, particularly immunocompromised patients

Associated with localized or referred pain







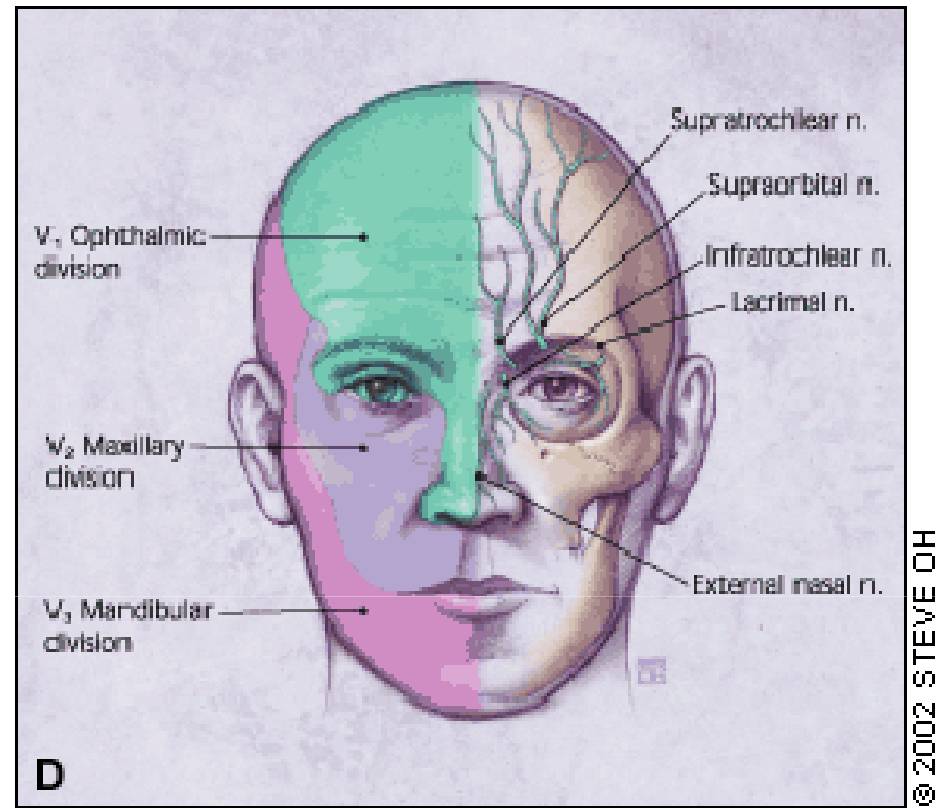
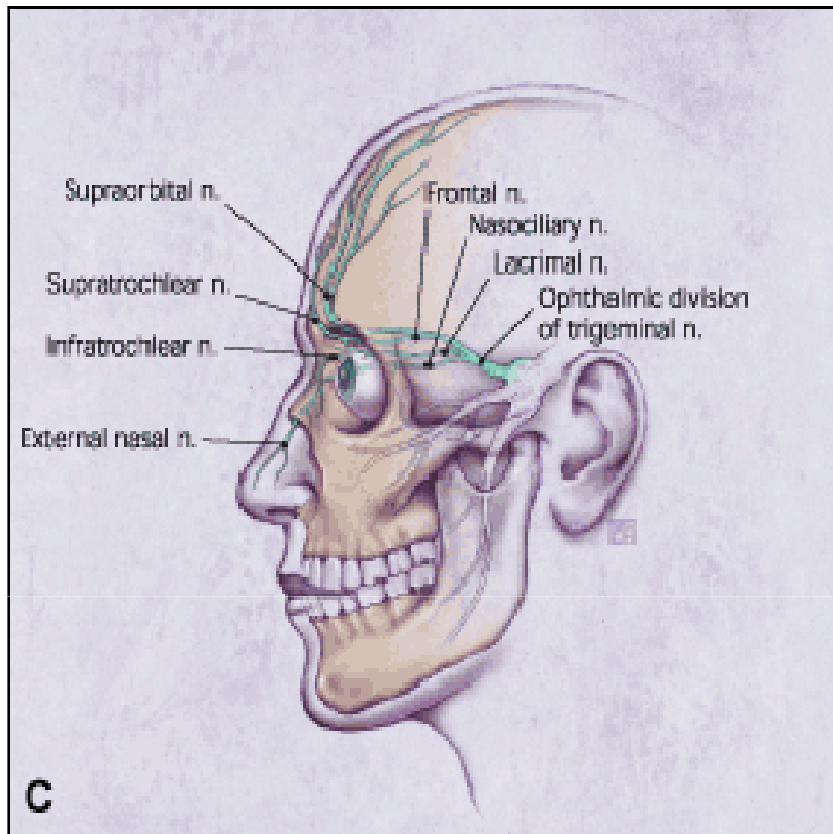












The hallmark of herpes zoster ophthalmicus is a vesicular rash that involves the first (ophthalmic) division of the fifth cranial nerve that presents in a dermatomal distribution and respects the midline. The upper eyelid is commonly involved with edema, inflammation, and resultant ptosis.

- *HZ ophthalmicus*: eruption on tip of nose, upper eyelid or forehead. Conjunctiva is red, swollen with superficial or deep keratitis.





Herpes Zoster

Linha média



FIG. 120
Herpes zoster three days
onset. Firm vesicles set
erythematous base. The le
confined to the right-hand
the face.



FIG. 121
Herpes zoster five days.
The lesions are becoming



FIG. 122
Herpes zoster ten days.
The lesions have become
slightly haemorrhagic. The
lid is now involved and the
of the cheek



FIG. 123
Herpes zoster fifteen days
onset. The crusts have been removed
and the raw surface of the under-
dermis is exposed.









HERPES ZOSTER



Poxviruses

- **Specific human poxviruses**
 - Variola and Molluscum contagiosum
- **Zootomic poxviruses**
 - Monkeypox virus
 - Cowpox virus
 - Bovine Papular Stomatitis virus
 - Vaccinia virus
 - Orf virus
 - Pseudocowpox virus
 - Tanapox virus
 - Yabapox virus

- **Monkey pox virus**

- Occurs naturally only in western and central Africa as a virus of wild life.

- Causes generalized exanthemata clinically very like smallpox.

- It is characterized by a febrile prodrome followed by vesicular or pustular rash typically centrifugal in distribution and it has a mortality of 10-20%.

- **Cowpox virus**

Humans may acquire it from cats, cows, and rodents.

- **Vaccinia virus**

was widely used to vaccinate humans against smallpox

- **Orf virus**

causes skin lesions in sheep and goats and it can be transmitted to humans.

❑ **Pseudocowpox virus**

Causes Milkers' nodules in humans infected from the teats of cows.

❑ **Tanapoxvirus** and **yabapoxvirus** Infect humans causing single or occasionally multiple skin lesions.

❑ Virus replication produces intracytoplasmic inclusion bodies (Guarnieri's in smallpox).





Smallpox

- Smallpox in England in the 18th century accounted for 7-12 % of all deaths and 1/3 of deaths among children.
- Smallpox was endemic in China by 1000 BC. In response, the practice of variolation was developed.
- **Edward Jenner** was nearly killed by variolation at the age of seven.
- On 14 May 1796, **Jenner** used cowpox infected material obtained from the hand of Sarah Nemes to successfully vaccinate 8-years-old James Phipps.

- Ali Maolin was the last person in the World to have a naturally occurring case of smallpox in Merca, southern Somalia on Oct 26, 1977.
- Two varieties of smallpox; variola major, the classic disease of early times, and variola minor (alastrim).
- Variola minor produced a much less severe toxemia and had a case fatality rate of 1% compared with 10-30 % for variola major.

Variola (Smallpox)



Progression and distribution Smallpox lesions









- **Complications of vaccination**

- Eczema vaccinatum
- Generalized vaccinia
- Inadvertent Inoculation
- Vaccinia keratitis
- Progressive vaccinia
- Post vaccinia encephalitis.

Molluscum Contagiosum

- A wart- like condition caused by a poxvirus infection of the prickle cell layer of the epidermis.
- The infected cells proliferate, vacuolate and enlarge protruding above the surface of the skin as typical pearly lesions.
- Lesions begin as small (3 to 6 mm) papules that are smooth, flesh-colored domes with a central dimple. Inside the papule is a white, curd-like core that can be easily expressed.
- They are always umbilicated with a small central cavity containing whitish, pulpy material.

- Lesions can occur anywhere on the skin and mucous membranes, but are usually grouped in one or two areas.
- Occasionally, they may be widely disseminated. Typically fewer than 20 lesions are present, but some individuals may have hundreds.
- The head, eyelids, trunk, and genitalia are most commonly affected, the genitalia being the predominant site in adults.
- The lesions are characteristically asymptomatic, but a few patients may complain of itching or may develop an eczematous reaction around the lesions.

- It is characterized by single or multiple skin colored or pearly-white, waxy, dome-shaped, small (1-5 mm) papules with umbilicated center which become more apparent after freezing with ethyl chloride.









Eradication Campaign

- Started in 1st January, 1967 and the goal was achieved in 10 Years, 9 months and 26 days.
- From a starting point of 10 to 15 million cases per year and against a background of civil strife, famine, and floods success came because of a major collaborative effort aided by virus specific factors.

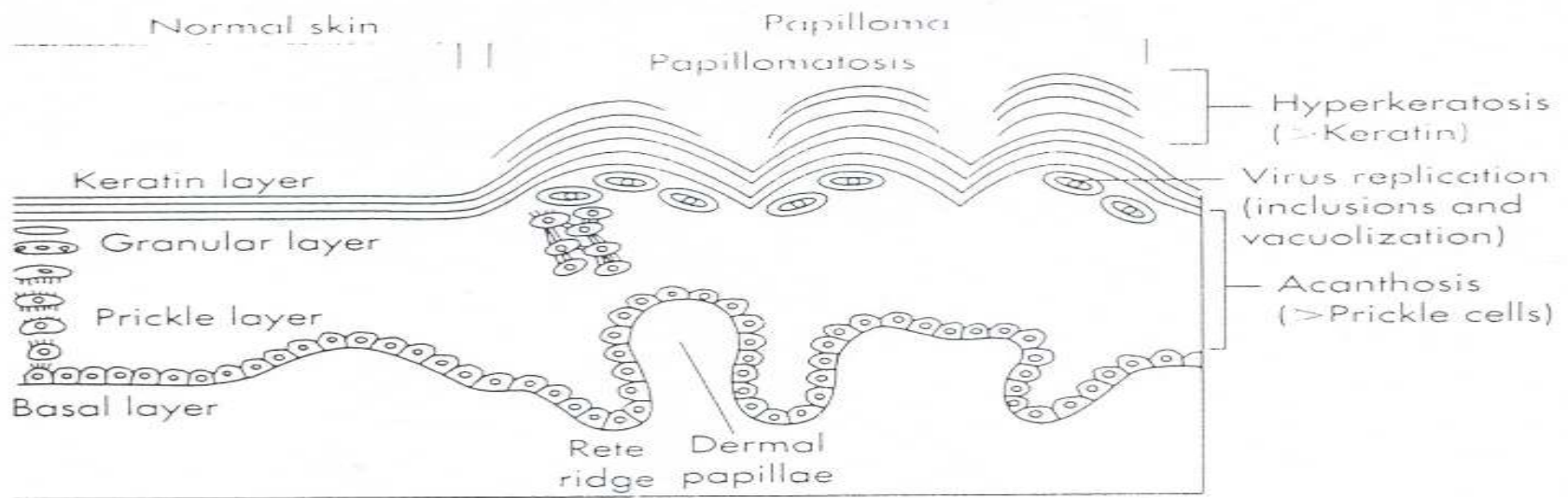
- **Virus Factors that Aided Eradication**
 - Cases were easy to detect.
 - Poor transmissibility and slow spread .
 - No subclinical cases.
 - No carrier state.
 - No transmission during incubation.
 - No animal reservoirs
 - Vaccine is technically simple to produce, simple to deliver, and stable for long shelf life.

Papilloma Viruses

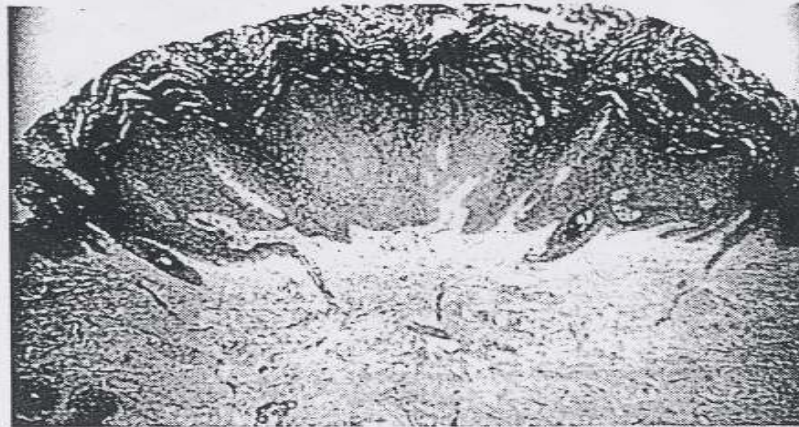
- The virus infects the skin and remains latent in the basal layer but replicates in the differentiating epithelial cells
- The specific nuclear factors expressed control transcription of viral genes and the replication of the genome.
- The replication of virus correlates with the expression of specific keratins.
- The virus must infect the basal cell in order to induce a lesion that can persist.

- Histologically, acanthosis and hyperkeratosis with some degree of papillomatosis.
- They have the same histology of benign lesions with hypertrophy of all the layers of the dermis and hyperkeratosis of the horny layer.
- In general, warts are benign self-limiting proliferative lesions that regress after a period of time.

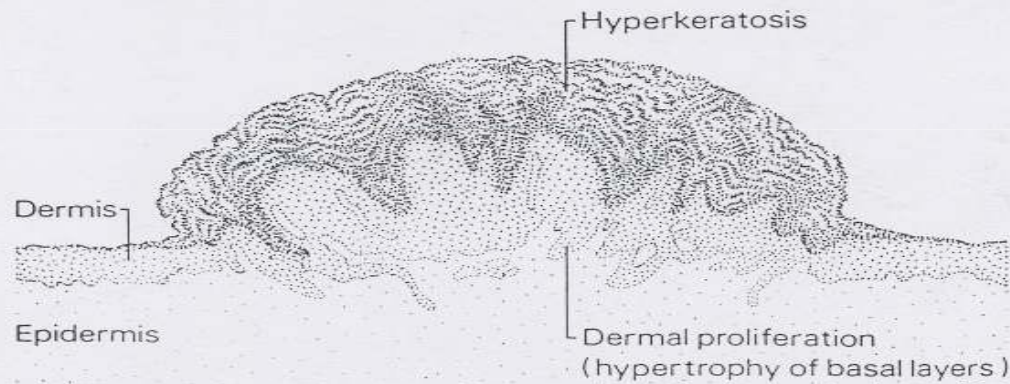
- A wart consists of localized epithelial hyperplasia with a defined boundary and an intact basement membrane.
- All layers of the differentiated epithelium are represented in the wart which results after the virus stimulates the proliferation of basal cells.
- HPV Types 1, 2, 3 and 4 commonly infect the keratinized epithelium of the hands and feet.



A



a



b

Fig. 45.4 Histology of a wart.

- Over 30 HPV types infect the mucosal epithelium in the anogenital tract and orolaryngeal cavity of which HPV types 6, 11, 16, 18, 31, 33 and 45 are the most common.
- HPV Types 2 and 57 can infect both skin and genital mucosa.
- HPV Types are categorized as low, intermediate or high risk according to the extent of their oncogenic potential.

Cutaneous warts

- **Common warts** (*verruca vulgaris*) HPV 2, 4, 7
- **Flat (plane) warts** (*verruca plana*) HPV 3, 10
- **Plantar warts** (*verruca plantaris*)
HPV 1, 4
- **Butchers warts** (common warts)
HPV 7

Common Warts (Verruca vulgaris)

- firm papules with verrucous hyperkeratotic surface occurring singly or in groups
- commonly on the dorsal aspects of fingers & hands. Periungual warts are common.



Common warts





Common wart on the hand











Plane warts

- slightly elevated, flat, smooth papules.
- Linear arrangement in scratch marks may be present “Koebner phenomenon”.



Planter Warts

- Affects sole of the foot esp. the pressure points.
- Sharply defined, rounded & slightly elevated lesions with keratotic surface.
- Pain is a common symptom.
- Mosaic wart: multiple warts coalescence into a large papule











Epidermodysplasia Verruciformis

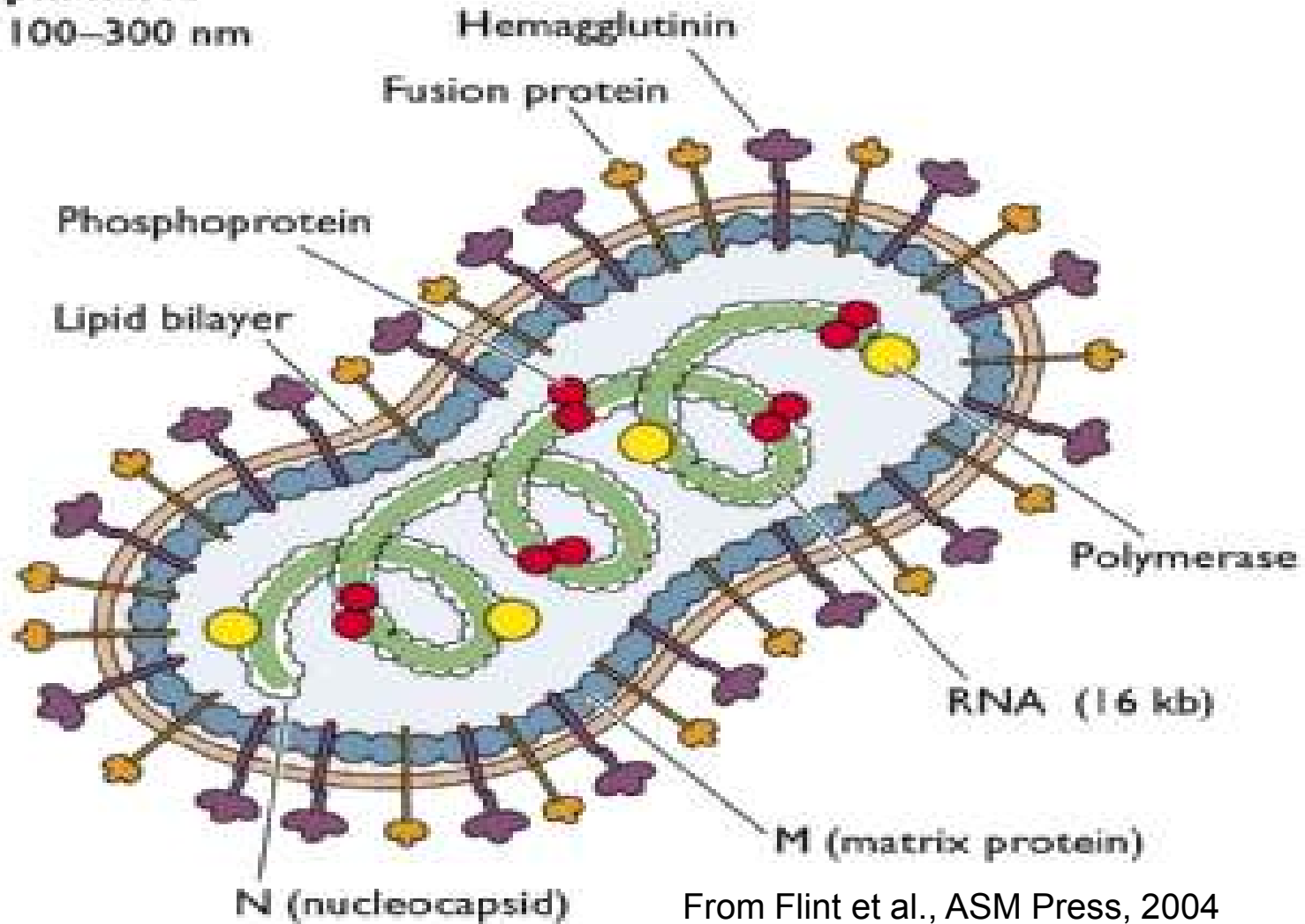
- A rare genetic skin disorder where there is a selective depletion of specific T cell clones (inability to resolve virus infection)
- some lesions may progress to malignancy.
- Begins in infancy or childhood.
- Numerous HPV types, but most commonly HPV 5, 8 and less so types 9, 12, 14, 15, 17 , 19-25.



Measles virus

A

Pleomorphic particles
100–300 nm



From Flint et al., ASM Press, 2004

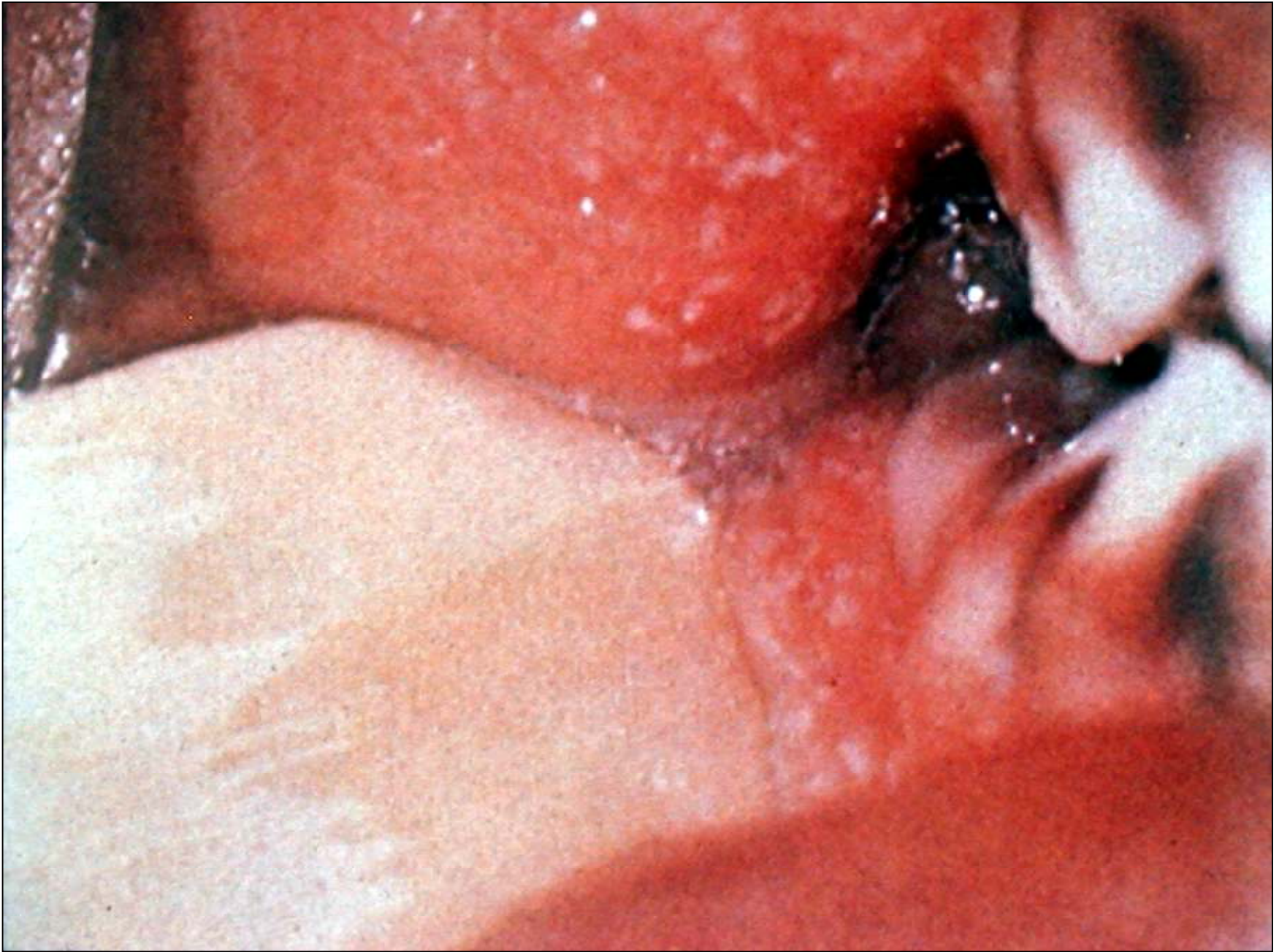
Measles Virus

- **Entry and spread**
 - Measles is typically a childhood infection of humans that spreads by the respiratory route.
 - Local replication (2-4 days) followed by extension to the local lymphatic tissue (Warthin-Finkeldey cells)
 - Viremia then disseminates the virus to a variety of organs.

- **Target Tissues and Cells**

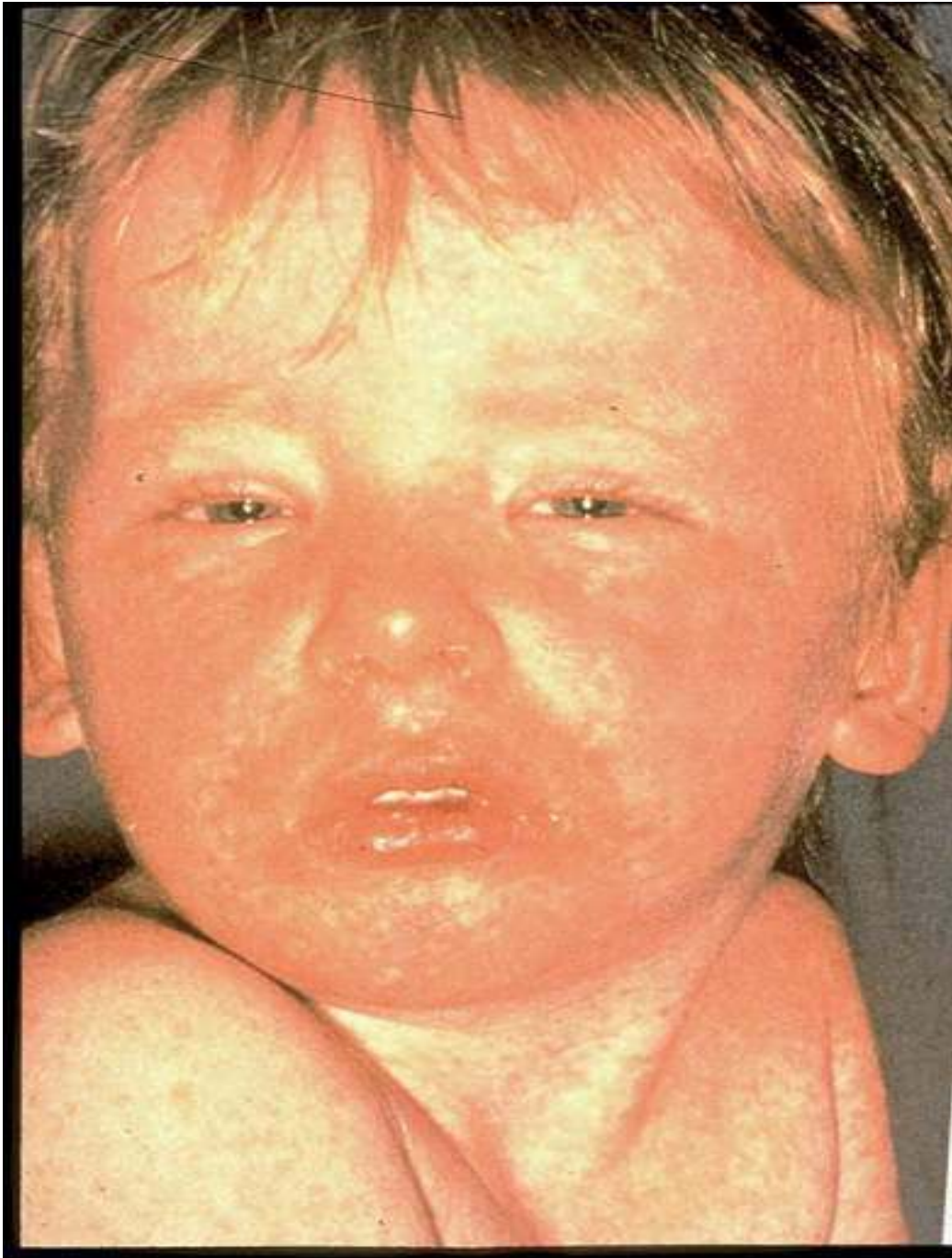
- Lymphoid tissues are the prominent sites.
- MV spreads to the skin, conjunctiva, kidney, lung, gastrointestinal tract, respiratory tract, genital tract, and liver.
- Primary replication in endothelial cells, epithelial cells, and monocytes/ macrophages.

- Vascular endothelial cells appear to play a central role in pathogenesis.
- Infection of dermal endothelial cells is followed by spread into the epithelial cells in the stratum granulosum leading to focal keratosis and edema.
- **Koplik's spots** are present on the buccal mucosa as small, irregular, bright red spots, with bluish-white specks at center.



Clinical Features

- Incubation is 10-14 days long
- Prodromal manifestations, fever and the three Cs, last 2-3 days.
- The prodrome ends when the rash appears.
- The rash appears first on the face about the 3rd or 4th day
- Rash begins to fade 3 to 4 days after it appears.









- In uncomplicated measles, clinical recovery begins soon after appearance of the rash.
- The rash fades to a café'au lait colour (often called staining).
- There is generalized involvement of lymphoid tissue
- Respiratory complications include pneumonia, giant cell pneumonia, croup and otitis media.



FIG. 135
Post-measles staining of the skin.



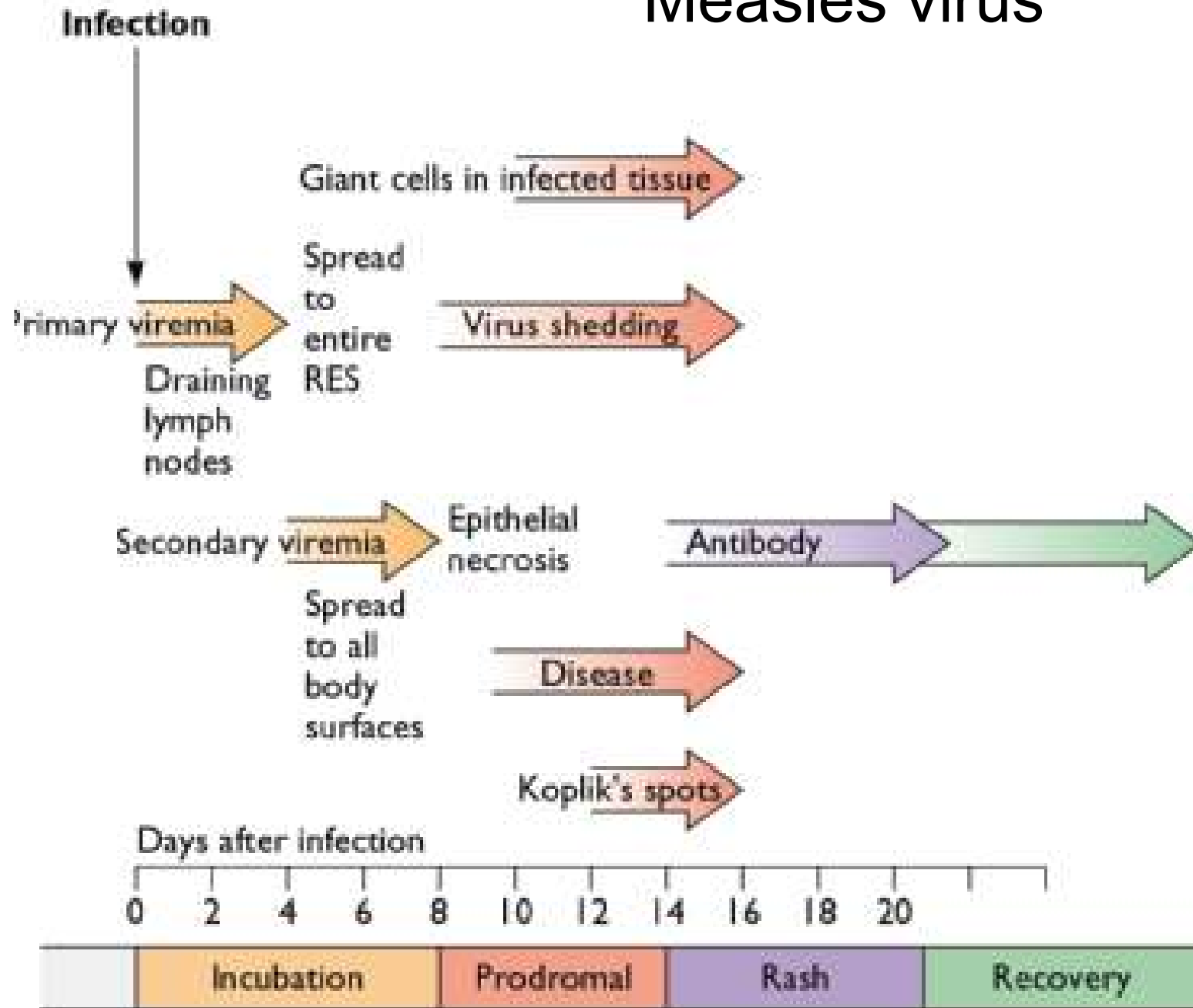






Measles virus

B



From Flint et al.,
ASM Press, 2004

Rubella virus

- Virus replicates at the portal of entry.
- Spread via lymphatics or a transient viremia seeds regional lymph nodes.
- Replication of virus in these nodes likely accounts for their enlargement
- Viremia ceases shortly after the rash appears, with the appearance of detectable circulating antibodies

- The infection caused by rubella virus in early childhood or adult life is usually mild, with most cases passing as subclinical or unrecognized events.
- Clinically apparent rubella is characterized by any combination of symptoms that include maculopapular rash, lymphadenopathy, low-grade fever, conjunctivitis, sore throat, and arthralgia.

- The rash is the most prominent feature of the illness and is the first manifestation of the disease in about 95% of all cases.
- An associated posterior cervical and suboccipital adenopathy is characteristic.
- Rash often fades on the face while progressing downwards.
- The lesions tend to be discrete at first, but rapidly coalesce to produce a flushed appearance.

Rash of Rubella

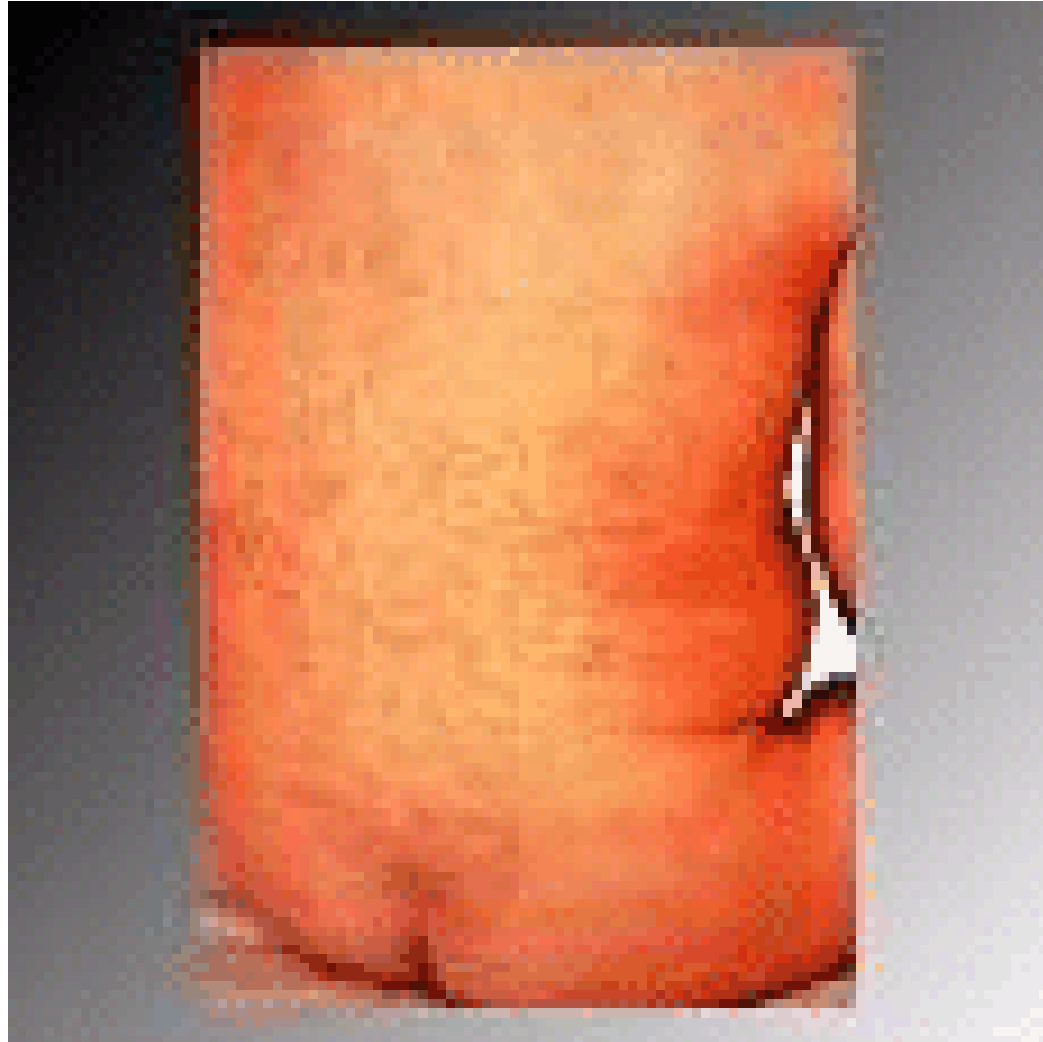
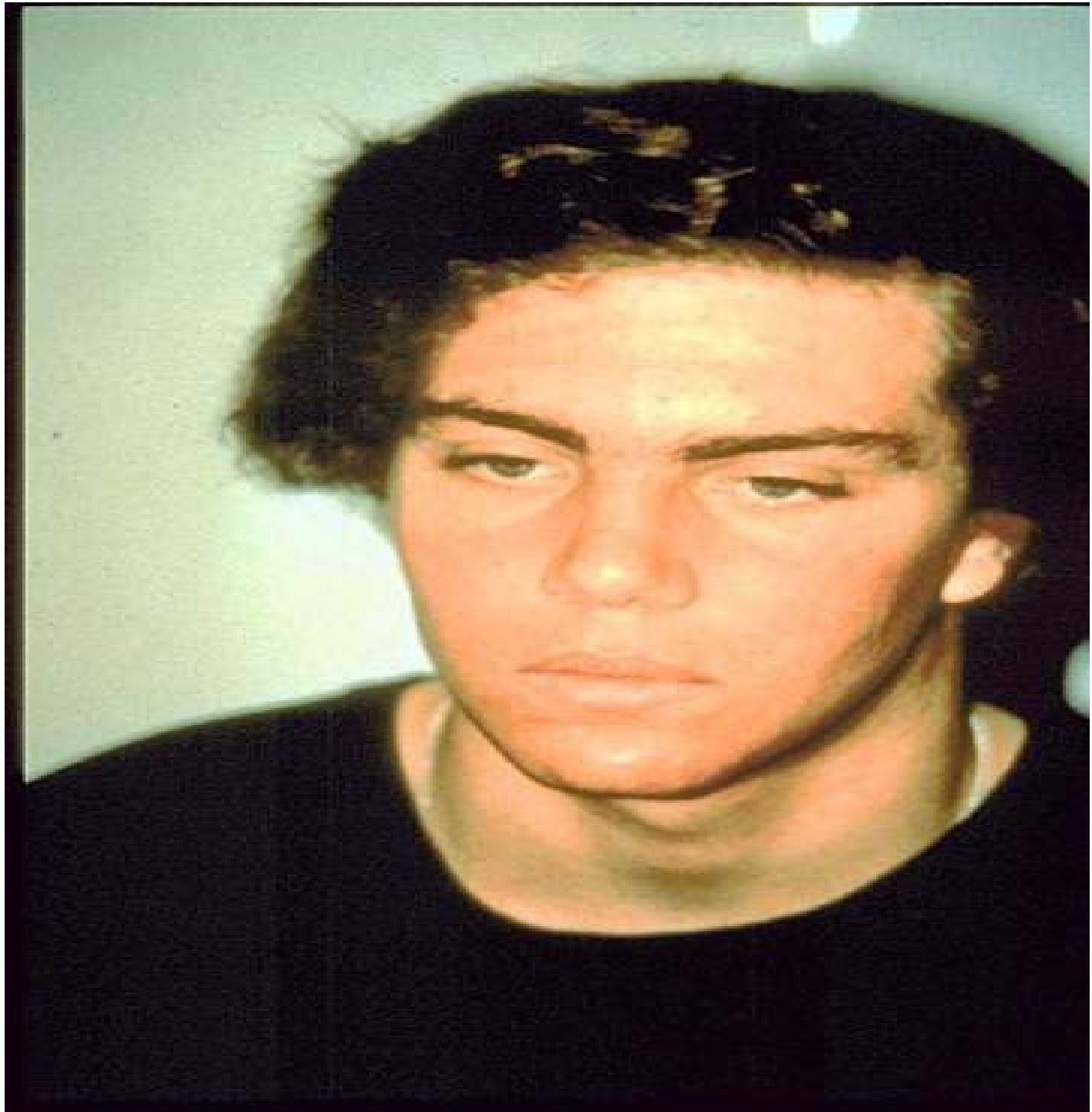






FIG. 140
A child with rubella.





Parvovirus B 19

Fifth Disease

- Acute infection with B19 parvovirus causes the common childhood exanthema, fifth disease (erythema infectiosum).
- Children with fifth disease usually are not very ill.
- The rash is characteristic “slapped cheek” facial erythema and a lacy, reticular evanescent maculopapular eruption over the trunk and proximal extremities.





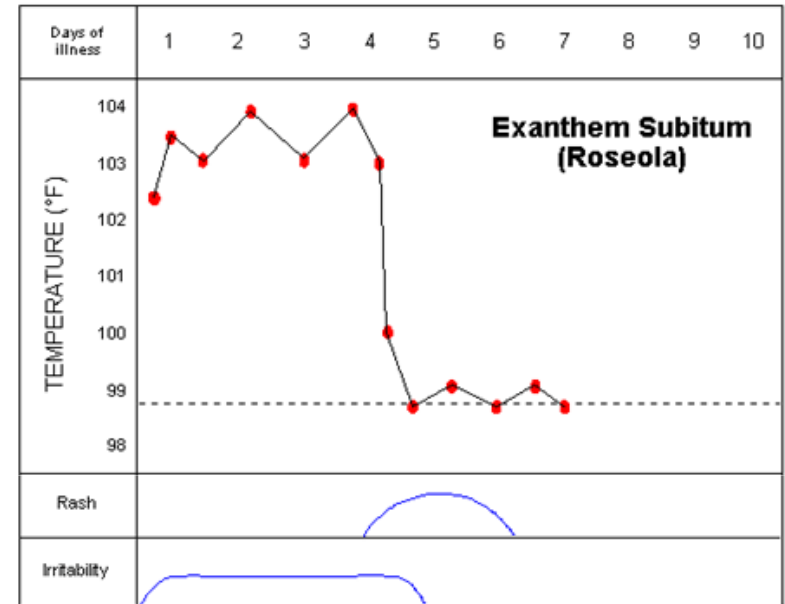
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- Fifth disease is often confused with rubella and other childhood exanthemas.
- Adults with fifth disease more commonly suffer joint pain or frank arthritis, than a rash. It may mimic rheumatoid arthritis.
- It may be associated with other CTD (SLE, vasculitis, polyarteritis nodosa) or neurological disease.
- Cases of ITP and HSP have apparently followed acute parvovirus infection.

Roseola Infantum (Exanthem Subitum)

- Human Herpes Virus 6
- Spreads via saliva
- 70-95% seropositivity in early age
- Signs and Symptoms:
irritability, diarrhea, cough,
fever 38-40, for 3-7 days; 10%
seizure



Roseola Infantum (Exanthem Subitum)

- Skin:
 - As fever resolves, faint macules develop on trunk and extremities that blanch upon pressure
 - Rash resolves in 1-2 days



Hand, Foot, and Mouth Disease

- It has particularly been associated with Coxsackie virus A 16, but A 4, 5, 9 and 10 and B 2 and 5 and Enterovirus 71 have been implicated.

Hand Foot and Mouth Disease

- Common acute febrile illness of children
- Resolves in 2-7 days
- Fecal oral route of transmission (Hand washing)
- Rare complications



HFM Disease



foot



mouth



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- **Pleurodynia** (Epidemic Myalgia, Bronholm disease, or Devil's Grip): It is generally caused by group B Coxsackie viruses.
- Echovirus 3 was responsible for epidemics of wandering myoclonus in China that most commonly affects young adults.
- Myoclonus and Rhabdomyolysis have been caused by West Nile Virus