Viral infections in the tropics

Variola vera (smallpox) 1.

- Smallpox is an infectious disease caused by the variola virus of which there are two types, variola major causing major smallpox, a life-threatening condition with a mortality of 30% (much higher in the hemorrhagic form of the disease, which is the commonest cause of death in smallpox), and variola minor, the agent of minor smallpox or, as it was referred to in South America, alastrim, which generally has a mortality of less than 1%.
- The viruses are members of the poxviridae group of viruses that includes the vaccinia virus and animal poxviruses such as monkeypox.
- It is possible that the smallpox virus evolved from an animal virus.

Variola vera (smallpox) 2.

Variola vera (smallpox) 3.

**The mummified head of Ramses V of Egypt (died 1157
BCE) showing the pustular eruption that may be due to smallpox.
(From Smith, 1912)**

Variola vera (smallpox) 4.

- Variola virus belongs to the family Poxviridae, subfamily Chordopoxvirinae, and genus orthopoxvirus, which includes vaccinia (smallpox vaccine), monkeypox virus, and several other animal poxviruses that cross-react serologically.
- The poxviruses contain single, linear, double-stranded DNA molecules of 130-to-375-kb pairs and replicate in cell cytoplasm.
- They are shaped like bricks on electron micrographs and measure about 300 by 250 by 200 nm.

Pathogenesis

- Studies of mousepox, rabbitpox, and monkeypox have provided information about the pathogenesis of poxviruses.
- The virus enters the respiratory tract, seeding the mucous membranes and passing rapidly into local lymph nodes.
- After a brief period of viremia, there is a latent period of 4 to 14 days, during which the virus multiplies in the reticuloendothelial system.
- Another brief period of viremia precedes the prodromal phase.

Pathogenesis

- During the prodromal phase, mucous membranes in the mouth and pharynx are infected.
- The virus invades the capillary epithelium of the dermal layer in skin, leading to the development of lesions.
- Oropharyngeal and skin lesions contain abundant viral particles, particularly early in the illness.
- Virus is also present in urine and conjunctival secretions, with the levels decreasing during convalescence.
- The spleen, lymph nodes, liver, bone marrow, kidneys, and other viscera may contain large quantities of virus.

Pathogenesis

- Neutralizing antibodies appear during the first week of illness but are delayed if the infection is severe; hemagglutination-inhibition antibodies are detectable by day 16 of the infection, and complement-fixation antibodies by day.
- Neutralizing antibodies remain present for many years, whereas levels of hemagglutination-inhibition and complement-fixation antibodies begin to decrease after one year.

Clinical manifestations 1.

- The incubation period for smallpox is 7 to 17 days (mean, 10 to 12).
- The prodromal phase, which lasts for two or three days, is characterized by severe headache, backache, and fever, all beginning abruptly.
- The temperature often rises to more than 40°C and then subsides over a period of two to three days.

Clinical manifestations 2.

- Enanthema over the tongue, mouth, and oropharynx precedes the rash by a day.
- The rash begins as small, reddish macules, which become papules with a diameter of 2 to 3 mm over a period of one or two days; after an additional one or two days, the papules become vesicles with a diameter of 2 to 5 mm.

Clinical manifestations 3.

- The lesions occur first on the face and extremities but gradually cover the body.
- Pustules that are 4 to 6 mm in diameter develop about four to seven days after the onset of the rash and remain for five to eight days, followed by umbilication and crusting.
- There may be a second, less pronounced temperature spike five to eight days after the onset of the rash, especially if the patient has a secondary bacterial infection.

Clinical manifestations 4.

- The crusts begin separating by the second week of the eruption.
- Smallpox lesions have a peripheral or centrifugal
- distribution and are generally all at the same stage of development.
- Lesions on the palms and soles persist the longest.
- Death from smallpox is ascribed to toxemia, associated with immune complexes, and to hypotension.

Clinical manifestations 5.

- After severe smallpox, pockmarks, or pitted lesions, are seen in 65 to 80 percent of survivors.
- These lesions are common on the face because the large sebaceous glands tend to become infected.
- Panophthalmitis and blindness from viral keratitis or secondary infection of the eye occurs in about 1 percent of patients.

Clinical manifestations 6.

- Arthritis develops in up to 2 percent of children who have smallpox; viral infection of the metaphysis of growing bones is thought to be the cause.
- Encephalitis occurs in less than 1 percent of patients with smallpox.
- Although cough is not a prominent symptom, the more severe the disease, the greater the likelihood of respiratory complications; pneumonia or bacteremia may result in high mortality.

Classifications 1.

- The classification is based on a study of 3544 patients in India.
- In that study, the “ordinary” type of smallpox, variola major (described above), accounted for nearly 90 percent of cases, with a case fatality rate of 30 percent.
- Hemorrhagic smallpox, which is difficult to diagnose, accounted for less than 3 percent of cases; almost all patients with this type of smallpox died within the first seven days of illness.

Classifications 2.

- The milder, “modified” type accounted for 2 percent of cases in unvaccinated persons and for 25 percent in previously vaccinated persons.
- The modified cases were rarely fatal; the lesions were fewer, smaller, and more superficial than those in patients with the first type, and they evolved more rapidly.

Classifications 3.

- Seven percent of cases were characterized by flat lesions that evolved more slowly than those of variola major and that coalesced; the case fatality rate for the flat type was 97 percent among unvaccinated patients.

Classifications 4.

- The last type of smallpox, variola sine eruptione, occurs
- in previously vaccinated contacts or in infants with maternal antibodies.
- Affected persons are asymptomatic or have a brief rise in temperature, headache, and influenza-like symptoms; the transmission of clinical smallpox has not been documented with variola sine eruptione.

Diagnosis 1.

- Many eruptive illnesses can be misdiagnosed as smallpox.
- Severe chickenpox is most frequently misdiagnosed as smallpox, especially in adults who have an extensive rash.
- The prodromal phase of chickenpox lasts for one or two days, fever occurs with the onset of the rash, and the eruption is concentrated over the torso; individual lesions are present at different stages and progress from vesicles, crusting within 24 hours.

Diagnosis 2.

- Human monkeypox, a zoonotic disease, has never occurred outside west and central Africa.
- The rash of human monkeypox resembles that of smallpox clinically, but patients with monkeypox often have lymphadenopathy, unlike those with smallpox, and monkeypox is not spread easily between humans.

Treatment 1.

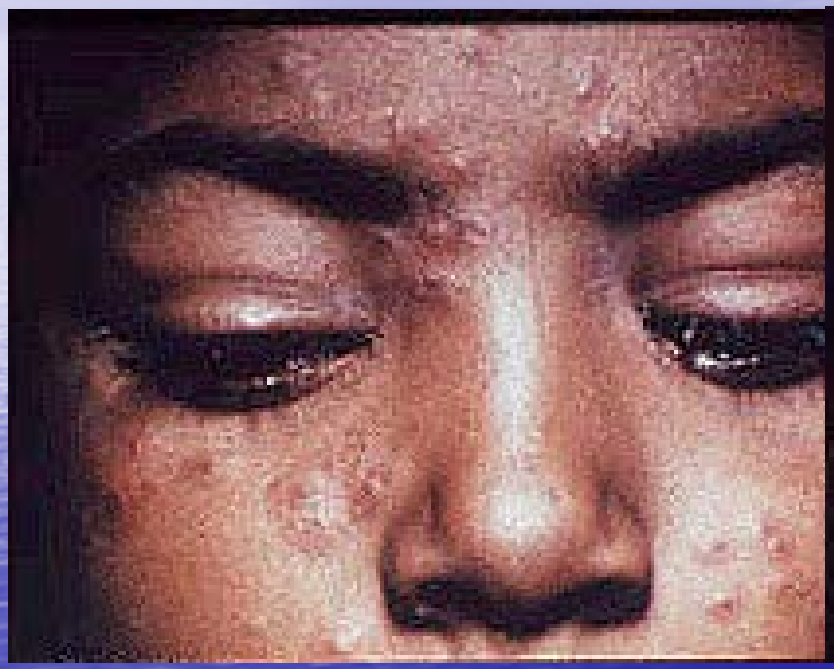
- A suspect case of smallpox should be managed in a negative-pressure room, if possible, and the patient should be vaccinated, particularly if the illness is in an early stage.
- Strict respiratory and contact isolation is imperative.
- When there are many patients, an isolation
- hospital or other facility should be designated.

Treatment 2.

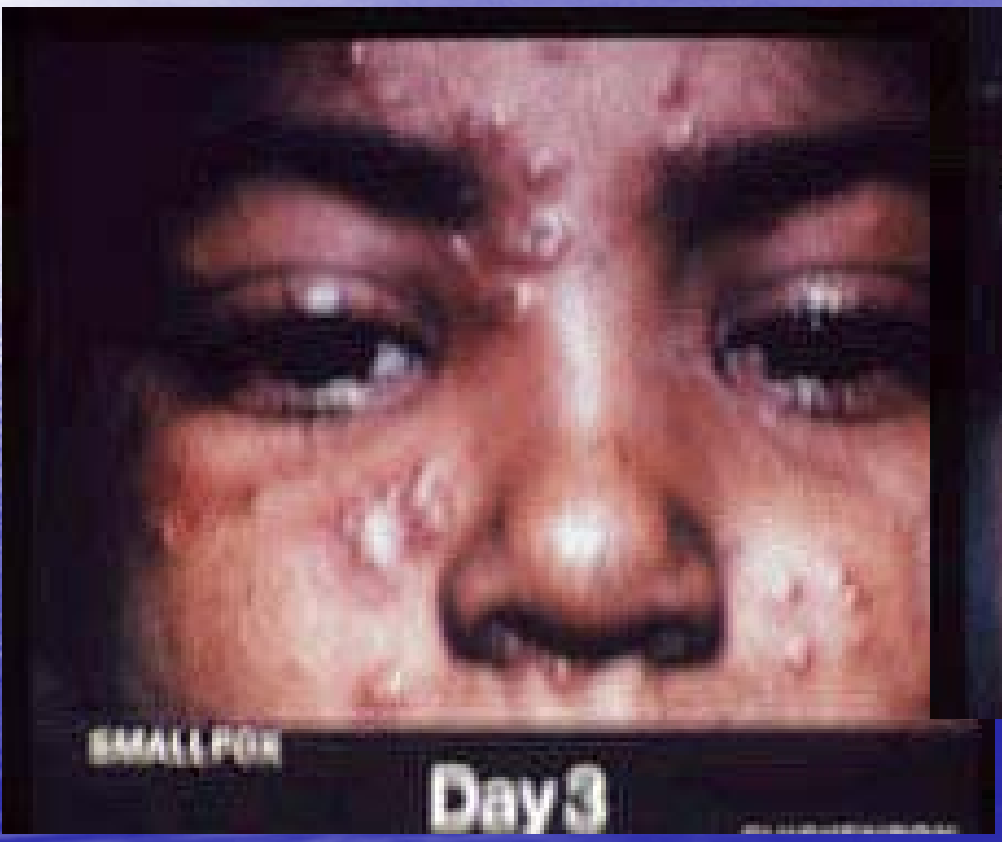
- There is no treatment approved by the Food and Drug Administration for orthopoxviruses. Penicillinase-resistant antimicrobial agents should be used if smallpox lesions are secondarily infected, if bacterial infection endangers the eyes, or if the eruption is very dense and widespread.
- Daily eye rinsing is required in severe cases.
- Patients need adequate hydration and nutrition, because substantial amounts of fluid and protein can be lost by febrile persons with dense, often weeping lesions.
- The drug decreases pulmonary viral levels and pneumonitis in animals with vaccinia orcowpox.
- In the event of a smallpox outbreak, the drug could be made available under an investigational-newdrug protocol for smallpox or adverse effects of vaccine.

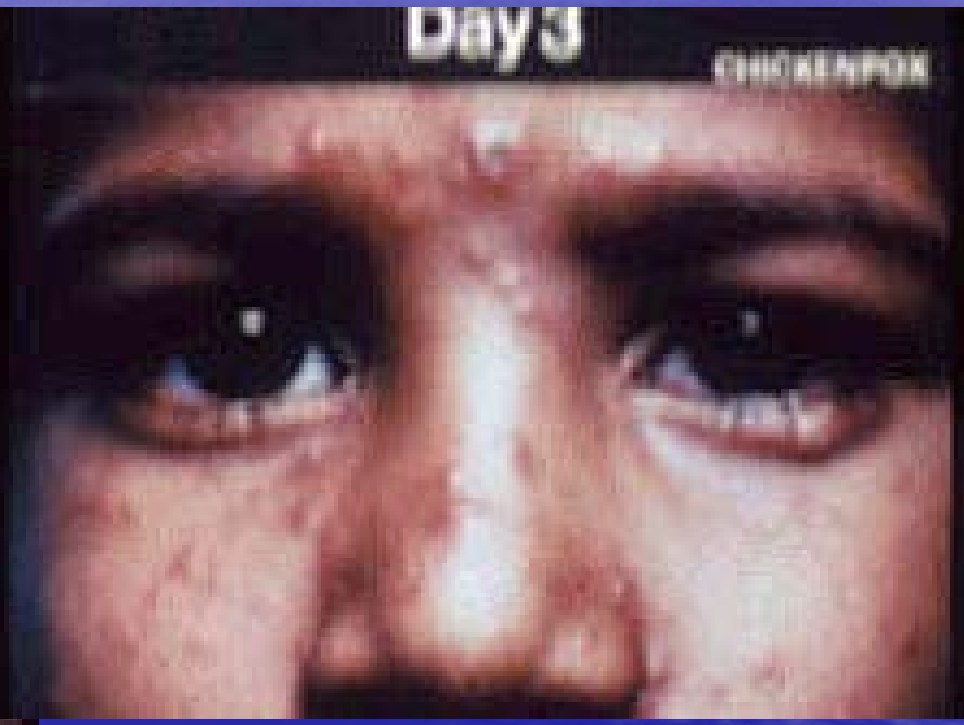
Intraepidermal multilocular vesicles with ballooning degeneration, cell necrosis, and serous exudation

Variola and varicella

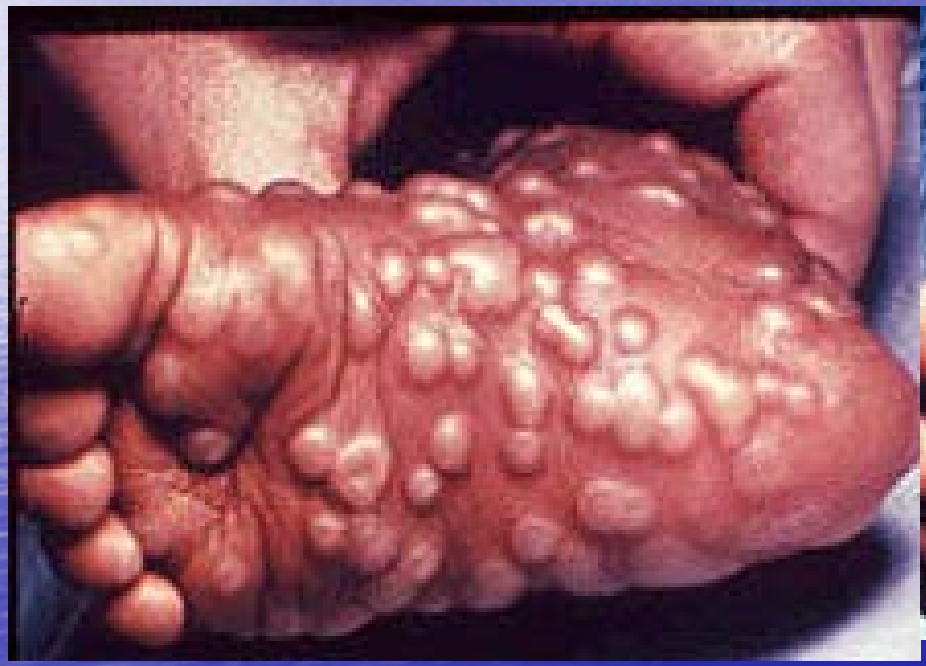


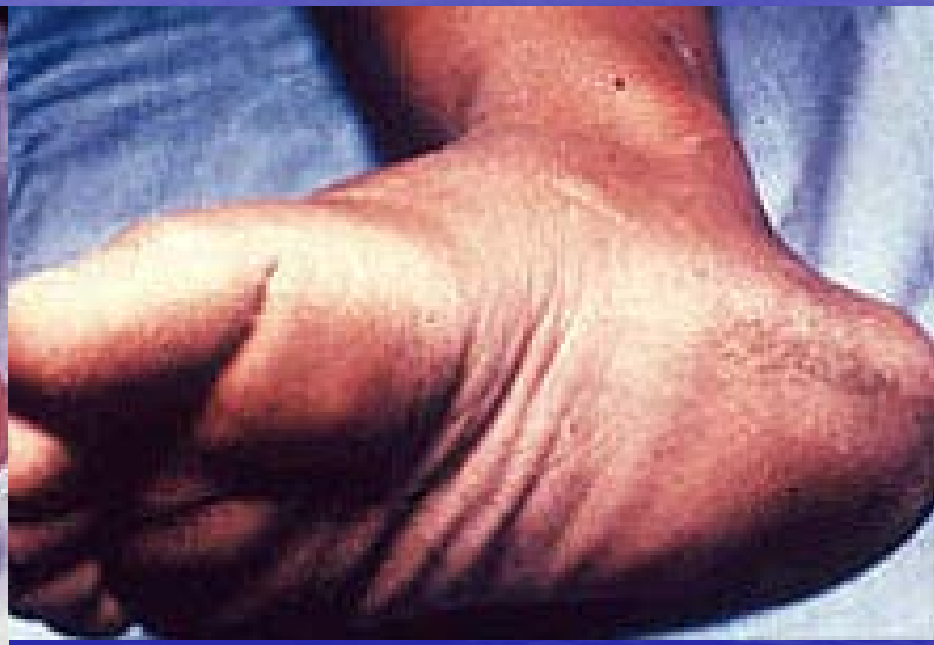
3. day



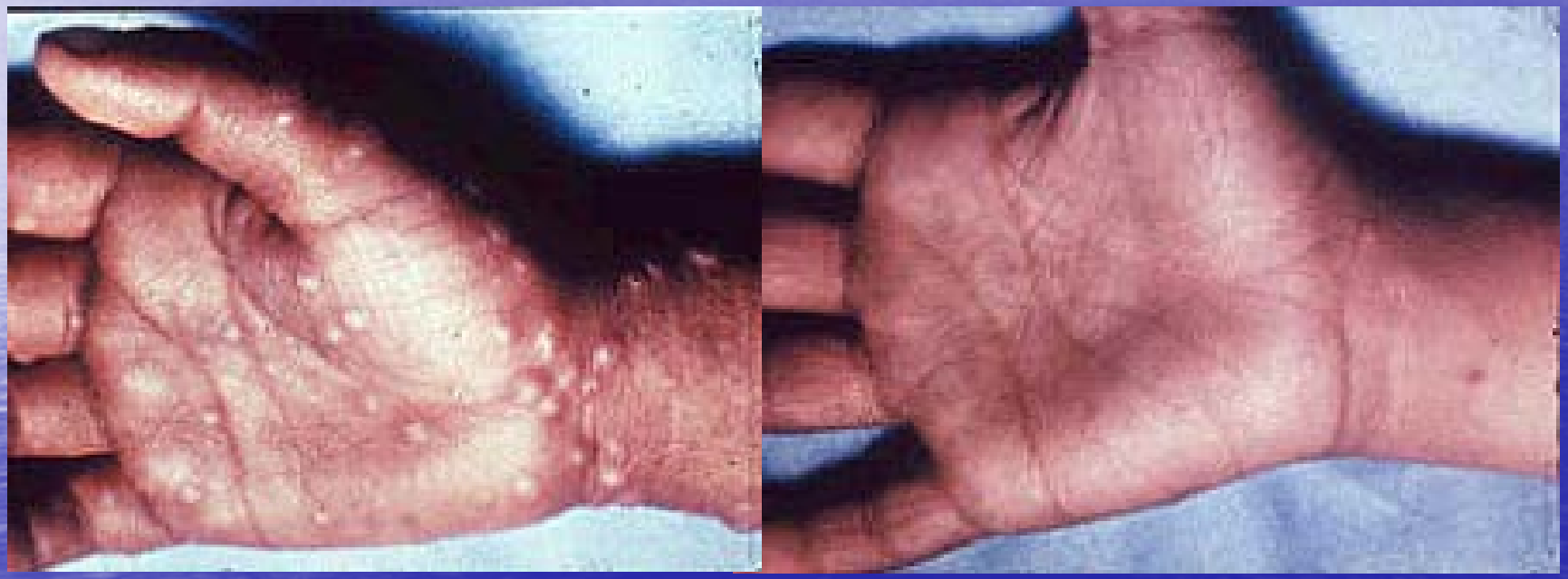


Variola and varicella on the feet

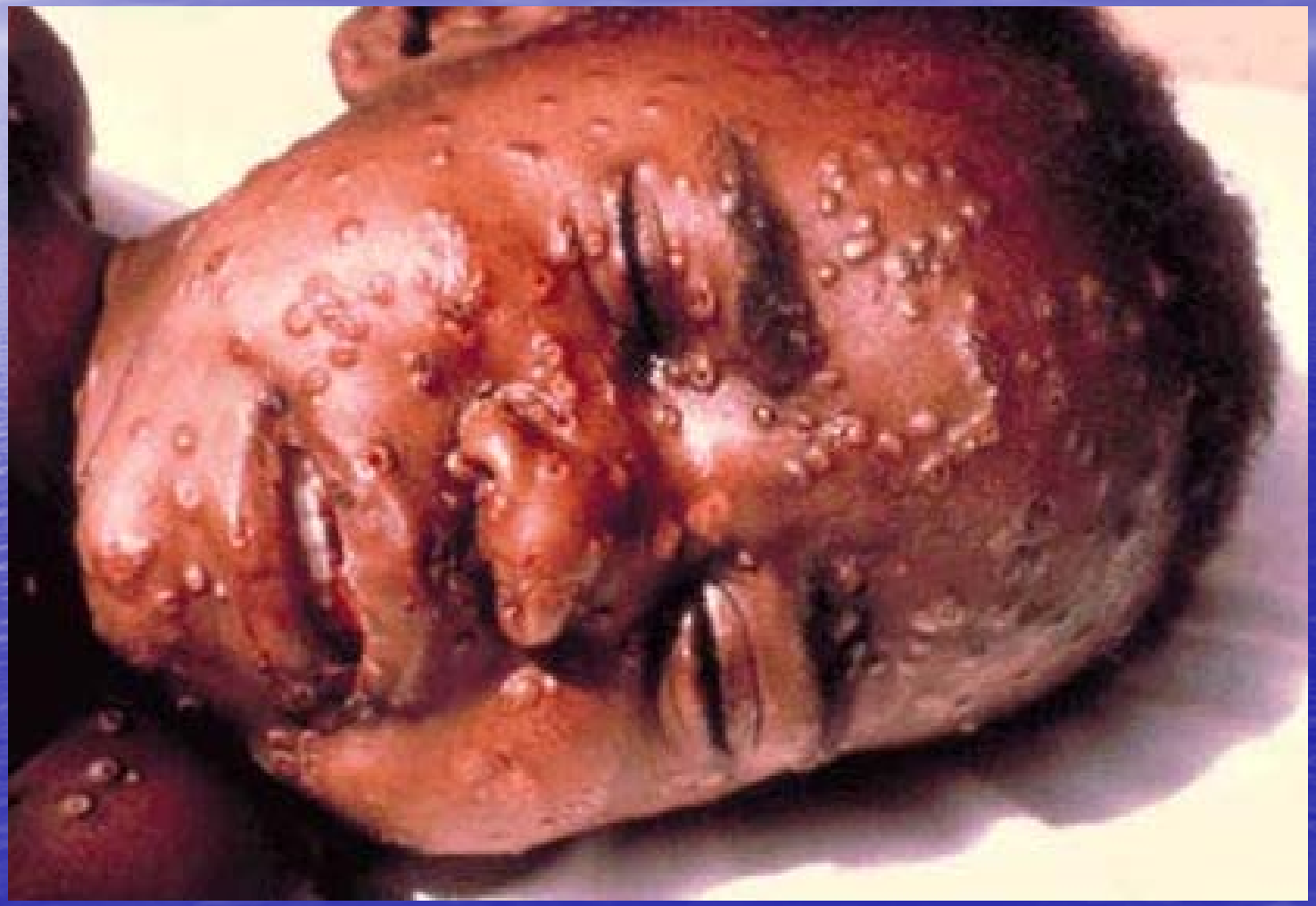




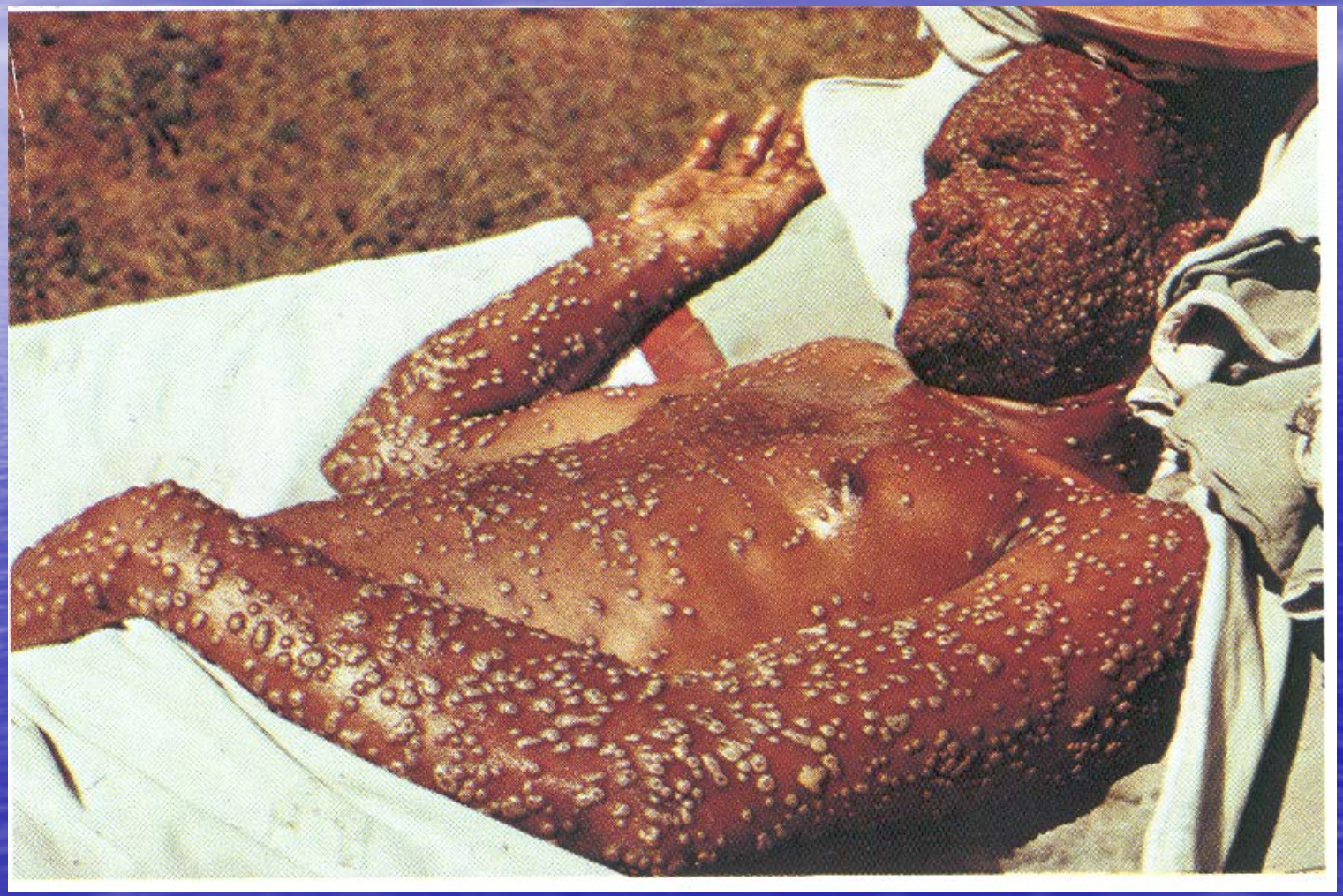
Variola and varicella on the palms



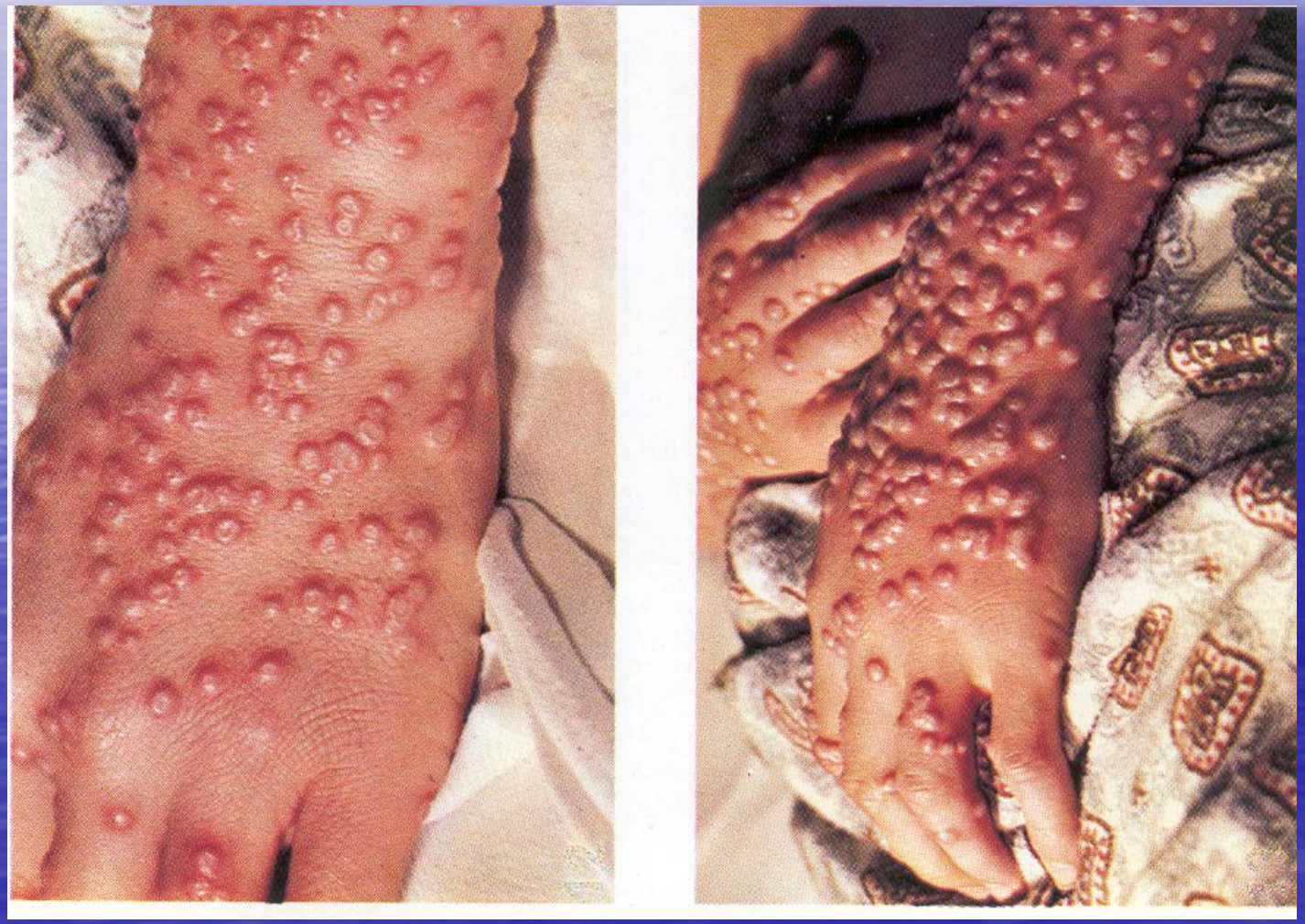
Facial variola



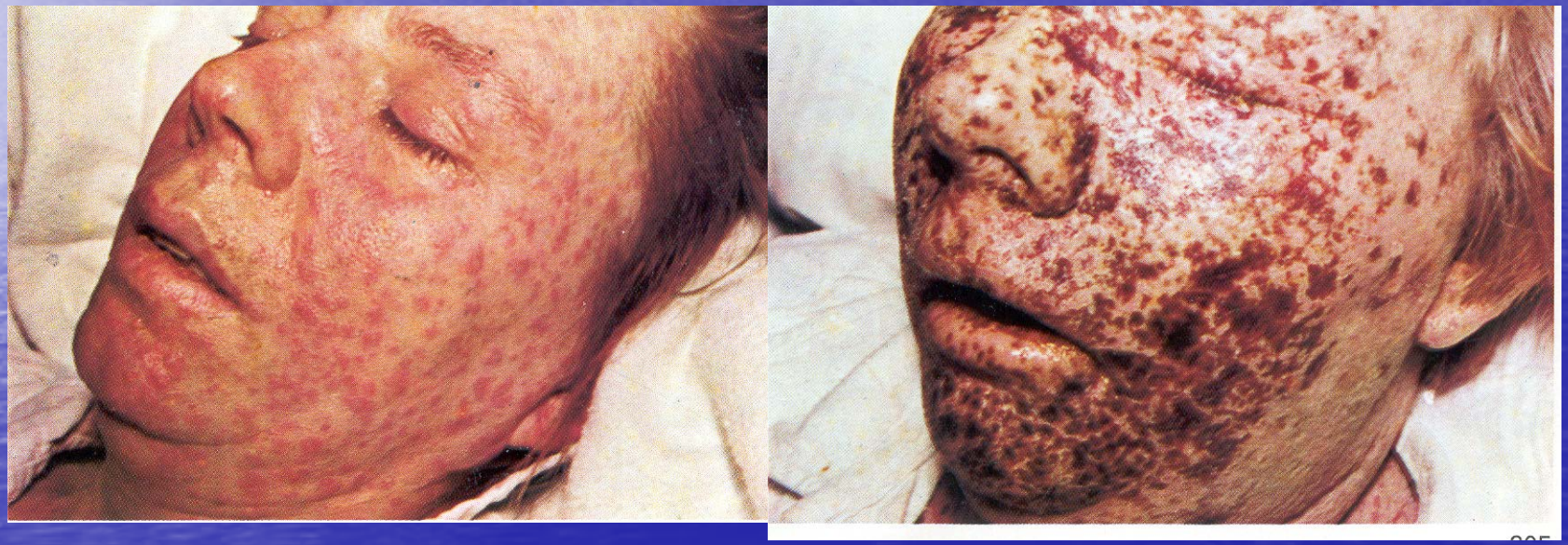
Distribution of the eruptions



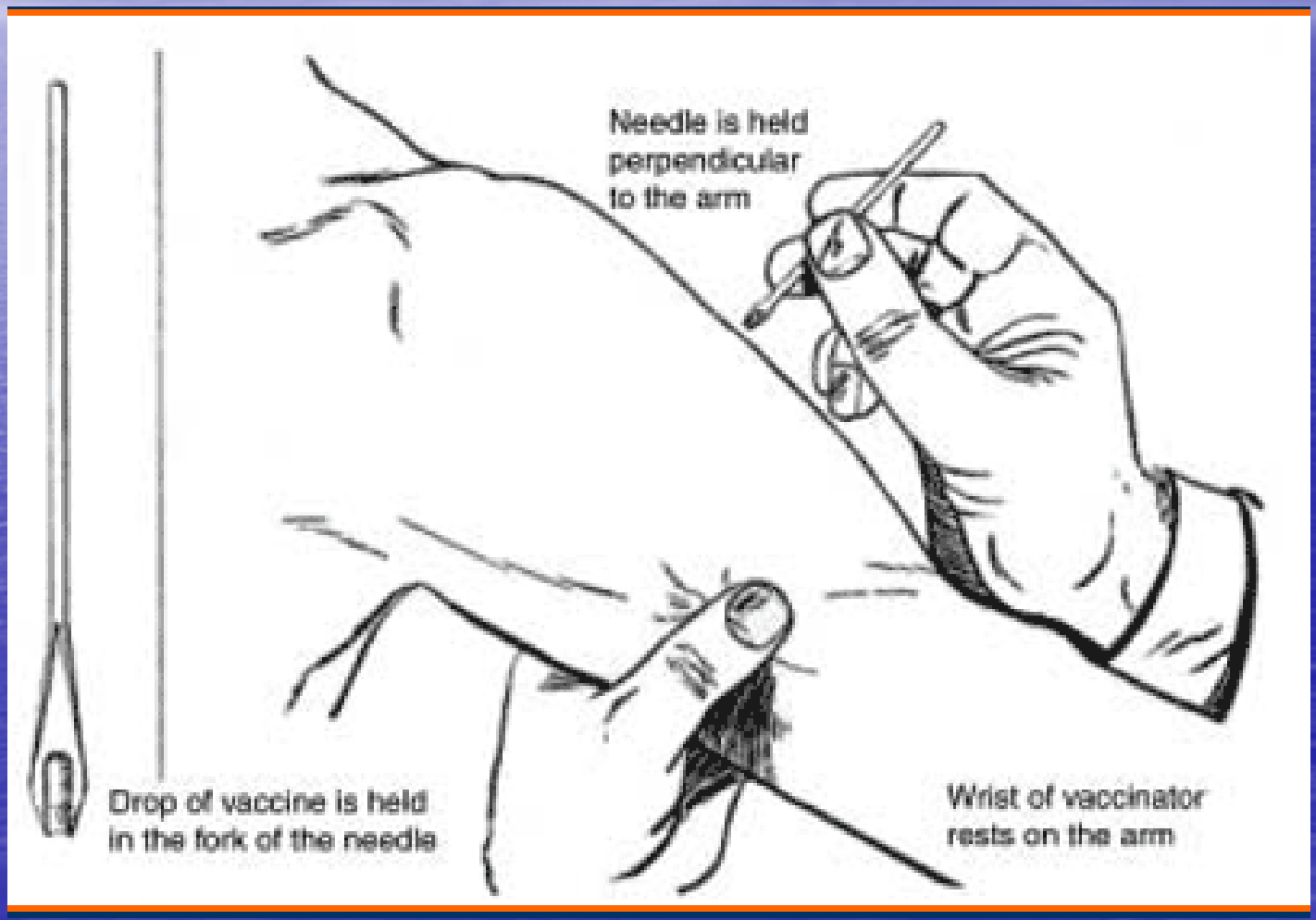
Variola on the hands



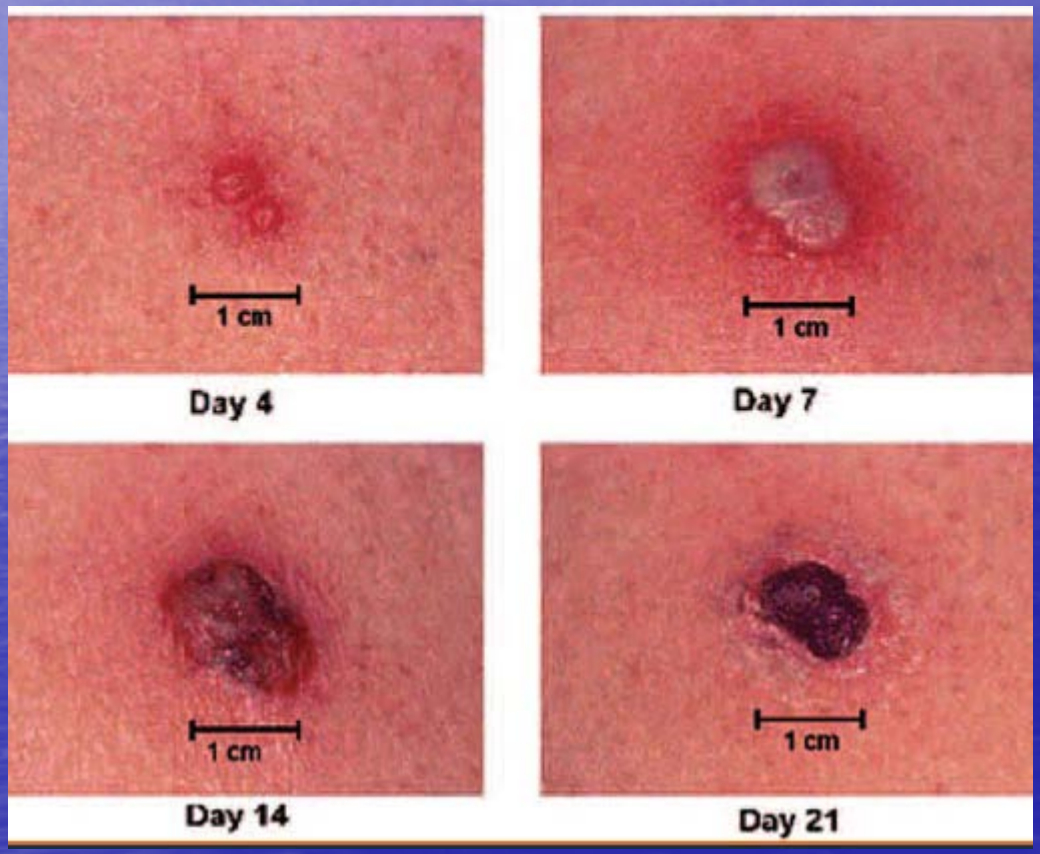
Haemorrhagic variola



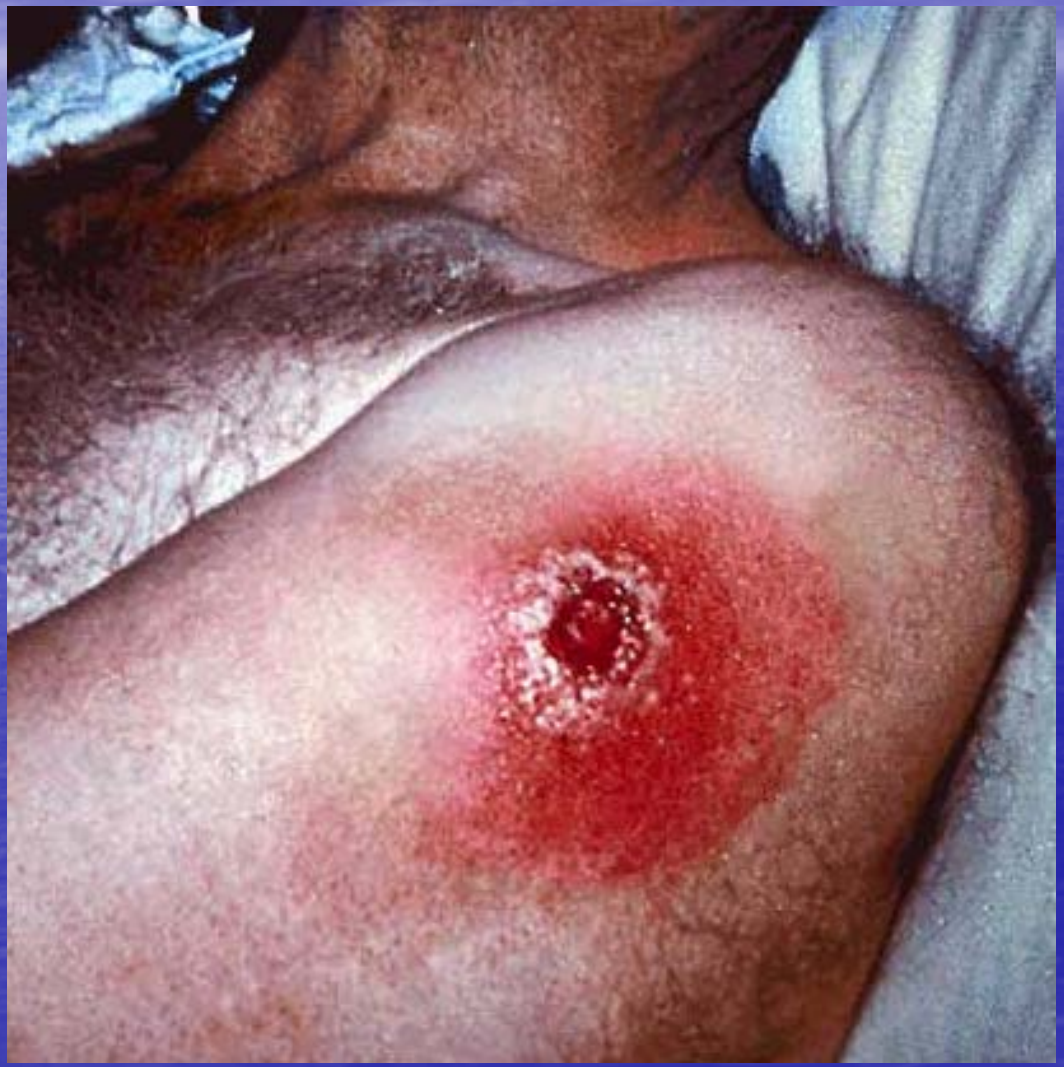
Classic vaccination



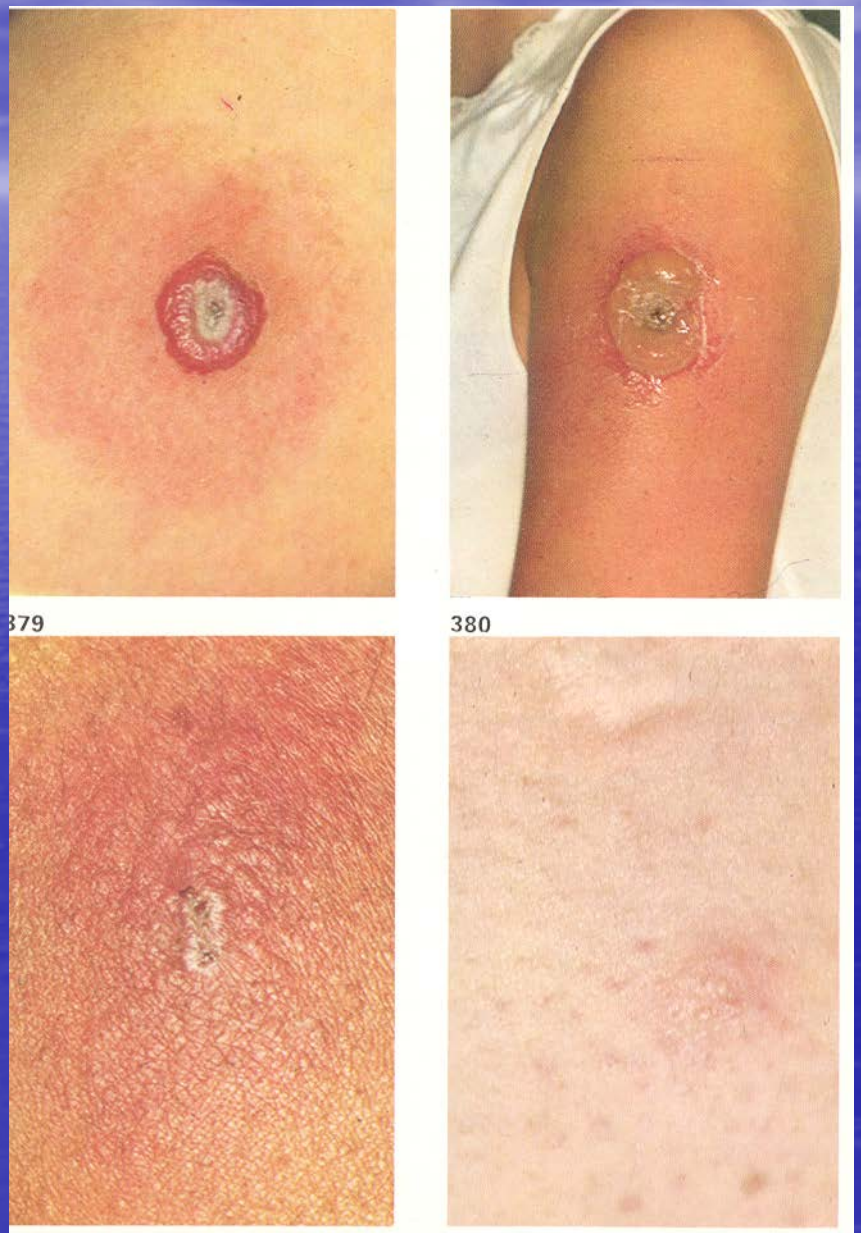
Normal reaction to the vaccine



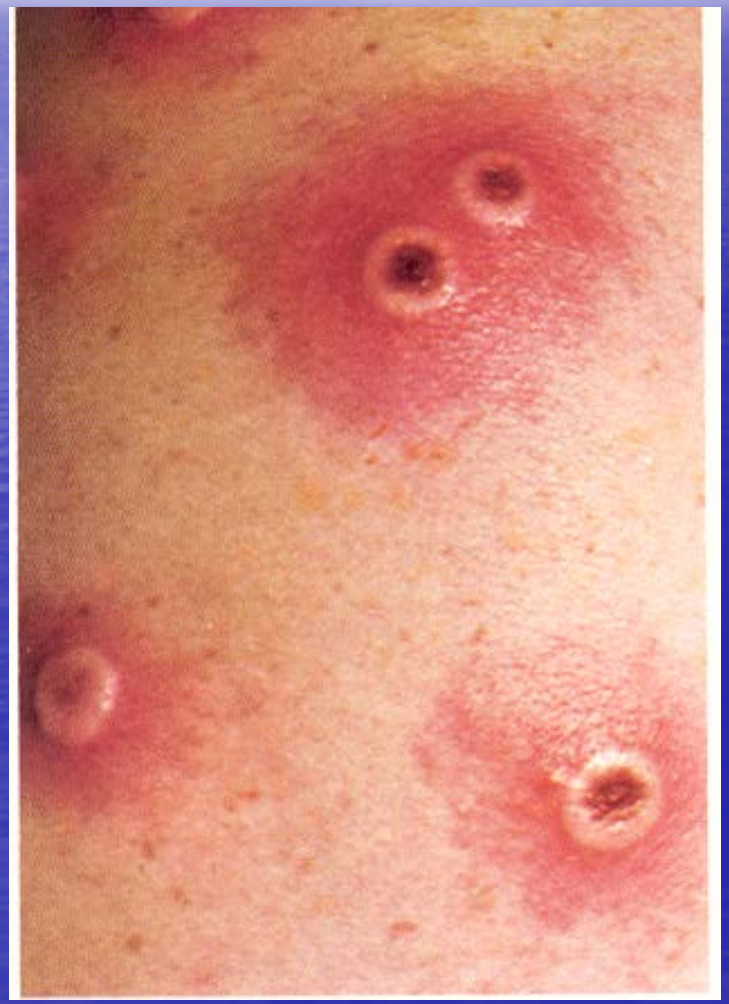
Necrotic complication



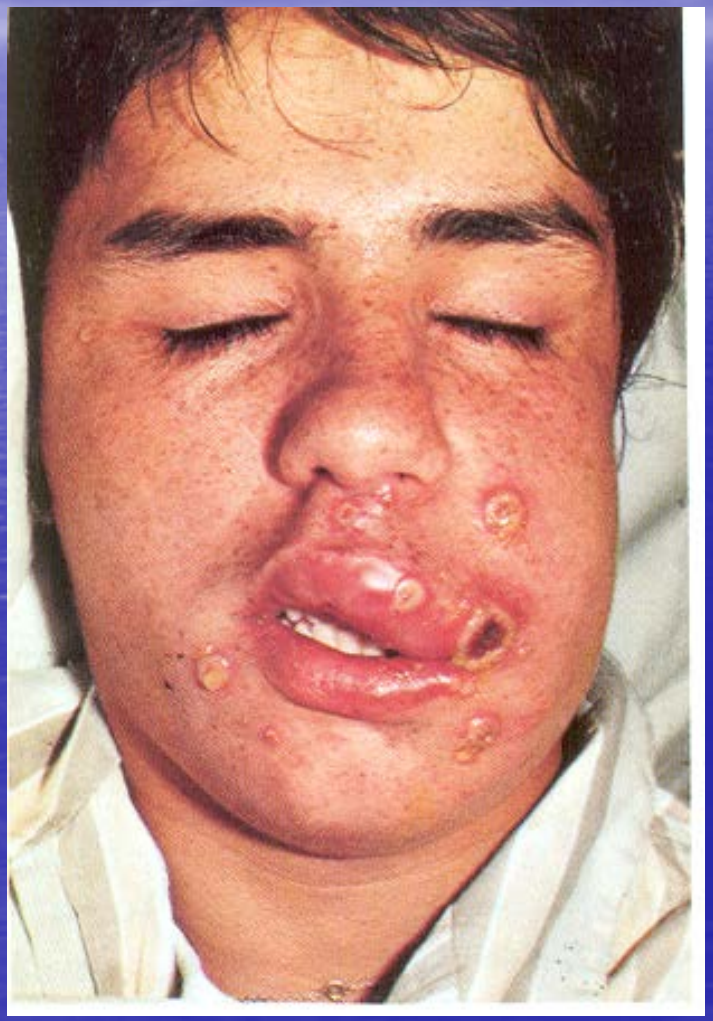
Reactions to vaccine



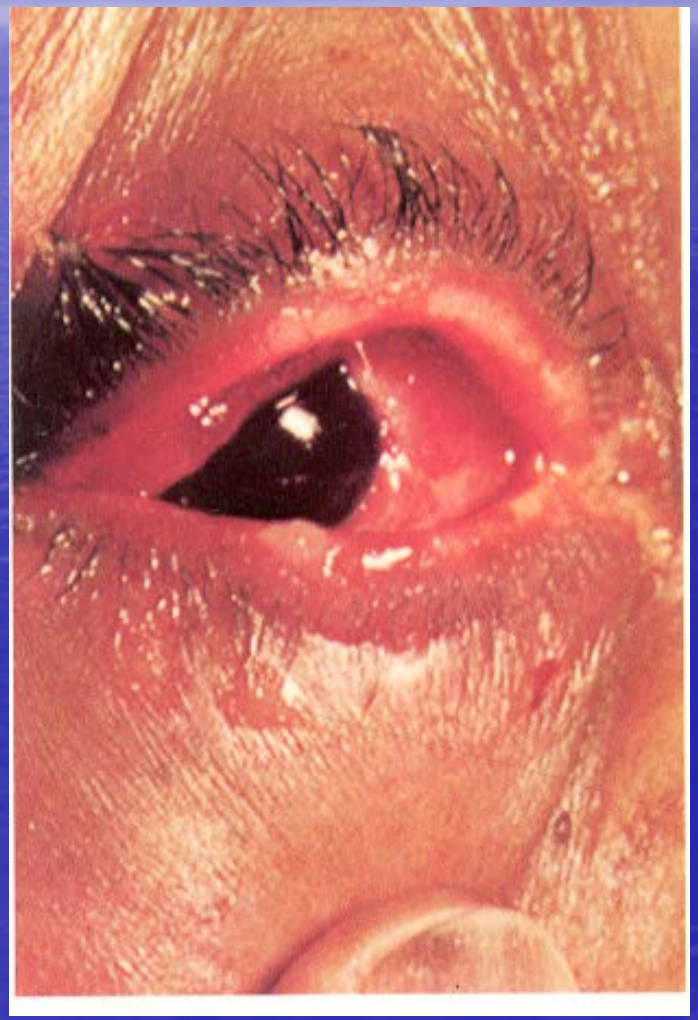
Spreading of the vaccinia virus



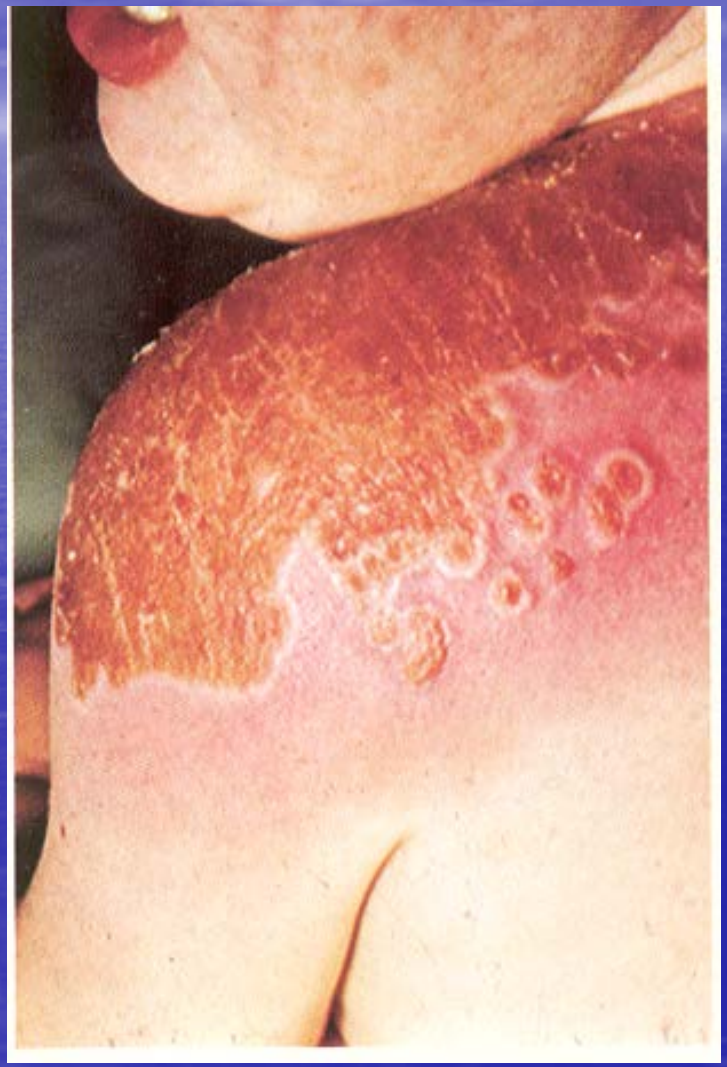
Autoinoculation of the face



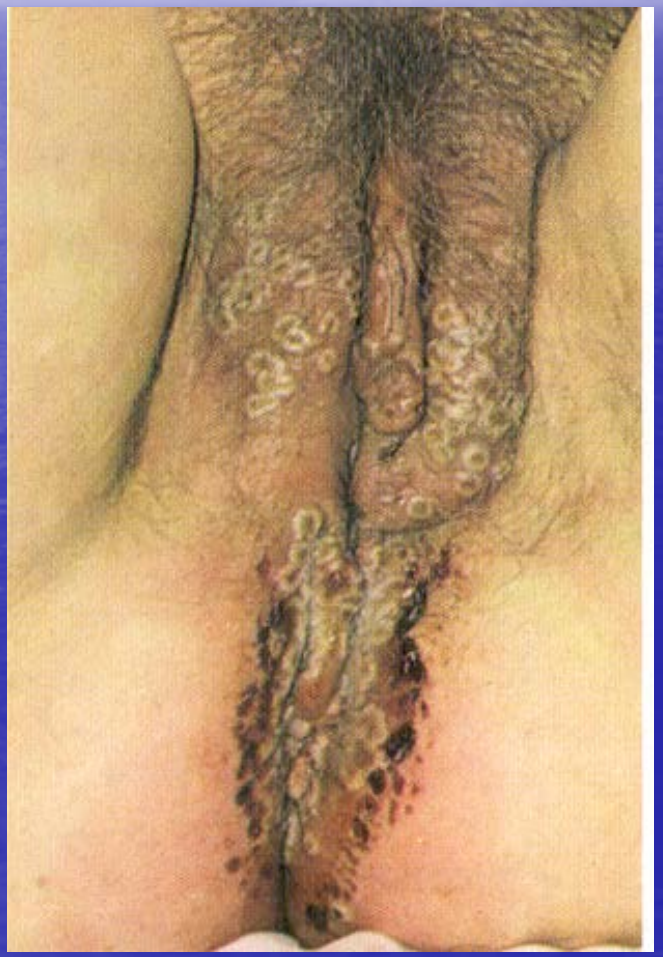
Vaccinia blepharitis



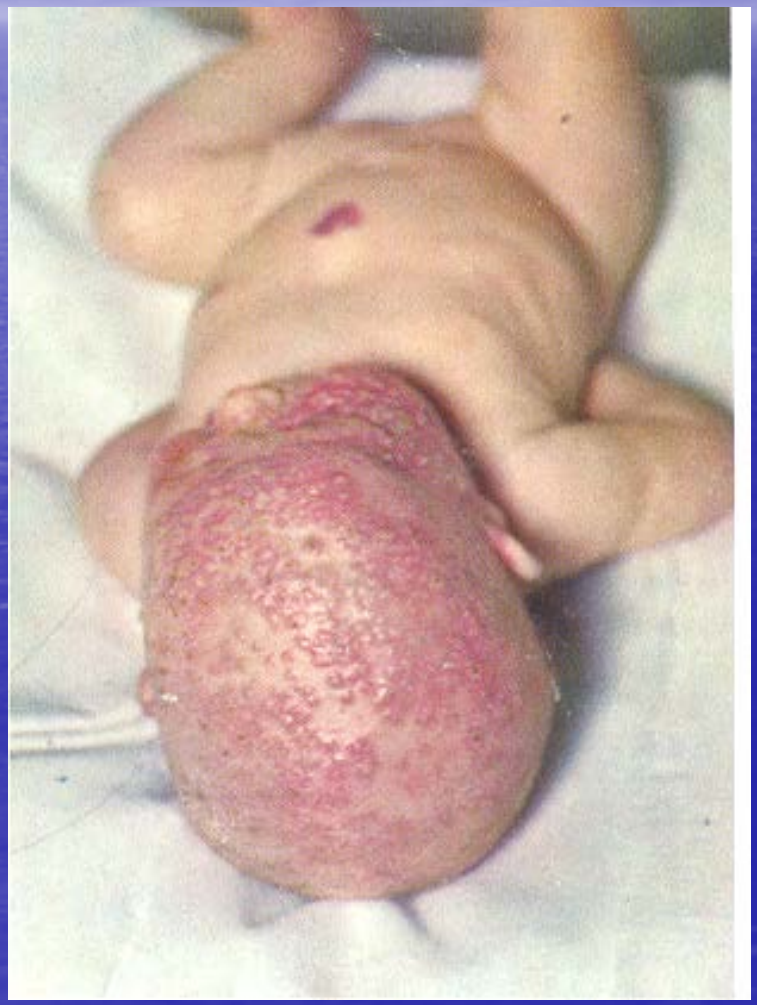
Spreading of the virus on the skin



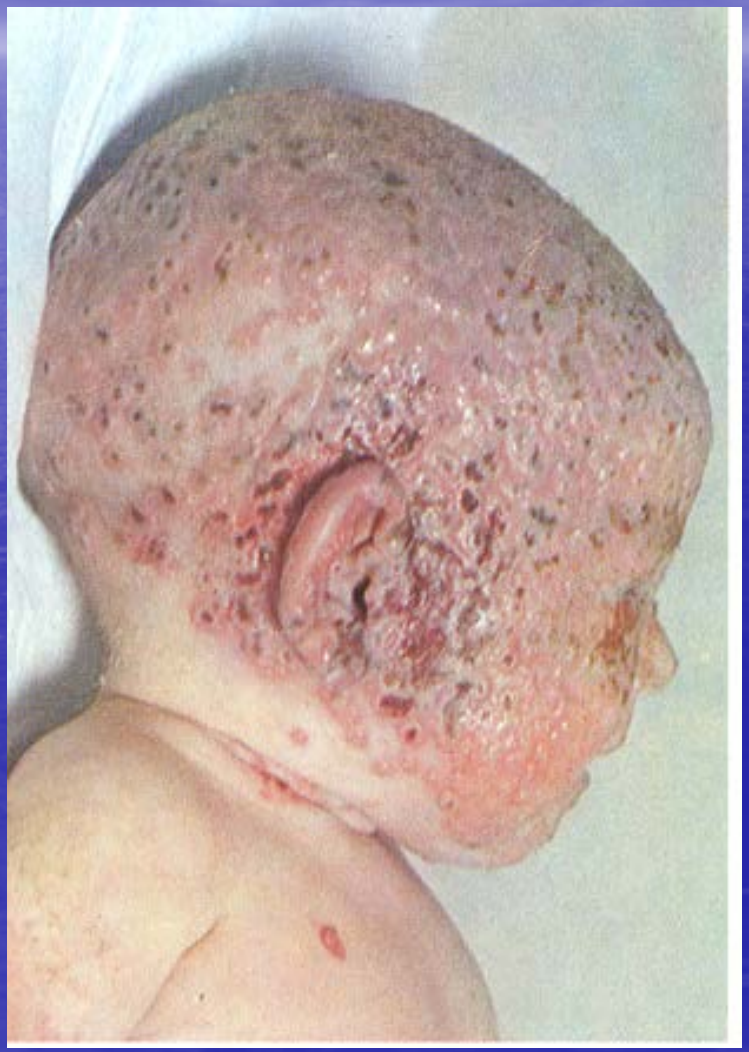
Vaccinia vulvo-vaginitis



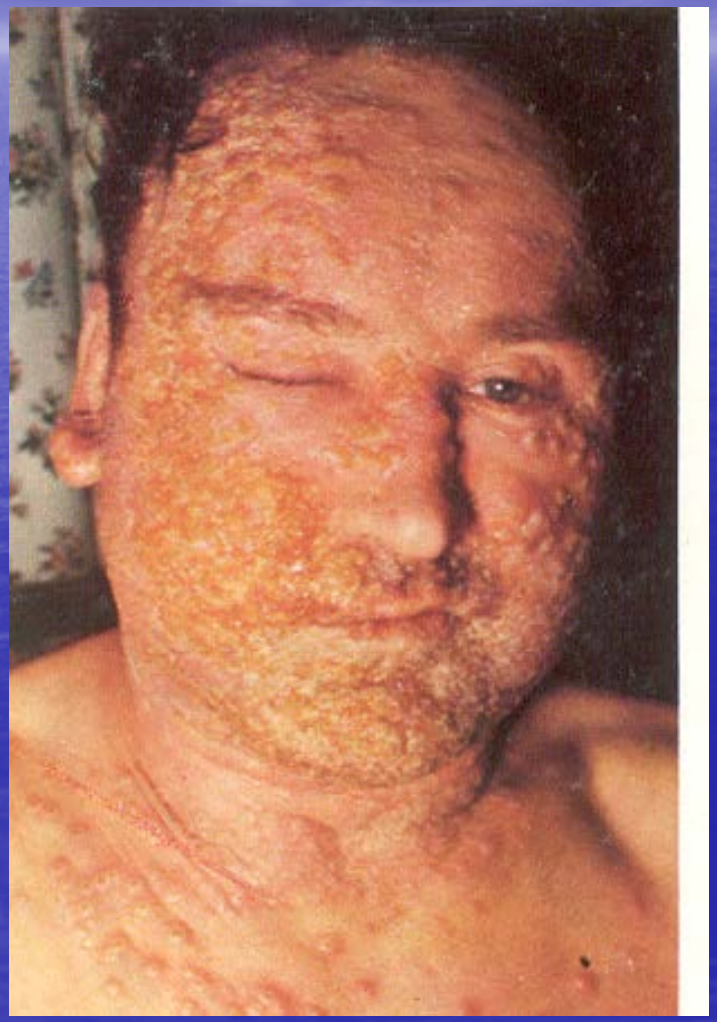
Eczema vaccinatum



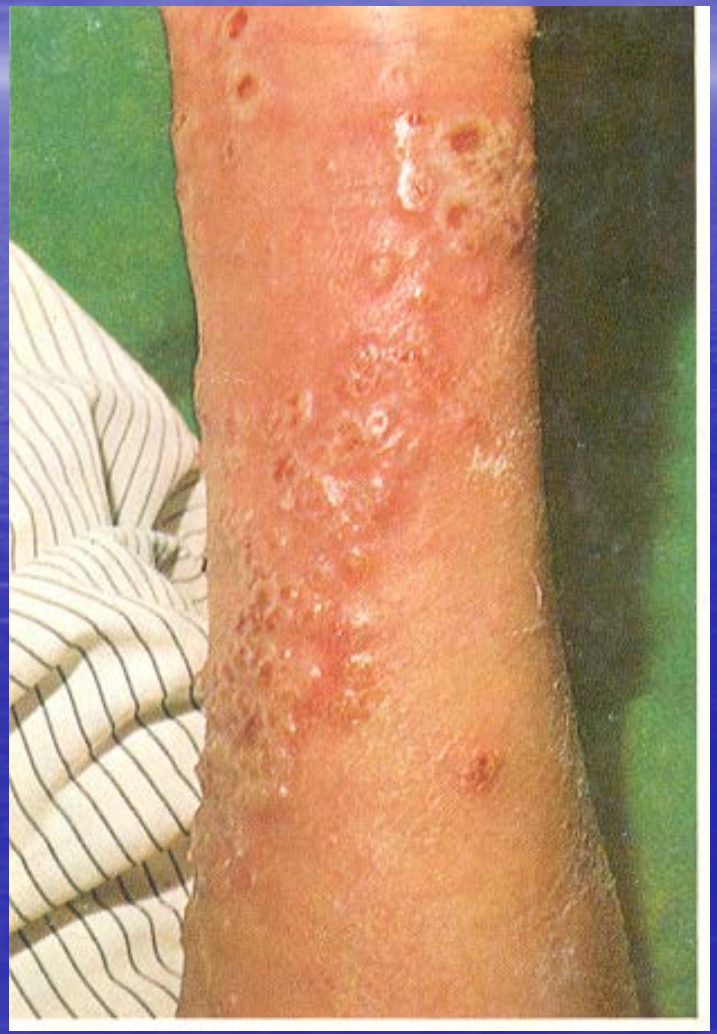
Eczema vaccinatum



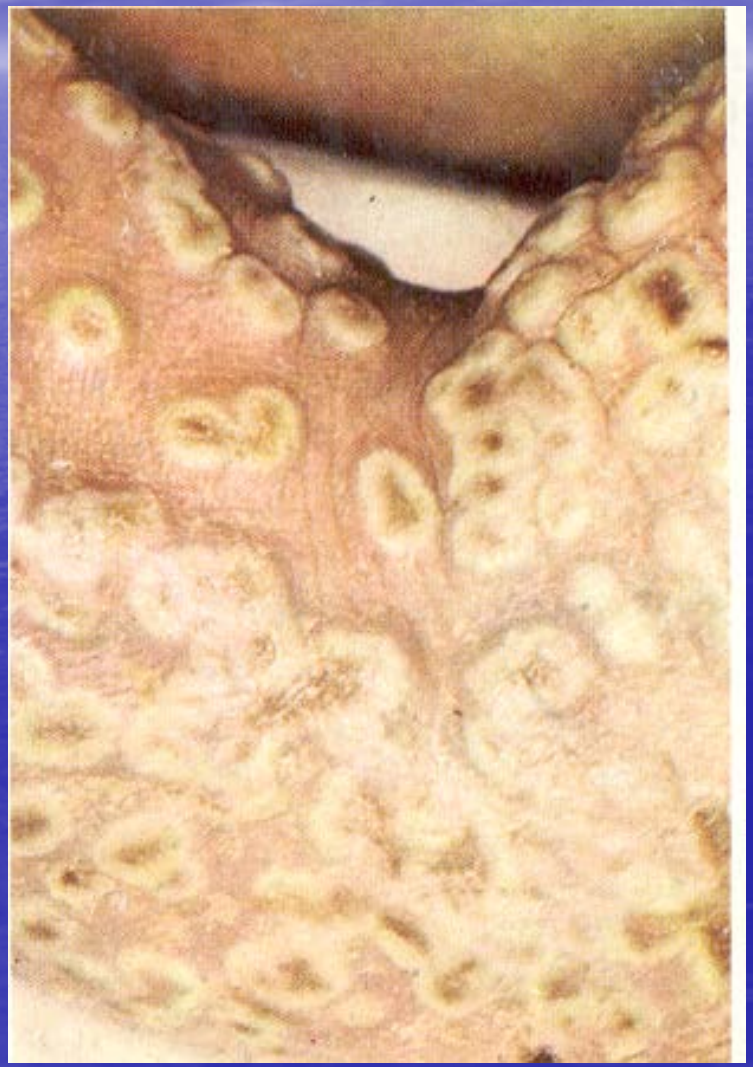
Eczema vaccinatum



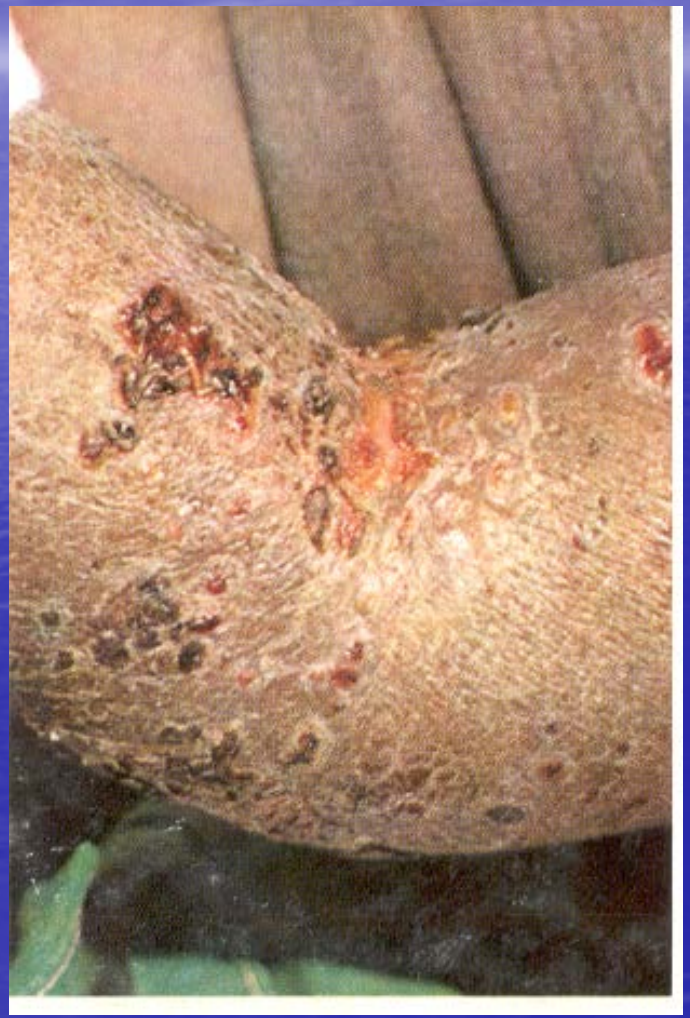
Eczema vaccinatum



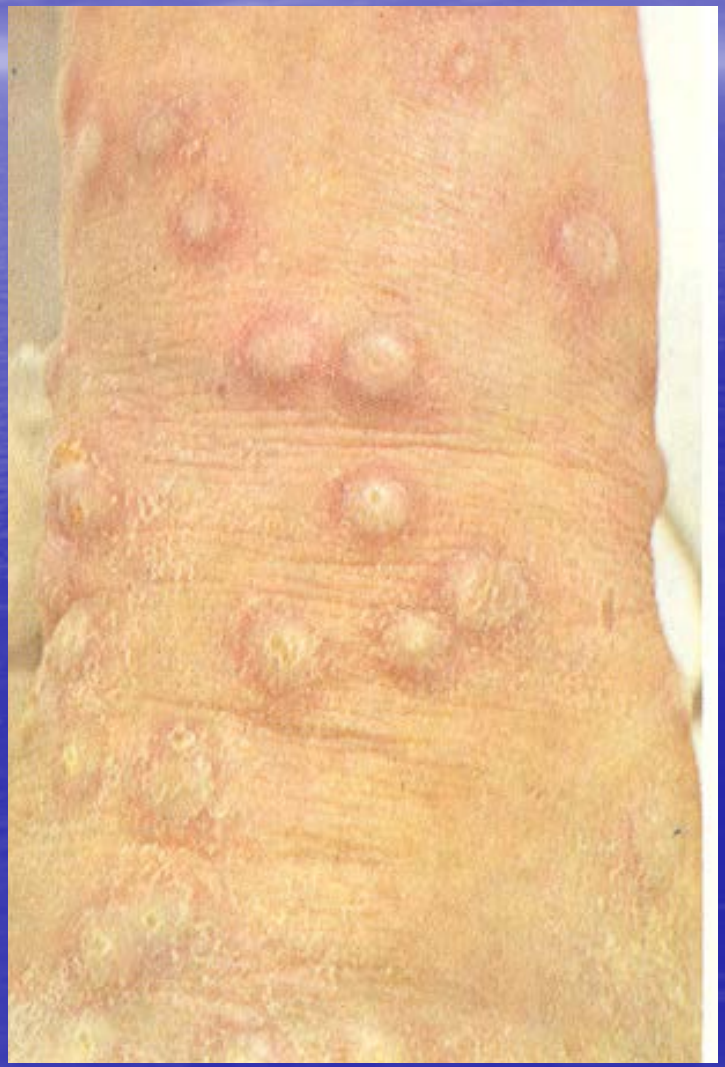
Eczema vaccinatum



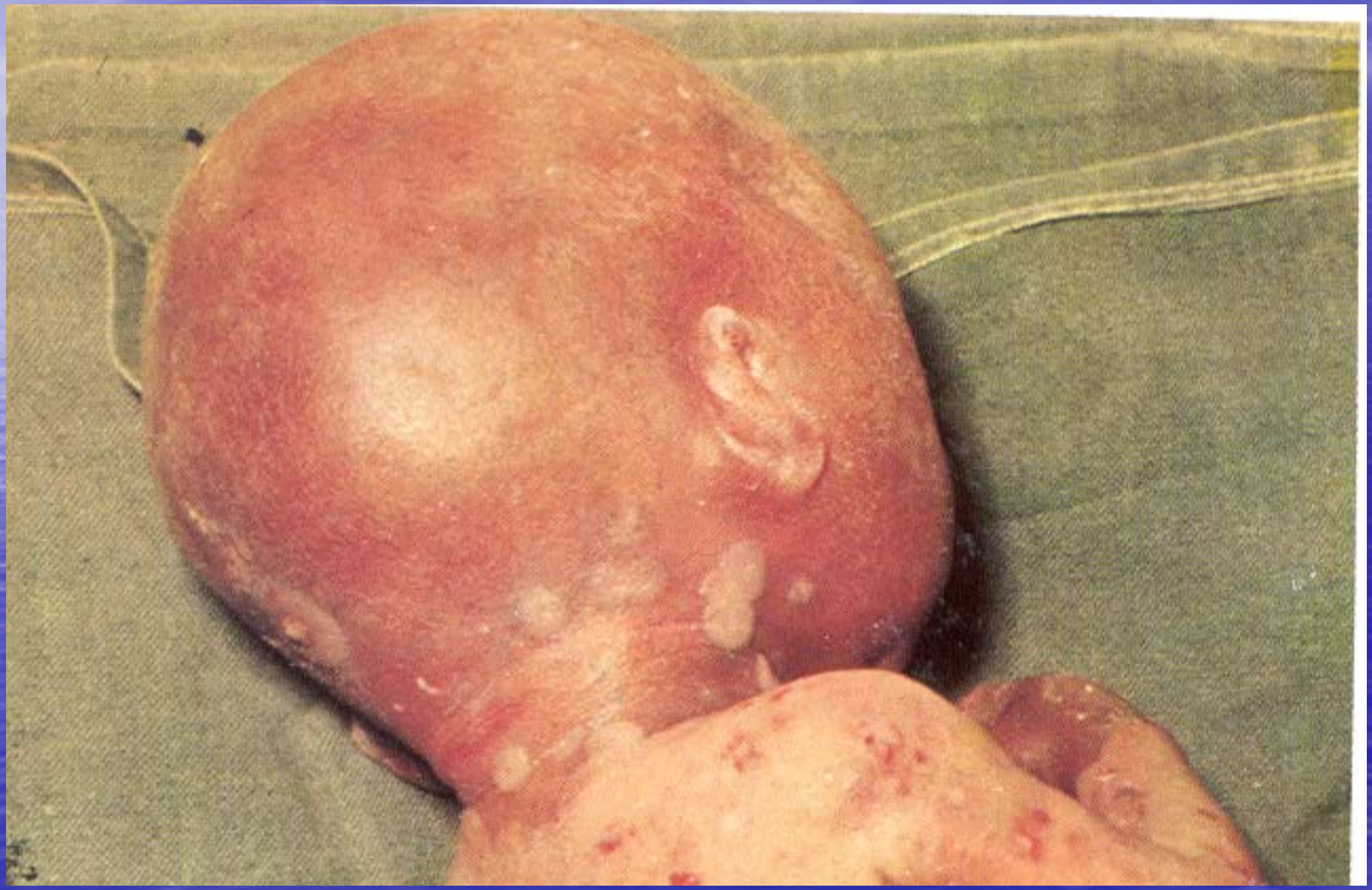
Eczema vaccinatum



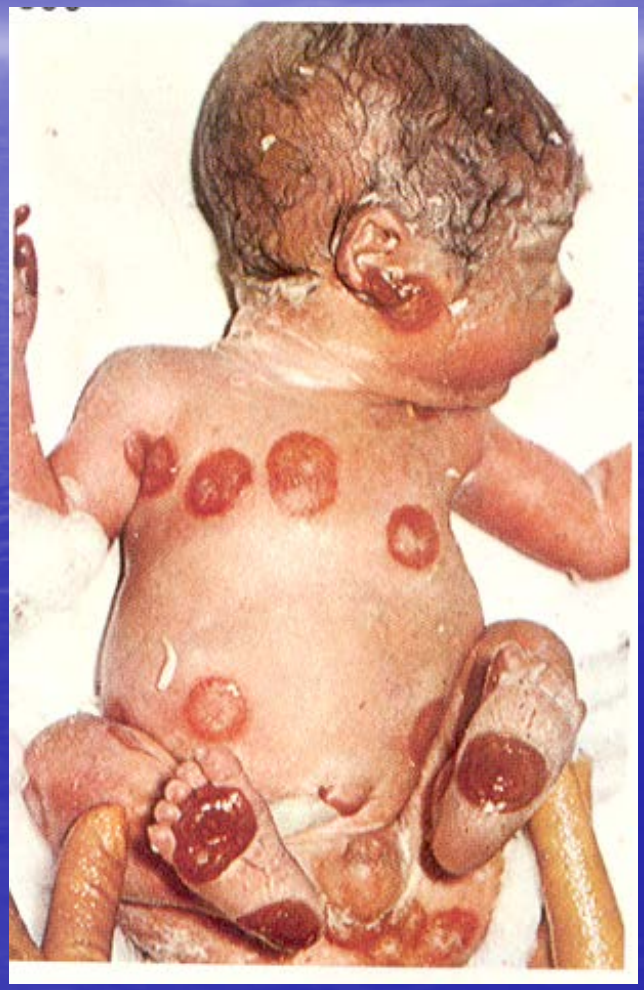
Eczema vaccinatum



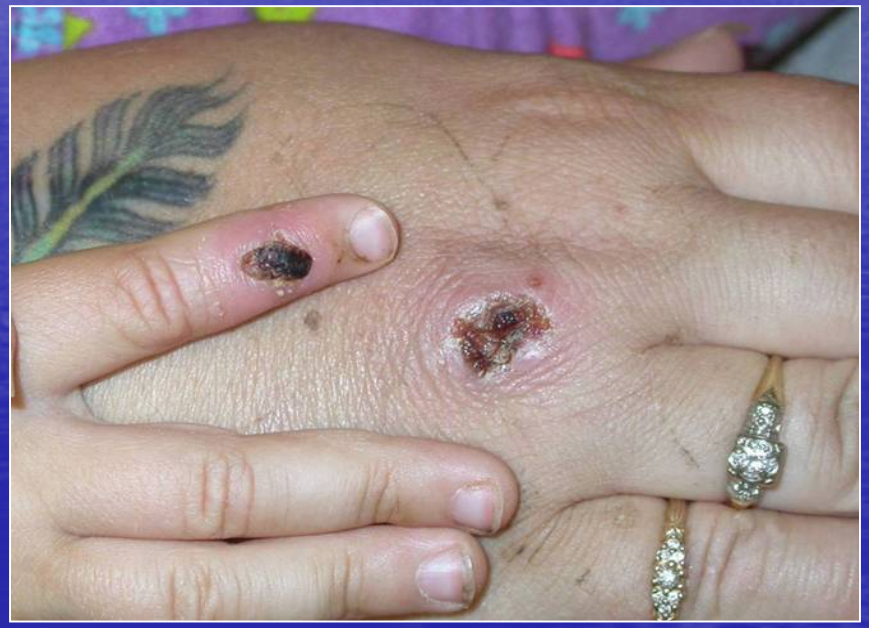
Vaccinia infection of the foetus



Congenital vaccinia infection

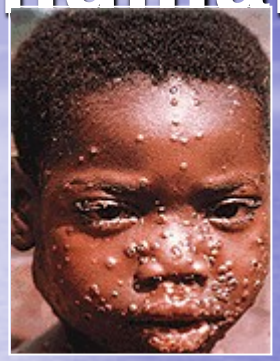


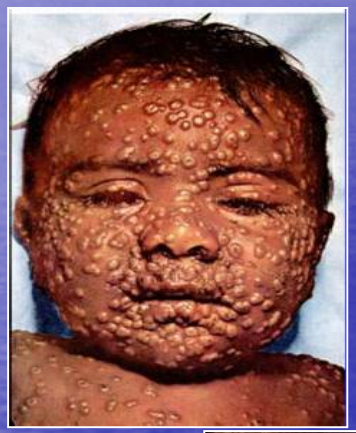
Did Smallpox hit the USA in May 2003?

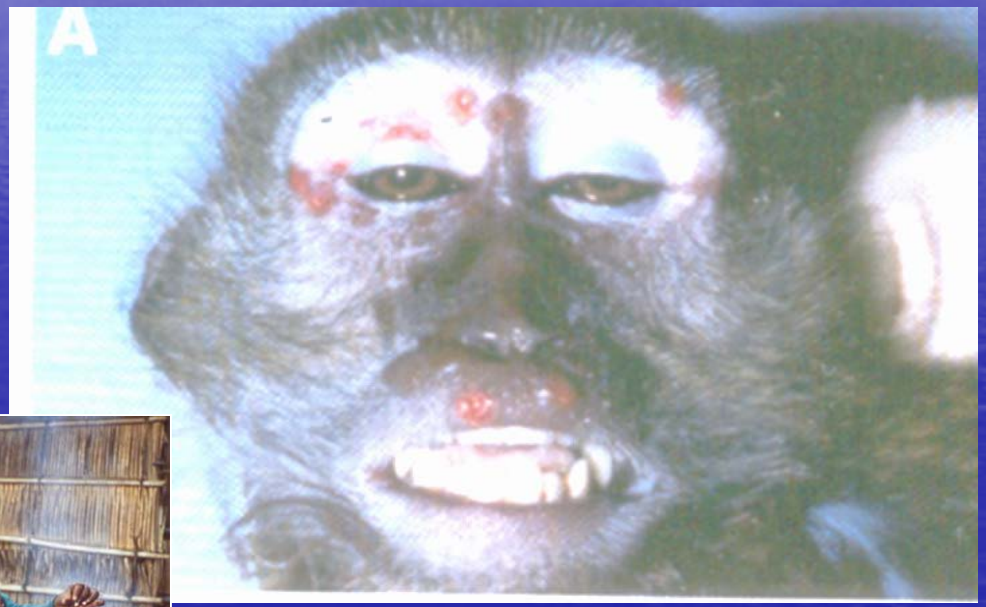


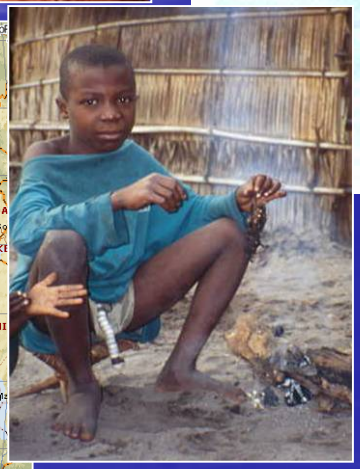
Fortunately not! It was Monkeypox

Monkeypox in monkeys and humans in West and Central Africa









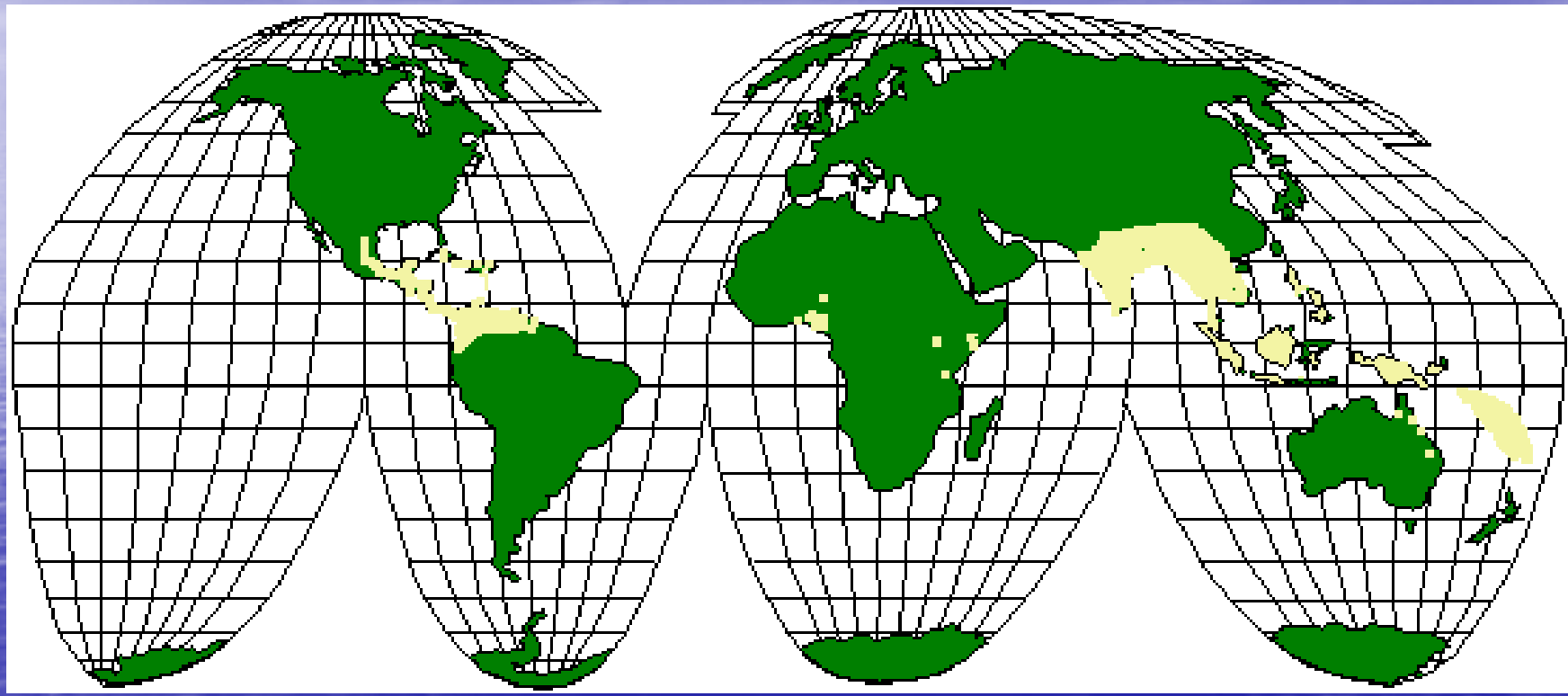
Dengue fever 1.

- Although not a new disease, dengue fever represents a serious emerging infectious disease that can have dire consequences, including death.
- Recent epidemics and the 1998 pandemic, in which more than 1.2 million cases of dengue fever and dengue hemorrhagic fever (DHF) were reported to the World Health Organization (WHO) from 56 countries, have resulted in dengue fever becoming a major international health concern.

Dengue fever 2.

- Major epidemics of dengue-like illnesses have been reported in the Americas, southern Europe, North Africa, the eastern Mediterranean, Asia, and Australia, as well as the islands in the Indian Ocean, the south and central Pacific Ocean, and the Caribbean as far back as the latter part of the eighteenth century.

Distribution of dengue



Dengue Virus

- The dengue viruses are members of the *Flaviviridae* family.
- Four antigenically related but distinct serotypes, designated DENV-1, DENV-2, DENV-3, and DENV-4, have been described.
- Like other flaviviruses, they have a single-stranded RNA genome surrounded by an icosahedral scaffold and covered by a lipid envelope.

Transmission

- The dengue viruses are transmitted to humans by the bite of infective female mosquitoes of the genus *Aedes*.
- Although the most efficient epidemic vector is *Ae. aegypti*, *Aedes albopictus* and *Aedes polynesienses* also are involved in outbreaks of dengue.
- Among factors implicated in the resurgence of dengue globally are failure to control the *Aedes* population, increased air travel to and from endemic areas, uncontrolled urbanization, and an unprecedented population growth, along with other features such as El Niño.7

Aedes aegypti

Clinical Features

- Each of the four dengue virus serotypes causes a spectrum of diseases ranging from mild infection to a potentially deadly disease.

Dengue fever 1.

- Dengue fever is a severe, flu-like illness that affects infants, children, adolescents, and adults.
- The incubation period for dengue fever after the mosquito bite occurs is between 3 and 8 days.
- The clinical features vary according to the age of the patient.
- Infants and young children usually have only a nonspecific febrile illness, with a rash that is hard to distinguish from other viral illnesses.

Dengue fever 2.

- The more severe cases usually occur in older children and adults and are characterized by a rapidly rising temperature (39°C) that lasts approximately 5 to 6 days and sometimes may be biphasic.
- During the febrile period, the patient may experience severe headache, retro-orbital pain, myalgia, arthralgia, nausea, and/or vomiting.

Dengue fever 3.

- More than half of infected patients report having a rash during this period that initially is macular or aculopapular and becomes diffusely erythematous.
- Minor hemorrhagic manifestations such as petechiae, epistaxis, and gingival bleeding occur.
- Severe hemorrhage is an unusual occurrence.
- Although dengue fever may be incapacitating, its prognosis is favorable and the patient generally recovers after having 7 to 10 days of illness.

DHF and Dengue Shock Syndrome (DSS) 1.

- DHF is an acute febrile illness with hemorrhagic manifestations, thrombocytopedia (100,000 cells/mm3), and evidence of an increased vascular permeability that results in loss of plasma from the vascular compartment.
- Hypoproteinanemia, an elevated hematocrit, and evidence of serous effusion are indicators of plasma leakage, which, if it becomes critical, may result in DSS.

DHF and Dengue Shock Syndrome (DSS) 2.

- DSS is defined by the WHO as DHF with circulatory failure as manifested by a rapid, weak pulse with narrowing of the pulse pressure (20 mm Hg, regardless of pressure levels; eg, 100/90 mm Hg) or hypotension with cold, clammy skin and restlessness.
- Death can occur within 12 to 24 hours, or the patient may recover quickly after receiving appropriate volume replacement therapy.

Treatment

- No specific treatment for dengue fever exists.
- Careful management of clinical symptoms and appropriate intensive supportive care has reduced the mortality rate to 1 percent.
- The central feature of management is maintenance of circulating fluid volume.

Yellow fever 1.

- Yellow fever is the original viral haemorrhagic fever (VHF), a pansystemic viral sepsis with viraemia, fever, prostration, hepatic, renal, and myocardial injury, haemorrhage, shock, and high lethality. In recent years, popular attention has been drawn to another VHF—Ebola—as the most frightening emerging infection of humankind.
- However, patients with yellow fever suffer as terrifying and untreatable a clinical disease, and yellow fever is responsible for 1000-fold more
- illness and death than Ebola.

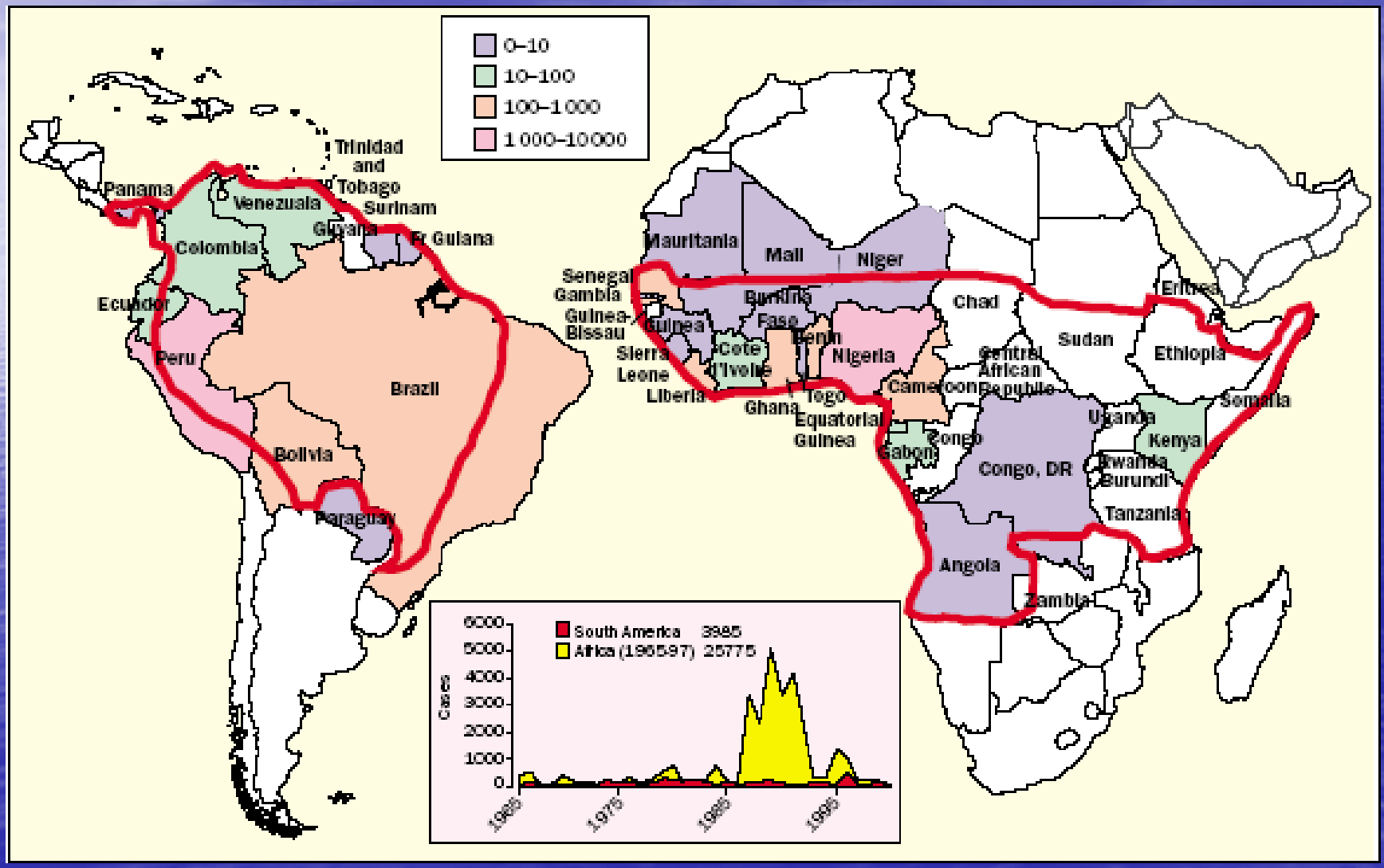
Yellow fever 2.

- Yellow fever virus is the prototype of the genus Flavivirus (family Flaviviridae) which comprises approximately 70 viruses, most of which are arthropod-borne.
- The earliest description of yellow fever is found in a Mayan manuscript in 1648, but by genome sequence analysis it appears that yellow fever virus evolved from other mosquito-borne viruses about 3000 years ago, probably in Africa from where it was imported to the New World during the slave trade.

Causative agent

- Flaviviruses are positive-sense, single-stranded RNA viruses—obligate intracellular pathogens that replicate in the cytoplasm of infected cells.
- The yellow fever genome contains a single open-reading frame of 10 233 nucleotides encoding three structural and seven onstructural (NS) proteins, flanked by short non-coding regions.
- Yellow fever virus is a single serotype.
- At the sequence level, five genotypes can be distinguished (three in Africa,and two in South America).

The distribution of YF



Incidence and epidemiology

- Yellow fever occurs in tropical regions of Africa and South America.
- Fortunately, the virus has never emerged in Asia, and vaccination for travel is not indicated here.
- Asia is considered vulnerable to the future introduction of the virus, due to the presence of a large susceptible human population and presence of the urban vector, *Aedes aegypti*.
- Possible explanations for absence of the disease in Asia include cross-protection afforded by hyperendemic dengue, low competence of local populations of *Ae aegypti*, and occurrence of yellow fever in remote areas in people who do not travel by air and are unlikely to spread the infection.

Transmission cycle

- Yellow fever is a zoonotic infection, maintained in nature by wild non-human primates and diurnally active mosquitoes that breed in tree holes in the forest canopy.
- People are sporadically exposed to infected mosquitoes when they encroach on this cycle during occupational or recreational activities (“jungle yellow fever”).

Transmission cycle

- In the moist savanna regions of Africa (the so called "zone of emergence"), tree-hole-breeding *Aedes* species mosquitoes reach very high densities and are implicated in endemic and epidemic transmission, transferring virus from monkey to people and between people.
- *Aedes aegypti*, a domestic mosquito that breeds in man-made containers, may transmit yellow fever virus between human beings ("urban yellow fever").
- The virus is maintained over the dry season by vertical transmission in mosquitoes.
- Ova containing virus survive in dry tree-holes and hatch infectious progeny mosquitoes when the rains resume.

The disease 1.

- Despite intense study, relatively little is known about the disease beyond purely descriptive accounts.
- In part, this is due to the occurrence of the disease in remote areas without access to sophisticated medical care.
- Although the human disease can be modelled quite precisely in non-human primates, virtually no research on its pathogenesis has been conducted in the past 20 years.

The disease 2.

- The clinical disease varies from non-specific, abortive illness to fatal haemorrhagic fever.
- The incubation period after the bite of an infected mosquito is 3–6 days.
- Disease onset is typically abrupt, with fever, chills, malaise, headache, lower back pain, generalised myalgia, nausea, and dizziness.
- On physical examination the patient is febrile and appears acutely ill, with congestion of the conjunctivae and face and a relative bradycardia with respect to the height of fever (Faget's sign).

The disease 3.

- Virus is present in blood at titres up to 10^5–10^6 infectious particles/mL, and the patient may thus serve as a source of infection for mosquitoes.
- The average fever is 39o C and lasts 3·3 days.
- Young children may experience febrile convulsions.
- Laboratory abnormalities include leukopenia (1·5–2·5 x 10^9/L) with a relative neutropenia.
- Between 48 and 72 h after onset and before the appearance of jaundice, serum transaminase levels may rise.

The disease 4.

- This so-called “period of infection” lasts several days and may be followed by a “period of remission”, with the disappearance of fever and symptoms lasting up to 24 h.
- During the period of remission, virus is cleared by antibodies and the cellular immune response.
- The blood may contain non-infectious immune complexes detectable by immunoassays or PCR.
- Patients with abortive infections may recover at this stage, without further signs or symptoms.

The disease 5.

- In approximately 15–25% of people affected, the illness reappears in a more severe form (the so-called “period of intoxication”) with fever, vomiting, epigastric pain, jaundice, renal failure, and a haemorrhagic diathesis.
- Serum transaminase levels rise and jaundice deepens, the direct bilirubin concentrations reaching 171–257 mol/L.
- Interestingly, serum aspartate aminotransferase (AST) concentrations often exceed alanine aminotransferase (ALT), presumably due to direct viral injury to myocardium and skeletal muscle.
- Serum transaminase levels reflect disease severity.
- In one study, AST and ALT concentrations were 2766 IU/L and 660 IU/L, respectively, in fatal cases, while in survivors with jaundice the mean concentrations were 929 IU/L and 351 IU/L, respectively

The disease 6.

- Protein concentrations in urine range between 3 and 20 g/L, urine volume diminishes, and serum creatinine rises to 265–1061 mol/L.
- Haemorrhagic manifestations include petechiae, ecchymoses, epistaxis, and oozing of blood from the gums and at needle puncture sites. In many cases there is major bleeding, coffee-grounds haematemesis, melaena, or metrorrhagia.
- Laboratory abnormalities include thrombocytopenia, prolonged clotting and prothrombin times, reduced fibrinogen and factors II, V, VII, VIII, IX, and X, and the presence of fibrin split products.

The disease 7.

- Platelet dysfunction, demonstrated by collagen and ADP stimulated aggregation, has been demonstrated in the monkey model.
- Myocardial injury is manifest by ST-T wave abnormalities on the electrocardiogram, and occasionally by acute cardiac enlargement.
- 20–50% of patients with hepatorenal disease die, typically 7–10 days after onset.
- Events preceding death include hypotension—an increasingly difficult symptom to manage with fluids and vasopressors.

The disease 8.

- Patients also experience agitated delirium, stupor, coma, Cheyne-Stokes respirations, metabolic acidosis, hyperkalaemia, hypoglycaemia, and hypothermia.
- The cerebrospinal fluid is under increased pressure, with raised albumin but no increase in white blood cells, which is consistent with cerebral oedema.
- Pathological changes in the brain include microscopic perivascular haemorrhages and oedema.
- True yellow fever viral encephalitis due to viral infection of brain tissue (as opposed to encephalopathy) is very rare.

Acute phase

Host range, pathogenesis, and pathophysiology

- The extreme lethality of yellow fever virus is evident when one considers that the 50% lethal dose for monkeys is less than 1 plaque forming unit.
- Fixed macrophages (Kupffer cells) in the liver are infected 24 hours after inoculation. Infection of the kidney, bone marrow, spleen and lymph nodes follow.
- Infection and degeneration of hepatocytes is a relatively late event, occurring in the last 24–48 h before death in the monkey and in the last phase of infection in people.

Host range, pathogenesis, and pathophysiology

- The infected hepatocyte undergoes eosinophilic degeneration with condensed nuclear chromatin (Councilman bodies) typical of apoptotic cell death and distinct from the ballooning and rarefaction necrosis seen in viral hepatitis.
- Apoptosis has been documented as a late event in human hepatoma cells infected with yellow fever virus.
- Hepatic injury from apoptosis rather than necrosis explains the virtual absence of inflammatory cells in yellow fever, preservation of the reticulin framework, and healing without fibrosis.

Treatment

- There is no specific antiviral treatment.
- Ribavirin failed in several studies in the monkey model.
- Passive antibody, the interferon inducer poly(I-poly(C), or interferon- are effective only before or within hours after infection, and these have no value except for early post-exposure prophylaxis in an individual (eg, laboratory worker) with known exposure.
- Corticosteroids have not been evaluated in treatment of yellow fever.
- Intensive supportive care may not rescue the patient with yellow fever from the inexorable course of fatal infection.

Treatment

- Some years ago, an expert panel recommended the following: maintenance of nutrition and prevention of hypoglycaemia; nasogastric suction to prevent gastric distension and aspiration; intravenous cimetidine to prevent gastric bleeding; treatment of hypotension by fluid replacement and vasoactive drugs (dopamine); administration of oxygen; correction of metabolic acidosis; treatment of bleeding with fresh-frozen plasma; dialysis if indicated by renal failure; and treatment of secondary infections with antibiotics.

Prevention of yellow fever

- A certificate of vaccination is required under the International Health Regulations for entry into yellow fever endemic countries or travel from endemic countries to *Ae aegypti*-infested countries at risk of introduction.
- Information on vaccination requirements can be obtained from travel clinics and the CDC website (www.cdc.gov/travel/reference.htm).
- Despite the legal requirement for a valid certificate, enforcement is lax in many countries.
- Yellow fever 17D is a highly effective, well-tolerated live, attenuated vaccine that has been used for over 60 years in approximately 400 million people.
- Routine use of the vaccine in children in endemic countries has a favourable cost-benefit ratio.


YELLOW FEVER
Santa Cruz, Bolivia

Lassa fever 1.

- The Lassa fever virus is a member of the Arenaviridae family.
- It is a single-stranded RNA virus and is zoonotic (carried by animals) with the multi-mammate rat the main vector for disease spread.
- The disease was first identified in Nigeria (Lassa town)and several hundred thousand cases still present annually in West Africa.
- Areas particularly affected include Guinea, Liberia, Sierra Leone and regions of Nigeria.

Lassa fever 2.

- Of the cases that require hospitalization 15% (1% of the total case load) will die as a result of the illness though outbreaks have been reported with mortalities nearer 60%.
- This amounts to about 5000 deaths per year emphasizing the serious impact the disease has in affected parts of the world.

Lassa fever 3.

- Lassa fever presents between 7 and 21 days following exposure to the virus.
- The virus is carried by rats from which it is shed in the urine and faeces, and it is direct or indirect contact with these sources that results in disease transmission to humans.
- Transmission has been reported as a result of inhalation of tiny particles contaminated by rat excretions.

Lassa fever 4.

- Once contracted by a human, person-to-person spread
- Viral haemorrhagic fevers an occur through direct contact with body fluids (including sexual contact) or with equipment contaminated with such fluids.
- Significantly the virus may be excreted in patients' urine for up to nine weeks.
- Skin-to-skin contact does not result in spread, however by the nature of the transmission characteristics, spread of the disease can and does occur commonly amongst healthcare workers caring for patients with the disease.

Lassa fever 5.

- This has been a particular problem due to many of the hospitals in endemic regions lacking disposable gowns, gloves and masks and having inadequate sterilization equipment.
- Presentation is often non-specific with fever, malaise, arthralgia, and diarrhoea and vomiting, cough, sore throat and bleeding from mucosal membranes.
- In severe cases multiple organ dysfunction may ensue with hypotension, pleural effusions, convulsions and head and neck oedema occurring commonly.

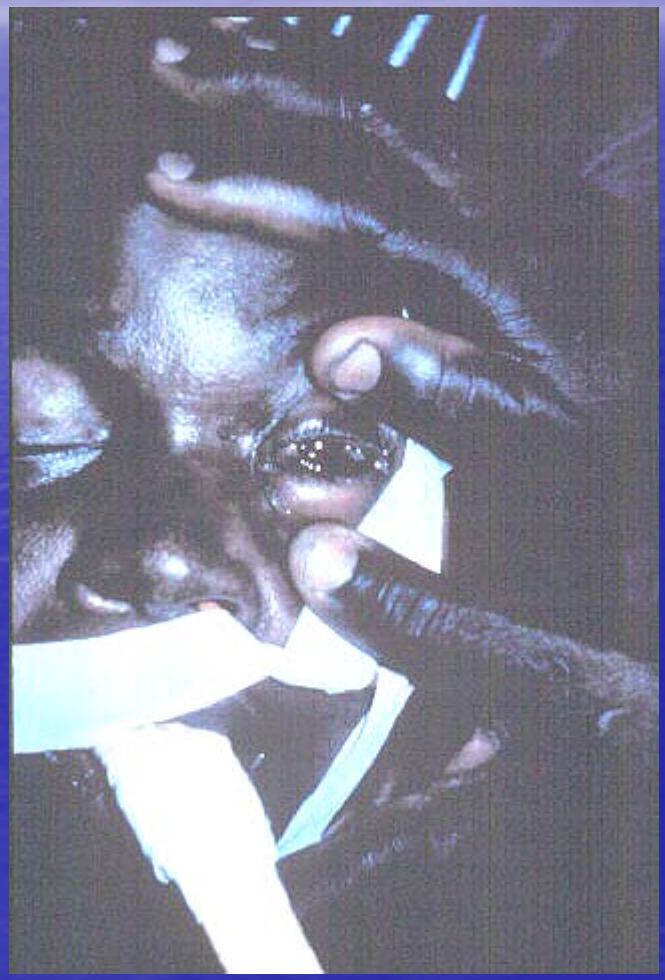
Lassa fever 6.

- The presence of symptoms and signs such as these in a patient who has visited an endemic country or been in contact with someone with similar symptoms (dead or alive) during the previous three weeks should prompt the clinician to consider Lassa fever in the differential diagnosis.
- Laboratory diagnosis is most commonly made using enzyme-linked immunosorbent assay (ELISA) although immuno-histochemistry may reveal post-mortem diagnoses.

Lassa fever 7.

- Treatment
  - As with all the life-threatening VHFs treatment is predominantly supportive although, in the case of Lassa fever, Ribavirin therapy has been used successfully with the greatest benefit achieved with early therapy.
  - Multi-organ dysfunction can occur with severe cases and such patients will require management in the critical care unit as detailed above.

Oedema and conjunctivitis (Lassa fever)



Ebola haemorrhagic fever

- The Ebola virus has resulted in 50–90% mortality during outbreaks making it one of the most virulent and dangerous viruses known to mankind.
- It first appeared during simultaneous outbreaksin Sudan and Zaire in 1976 but has since been reported in Gabon, Sudan, the Ivory Coast, Uganda and the Republic of the Congo though transmission in humans has not been maintained.

Ebola haemorrhagic fever 2.

- Filoviridae family, the other being the equally virulent Marburg virus.
- Despite progress in the understanding of the virus, neither the natural reservoir nor the trigger for its re-emergence during human outbreaks has been identified.
- Given the zoonotic nature of similar viruses, it seems likely that the virus is maintained in nature by an animal host native to the African continent.

Ebola haemorrhagic fever 3.

- Of interest, a seasonal emergence of the virus has been found in the great apes, civet cats and several other bush species.
- Such animals are a source of bush meat for local hunters who acquire the meat during the rainy seasons.
- Some of this meat is used for local consumption however there is an increasing international market for such meat that may travel long distances and could potentially act as a viral reservoir.

Ebola haemorrhagic fever 4.

- Transmission may occur by contact with body fluids or tissue from living or dead carriers of the virus.
- Healthcare staff have been involved in significant numbers during past outbreaks, with two-thirds of the deaths during the 1995 outbreak in Kikwit being amongst health workers.
- Contaminated needles have been implicated in a number of these cases.
- Airborne spread has not been reported and those living in close quarters to infected individuals have not been shown to be at increased risk.

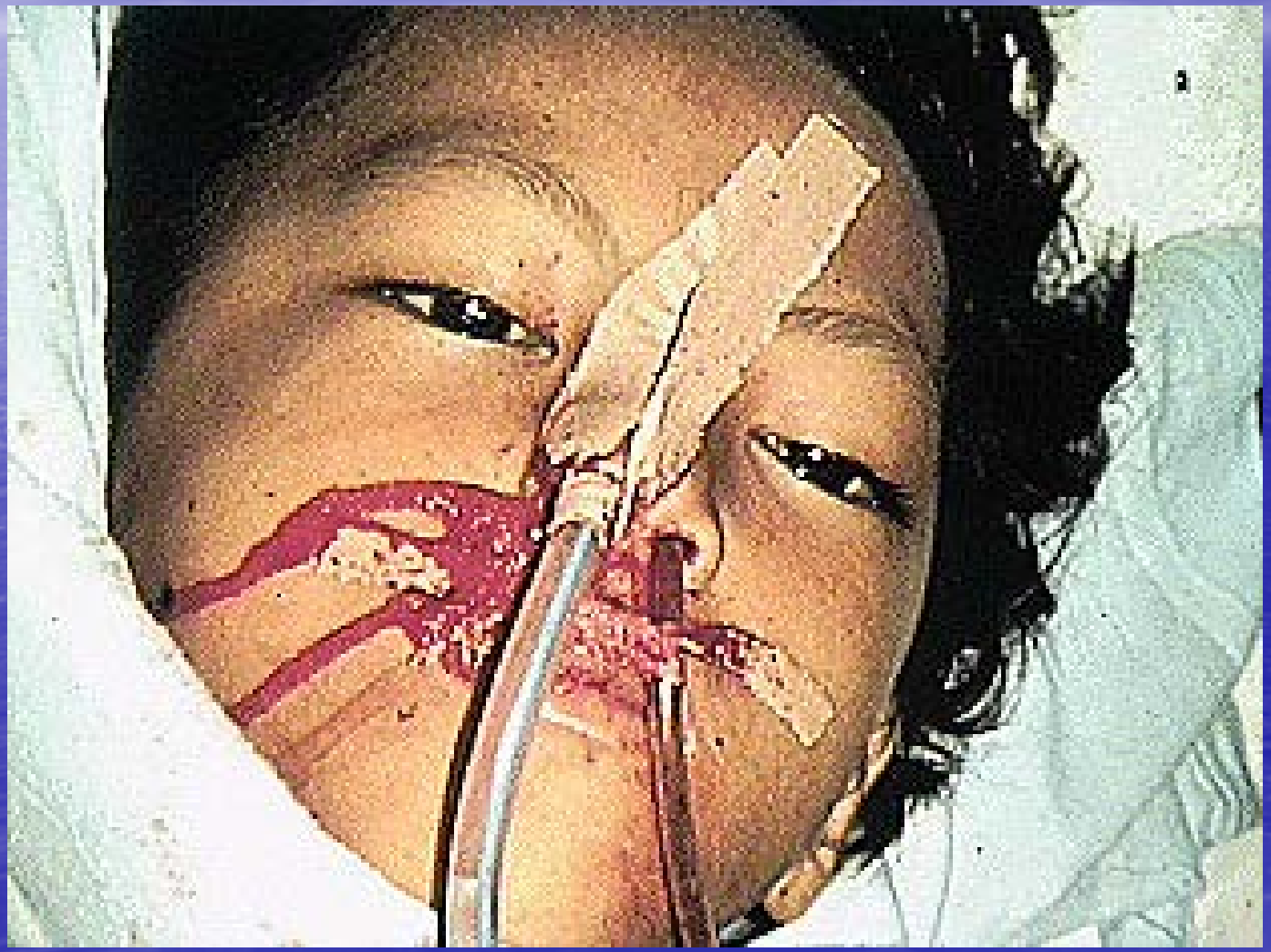
Ebola haemorrhagic fever 5.

- The incubation period for the human disease is between 2 and 21 days, with most cases presenting between 1 and 2 weeks after initial exposure.
- Symptoms include sudden onset of fever, myalgia, weakness, sore throat and headache followed by vomiting, bloody diarrhoea, rash, renal and liver dysfunction, and both internal and external bleeding.
- Laboratory diagnosis requires specialized equipment that detects viral antigens or genes, isolates the virus in cell culture or identifies antibodies.

Ebola haemorrhagic fever 6.

- In the event of a patient exhibiting symptoms or signs of haemorrhagic fever the general measures detailed above should immediately be instituted.
- In the meantime detailed history of possible exposure including foreign travel and contact with other hospitalized patients should be ascertained in order to assess the likelihood that the patient may have contracted a viral haemorrhagic fever.
- Treatment is based on organ support as detailed above.

Ebola vírus



Marburg haemorrhagic fever 1.

- Marburg virus was the first of the filoviridea family to be recognized.
- It was identified in 1967 when a number of laboratory workers in Germany developed haemorrhagic fever following the handling of tissues from green monkeys.
- It is a rare type of haemorrhagic fever that, like Ebola, has appeared sporadically over the past four decades and for which the natural reservoir has yet to be identified.

Marburg haemorrhagic fever 2.

- Although the initial identification of the virus was made in Europe, the monkeys who had acted as the vector had been transported from Uganda, and all the outbreaks since have been in Africa with cases reported in Kenya, Uganda, Zimbabwe, South Africa, urba and the Democratic Republic of the Congo.

Marburg haemorrhagic fever 3.

- As with Ebola virus, the animal host for Marburg is unknown however once human infection has occurred, person-to-person spread can occur through contact with body fluids and tissue.
- Droplets of body fluids have been suspected as the source of spread in some cases.
- The reported mortality is less than with Ebola though still significant at about 25%.
- Those at risk of the illness include those in close contact with infected patients, including health care workers, and laboratory and quarantine facility workers who have handled non-human primates associated with the disease.

Marburg haemorrhagic fever 4.

- Once infected, the incubation period is between 5 and 10 days following which symptoms of fever, malaise, and nausea and vomiting, abdominal pain, sore throat, diarrhoea and a rash may develop.
- As with the other severe haemorrhagic fevers, the disease may progress to fulminant multiple organ failure.
- Laboratory diagnosis is usually by ELISA however several techniques are available for post-mortem diagnosis.

Marburg haemorrhagic fever 5.

- Meticulous attention should be given to the general measures detailed above and supportive care should be provided.
- Ribavirin has not been shown to be of benefit though given the difficulties differentiating the haemorrhagic fevers clinically and the time that can lapse before definitive diagnosis, therapy should be considered for the patient and close contacts.
- A number of complications following recovery from Marburg virus have been reported including hepatitis, transverse myelitis and orchitis.
- No vaccine exists at the time of writing.

2005 Outbreak in Angola

- Between October 1, 2004, and March 29, 2005, a total of 124 cases were identified, of which 117 were fatal.
- All of the cases had originated in Uige Province. Approximately 75 percent of the reported cases had occurred in children aged 5 years or younger.
- By April 6, 156 people were reported dead, and working conditions were extremely difficult for healthcare providers, who were facing a huge challenge.
- Swathed in head-to-toe protective medical gear that requires half an hour to put on and 45 minutes to remove, physicians were contending with extreme heat as well as a feeling of helplessness, knowing that there is no cure for the disease

Bacterial infections in the tropics

- Leprosy:
  - Leprosy is a chronic granulomatous infection of the skin and peripheral nerves with the intracellular bacterium *Mycobacterium leprae*.
  - The damage to peripheral nerves results in sensory and motor impairment with characteristic deformities and disability.
  - Leprosy was once widely distributed in Europe and Asia but now occurs mainly in resource-poor countries in tropical and warm temperate regions.
  - However, patients may present with the disease long after leaving an endemic region, and clinicians must be able to recognise it.

Leprosy 2.

- The fact that the organism cannot be grown in culture has hindered studies in vitro, and clinical trials are difficult in this slowly progressive, chronic infection.
- Over the past 5–10 years, however, there have been major advances in understanding of the biology of both *M leprae* and the host response to the organism, and more than 11 million patients have been treated with multi-drug therapy (MDT).

Epidemiology of leprosy

- During the 1990s a bold, ambitious leprosy elimination campaign was launched, after the adoption by the World Health Assembly of the goal of the “elimination of leprosy as a public health problem by the year 2000”.
- Elimination was defined as a reduction in the prevalence of leprosy patients receiving antimicrobial therapy to less than 1 per 10 000 population.
- The rationale for this definition lay in the recognition that combination antibiotic therapy was highly effective and the assumption that once the pool of infectious patients was reduced, the disease would gradually disappear.

Epidemiology of leprosy

- The MDT regimens were very effective both for individual patients and in leprosy control programmes and were widely implemented.
- In 1985, there were an estimated 12 million people with leprosy worldwide, a prevalence of 12 per 10 000.
- In 2002, WHO reported that there were 597 000 registered cases and 719 000 new cases detected during 2000, resulting in a global prevalence of registered leprosy patients of just below 1 per 10 000.

Epidemiology of leprosy

- 15 endemic countries still have a prevalence of more than 1 per 10 000, mainly in Asia, Africa, and South America, but 107 of the 122 countries endemic for leprosy in 1985 have reached the elimination target.
- There is a concentration of 83% of the registered cases in only six countries: India, Brazil, Burma,Indonesia, Madagascar, and Nepal, with India accounting for 64% of all leprosy cases worldwide.
- Leprosy also shows clustering to limited geographical regions or ethnic groups within a country.

Epidemiology of leprosy at 2005.

Country	Prevalence cases 1-Jan-02	Prevalence rate per 10,000	Cases detected in 2001	Detection rate per 100,000
India	439,782	4.3	617,993	60.1
Brazil	77,676	4.5	41,070	23.8
Nepal	10,657	4.4	13,830	56.5
Mozambique	6,775	3.4	5,713	28.5
Angola	4,115	3.1	2,540	19.1
Myanmar	8,237	1.8	9,684	21
Total(World)	635,404	1	763,315	12.3

Leprosy

- The main consequence of leprosy infection for patients is the disability secondary to impairment of nerve function.
- The proportion of new patients with visible disability, such as skin ulceration or muscle wasting and contracture, varies between countries and is affected by the type of leprosy and delay in diagnosis.
- An estimated 3 million leprosy patients have completed MDT and have sustained disability from nerve damage; these patients need continuing care to limit further secondary damage.

Leprosy

- Leprosy shows a wide range of clinical presentations from tuberculoid through borderline forms to lepromatous, classified by Ridley and Jopling largely on pathological grounds, but later confirmed by immunological analysis.
- The incubation period between infection and overt disease varies widely from months to 30 years, and the mean is estimated to be 4 years for tuberculoid and 10 years for lepromatous leprosy.
- A low rate of leprosy transmission can continue for many decades, as shown by the appearance of new cases in regions of South Africa with longstanding control programmes.

Leprosy transmission 1.

- The principal means of transmission of *M leprae* is probably by aerosol spread of nasal secretions and uptake through nasal or respiratory mucosa.
- *M leprae* cannot traverse intact skin in either direction, and the infection is not spread by touching.
- Acid-fast mycobacteria and *M leprae* DNA are found in the nasal secretions of patients with lepromatous leprosy.17 *M leprae* DNA can also be detected in nasal swabs from up to 5% of healthy individuals in India and Indonesia, which suggests that subclinical infection occurs more frequently in these areas than previously thought.

Leprosy transmission 2.

- Proximity to leprosy patients is an important determinant of transmission.
- The relative risk for leprosy disease in household contacts is 8–10 for lepromatous disease and 2–4 for tuberculoid forms.
- As leprosy prevalence falls in a community, the relative importance of household transmission increases; this association might justify prophylactic therapy in family or other close contacts of leprosy patients.

Leprosy transmission 3.

- Immunity against *M leprae* depends on intact T-cell function, but in contrast to tuberculosis, coinfection with HIV has no strong effect on the development of clinical leprosy.
- Contrary to expectations early in the HIV epidemic, case-control studies have shown that HIV-1infection is not a risk factor for leprosy.
- Patients coinfected with HIV and leprosy have typical skin lesions and the usual patterns of leprosy histology and granuloma formation, even in the presence of low numbers of circulating CD4-positive T cells, and are at continued risk of developing immune-mediated reactions.

Biology of *M leprae*

- The completion of the genomic sequence of *M leprae* is a major advance, which will assist in elucidation of the unique biology of the organism.
- Previously, detailed studies on *M leprae* were prevented by the inability to grow the mycobacteria in culture.
- *M leprae* is an acid-fast gram-positive bacillus and an obligate intracellular parasite with tropism for macrophages and Schwann cells.

Biology of *M leprae*

- The bacilli show preference for growth in cooler regions of the body.
- The organism can replicate in the mouse footpad and the nine-banded armadillo, which have provided bacteria for study.
- The *M leprae* genome includes 1605 genes encoding proteins and 50 genes for stable RNA molecules.
- The unique predilection of *M leprae* for Schwann cells is probably determined by the mycobacterium's binding to the G domain of the 2 chain of laminin 2, which is a component of the basal lamina of Schwann cells.
- The Schwann cells can express HLA class 2 molecules and play an active part in the immunological reaction by presenting mycobacterial peptides to HLAclass-2-restricted CD4-positive T cells.
- Swelling within the inflexible perineurium leads to ischaemia, further nerve damage, and eventually fibrosis with axonal death.

Biology of *M leprae*

- The varying clinical forms of leprosy14 are determined by the underlying immunological response to *M leprae*.
- At one pole, patients with tuberculoid leprosy (TT) have a vigorous cellular immune response to the mycobacterium, which limits the disease to a few well-defined skin patches or nerve trunks.
- The lesions are infiltrated by interferon--secreting CD4-positive T lymphocytes,which form well-demarcated granulomas, containing epithelioid and multinucleate giant cells, around dermal nerves.
- Few, if any, acid-fast mycobacteria can be found in the lesions.

Biology of *M leprae*

- At the other pole, lepromatous leprosy (LL) ischaracterised by the absence of specific cellular immunity but intact immunity to the related *M tuberculosis*.
- There is therefore uncontrolled proliferation of leprosy bacilli with many lesions and extensive infiltration of the skin and nerves.
- The dermis contains foamy macrophages filled with many bacteria, but few CD4-positive and CD8-positive T lymphocytes and no organised granulomas.
- There are high titres of antibodies to PGL-I and protein antigens specific for *M leprae*, and mycobacterial antigens are readily identified in the urine and blood

Biology of *M leprae*

- Most patients have the intermediate forms of borderlinetuberculoid (BT), mid-borderline (BB), and borderlinelepromatous (BL) leprosy.
- These forms are characterised by a progressive reduction from BT to BL leprosy in cellular responses, associated with an increasing bacillary load, more frequent skin and nerve lesions, and higher antibody titres.
- The borderline forms are clinically unstable, and patients either show slow change towards the lepromatous pole or experience sudden type I or reversal reactions

Clinical features of disease

- Leprosy affects skin, nerves, and eyes, and causes systemic features in lepromatous disease.
- Patients commonly present with skin lesions, weakness or numbness caused by a peripheral-nerve lesion, or a burn or ulcer in an anaesthetic hand or foot.
- Borderline patients may present in leprosy reactions with nerve pain, sudden palsy, many new skin lesions, eye pain, or a systemic febrile illness.

Skin involvement

- The commonest skin lesions are macules or plaques; more rarely papules and nodules are seen.
- Lesions are hypopigmented in borderline-tuberculoid and tuberculoid leprosy and infiltrated with a raised edge.
- On pale skins, lesions can appear erythematous.
- In lepromatous leprosy, diffuse infiltration of the skin commonly occurs.
- Patients with tuberculoid disease have few, hypopigmented lesions with reduced sensation, whereas those with lepromatous forms have many lesions, confluent in some cases, and many of them are not hypoaesthetic.
- Inspection of the whole body in good light is important because otherwise lesions might be missed, particularly on the buttocks in borderline disease.
- Skin lesions should be examined for hypoaesthesia to light touch, pin-prick, and temperature and for anhidrosis.

Nerve damage 1.

- Damage to the nerves occurs in two settings—peripheral nerve trunks and small dermal nerves.
- Peripheral nerves are affected in fibro-osseous tunnels near the surface of the skin, including the great auricular nerve (neck), ulnar nerve (elbow), radial-cutaneous nerve (wrist), median nerve (wrist), lateral popliteal nerve (neck of the fibula), and posterior tibial nerve (medial malleolus).
- The posterior tibial nerve is the most commonly affected, followed by the ulnar, median, lateral popliteal, and facial nerves

Nerve damage 2.

- Involvement of these nerves produces enlargement, with or without tenderness, and standard regional patterns of sensory and motor loss.
- Small dermal sensory and autonomic nerves are affected producing hypoaesthesia and anhidrosis within borderlinetuberculoid and tuberculoid lesions and glove and stocking sensory loss in epromatous disease.
- Sensation on the hands and feet can be assessed and monitored by use of Semmes-Weins monofilaments.
- Pure neuritic leprosy presents with asymmetrical involvement of peripheral nerve trunks and no visible skin lesions.
- Histology of a cutaneous-nerve biopsy sample might reveal any type of leprosy.
- This form is seen most frequently, but not exclusively, in India and Nepal, where it accounts for 5–10% of patients.

Systemic features

- These features are seen mainly in lepromatous patients and are due to bacillary infiltration affecting nasal mucosa, bones, and testes.
- Testicular atrophy results from diffuse infiltration and the acute orchiitis that occurs with ENL reactions.
- The consequent loss of testosterone leads to azoospermia and gynaecomastia.
- Renal involvement and amyloidosis are now rarely seen with effective MDT.

Eye involvement

- Blindness resulting from leprosy is devastating for a patient with anaesthetic hands and feet.
- Eye damage results from both nerve damage and direct bacillary invasion.
- A recent cohort study found that 2·8% of multibacillary patients were blind at diagnosis and a further 11% had potentially blinding ocular pathology.

Diagnostic criteria for leprosy

- Diagnosis of leprosy is clinical and is based on patients having one or more of three cardinal signs (panel).
- The reliability of these signs has been extensively reviewed.
- Skin smears, taken to detect intradermal acidfast bacilli, have high specificity, but low sensitivity, because about 70% of all leprosy patients are smear negative.
- Nevertheless, skin smears are important because they identify the most infectious patients and those at greatest risk of relapse.
- Histological diagnosis, when available, is deemed the gold standard for diagnosis.
- The presence of neural inflammation histologically differentiates leprosy from other granulomatous disorders.

Treatment of leprosy

- Chemotherapy:
  - The first-line drugs against leprosy are rifampicin,clofazimine, and dapsone.
  - All patients should receive a multidrug combination with monthly supervision.
  - Current controversies focus on the length of treatment, the mode of treatment, and relapse rates.
  - Dapsone was the first effective antimicrobial agent against *M leprae.*
  - The multidrug combinations were introduced without formal clinical trials in the 1982 when rates of primary and secondary dapsone resistance of 30% were reported.

Treatment of leprosy

- Rifampicin is a potent bactericidal for *M leprae*.
- 4 days after a single 600 mg dose, bacilli from a previously untreated multibacillary patient are no longer viable in the mouse footpad test.
- Rifampicin acts by inhibiting the DNA-dependent RNA polymerase, and resistance is due to mutations in a small region of *rpoB.*
- Because *M leprae* resistance to rifampicin can develop as a one-step process, the drug should always be given in combination with other agents against leprosy.
- In untreated lepromatous patients, a single monthly dose of rifampicin (1200 mg) plus daily dapsone was as effective as daily rifampicin (450 mg) plus dapsone; thus, monthly rifampicin is satisfactory therapy.

Treatment of leprosy

- Clofazimine has a weakly bactericidal action, the mechanism of which is unknown.
- It also has an antiinflammatory effect that has reduced the incidence of ENL reactions.
- Skin discolouration is the most troublesome side-effect, ranging from red to purple-black.
- The pigmentation fades slowly in most cases after withdrawal of clofazimine.
- This drug also produces a characteristic icthyosis on the shins and forearms.

Treatment of leprosy

- Minocycline, the macrolide clarithromycin, and the fluoroquinolones pefloxacin and ofloxacin are all highly active against *M leprae* in mouse footpad infection and in patients, but because of their cost are rarely used in field programmes.
- They can, however, be used as second-line drugs in the case of dapsone allergy or if clofazimine pigmentation is challenging for the patient.
- Minocycline can also cause a long-lasting grey-black pigmentation of active leprosy lesions.

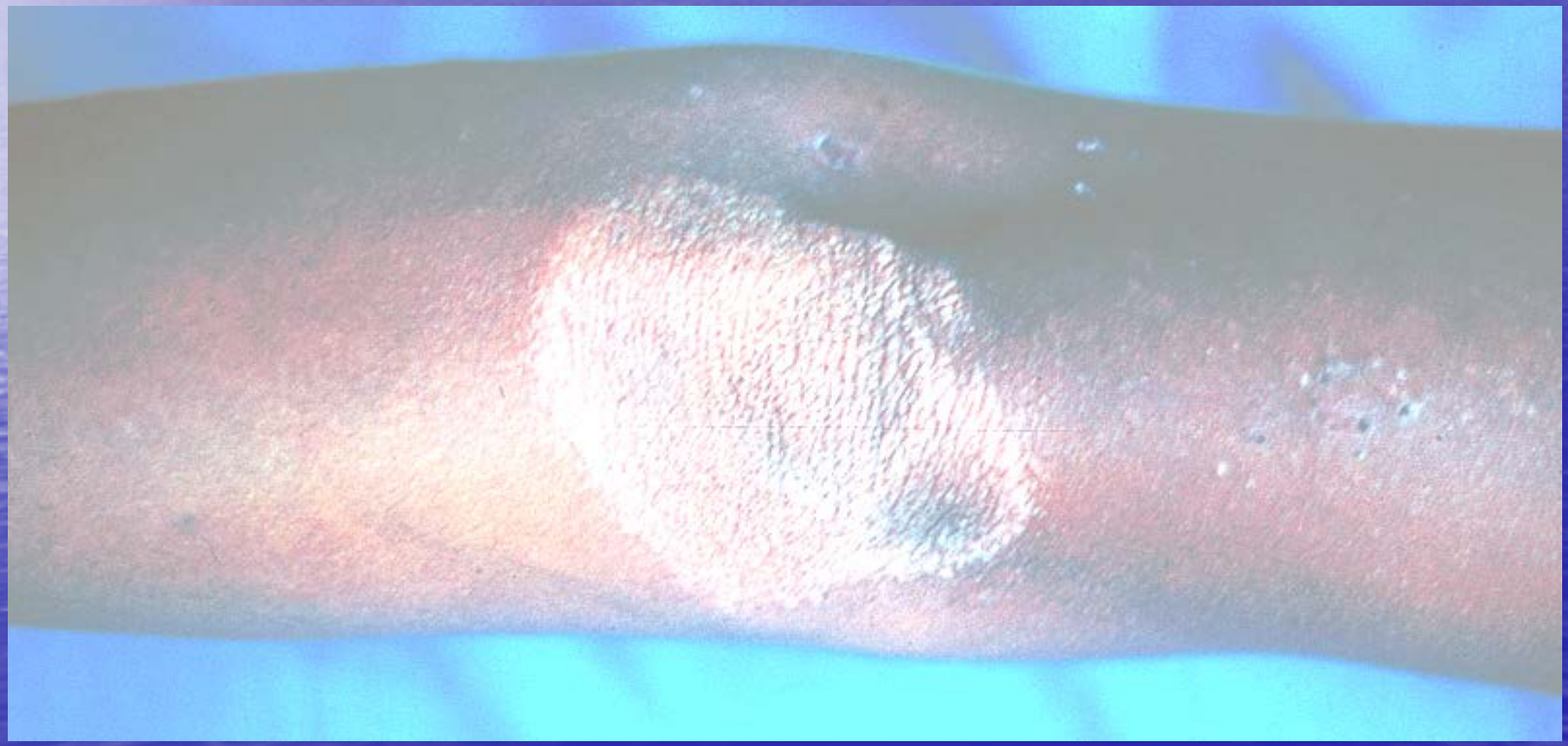
Treatment of leprosy

- The recommended duration of treatment for multibacillary patients has lately been reduced from 24 months to 12 months.
- There was no evidence from controlled trials to guide this decision, but the classification of multibacillary patients had been widened so that some patients who previously would have received paucibacillary treatment from 6 months were now receiving multibacillary treatment for 12 months.

Treatment of leprosy

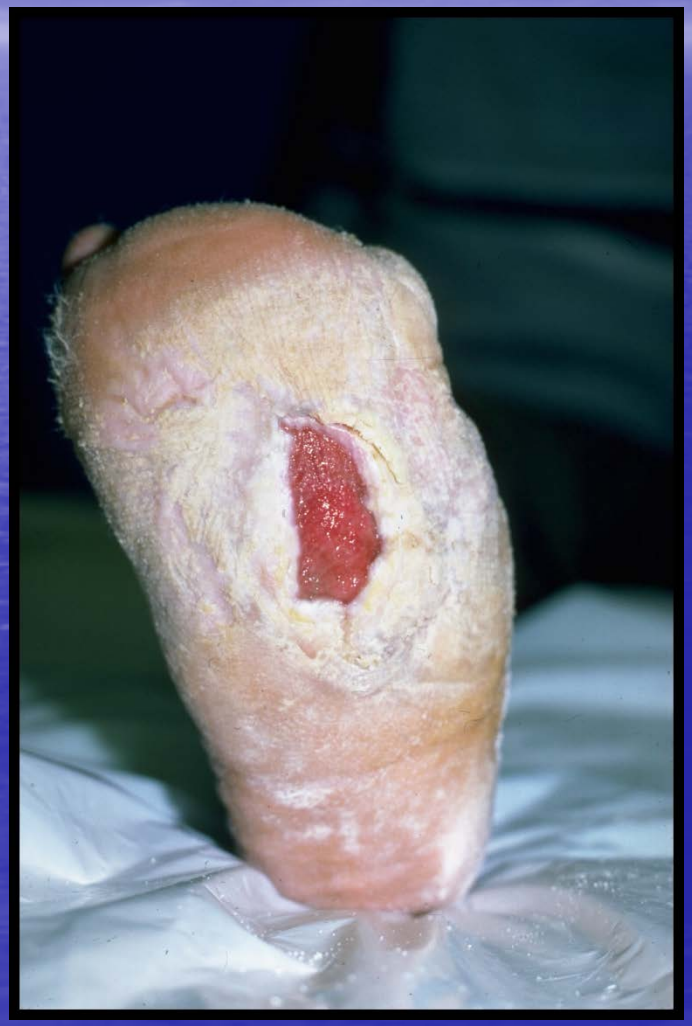
- The place of the drug combination rifampicin, ofloxacin, and minocycline is also unclear.
- It was recommended for single skin lesions, but it is less effective than the 6-month paucibacillary MDT regimen.
- Monthly doses of this regimen have been used in both paucibacillary and multibacillary disease with good clinical responses.
- Although there may be a good initial response to rifampicin, ofloxacin, and minocycline, the important issue is the relapse rate over the next 10 years.

Tuberculoid lepra

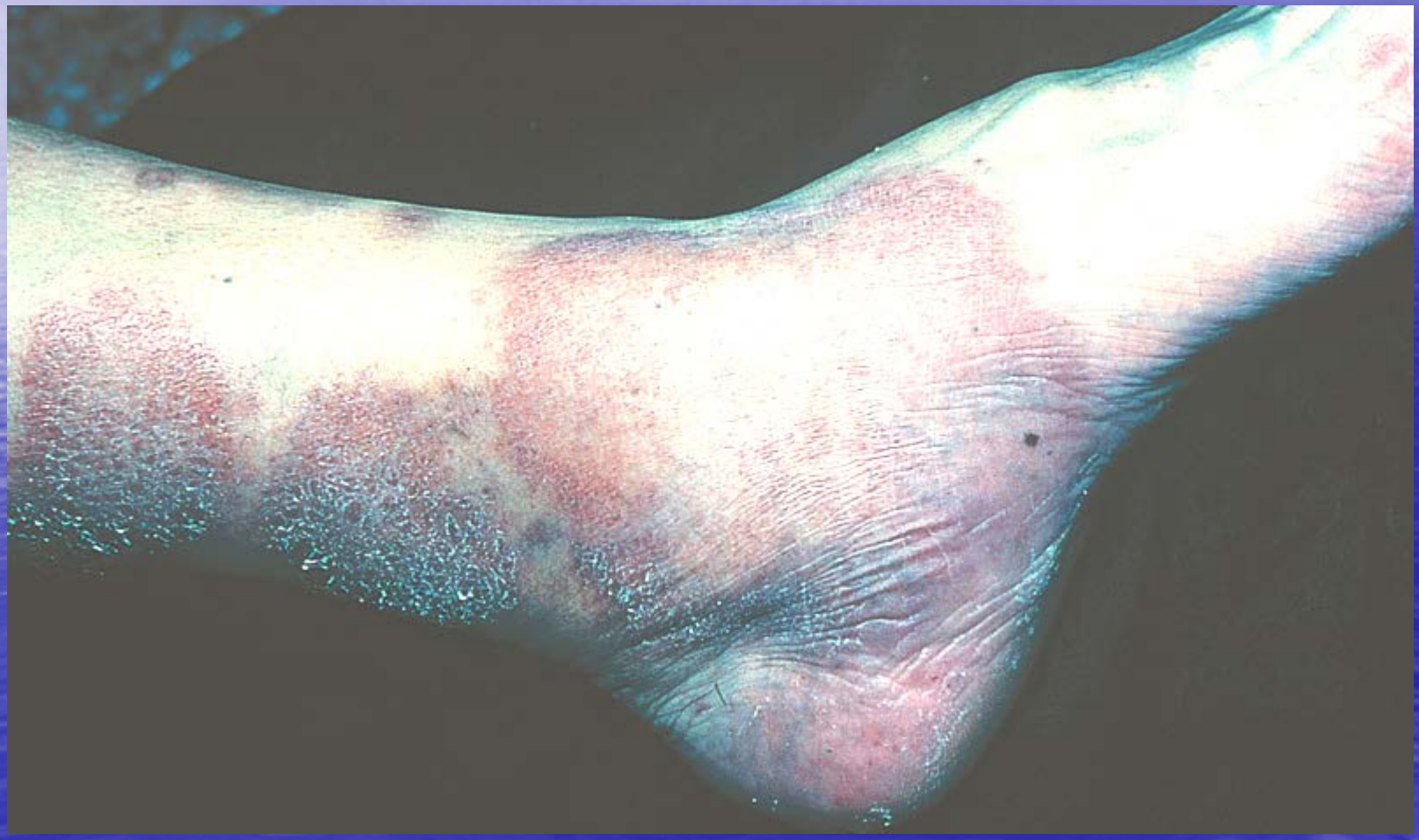


Tuberculoid lepra a beteg bal karján.

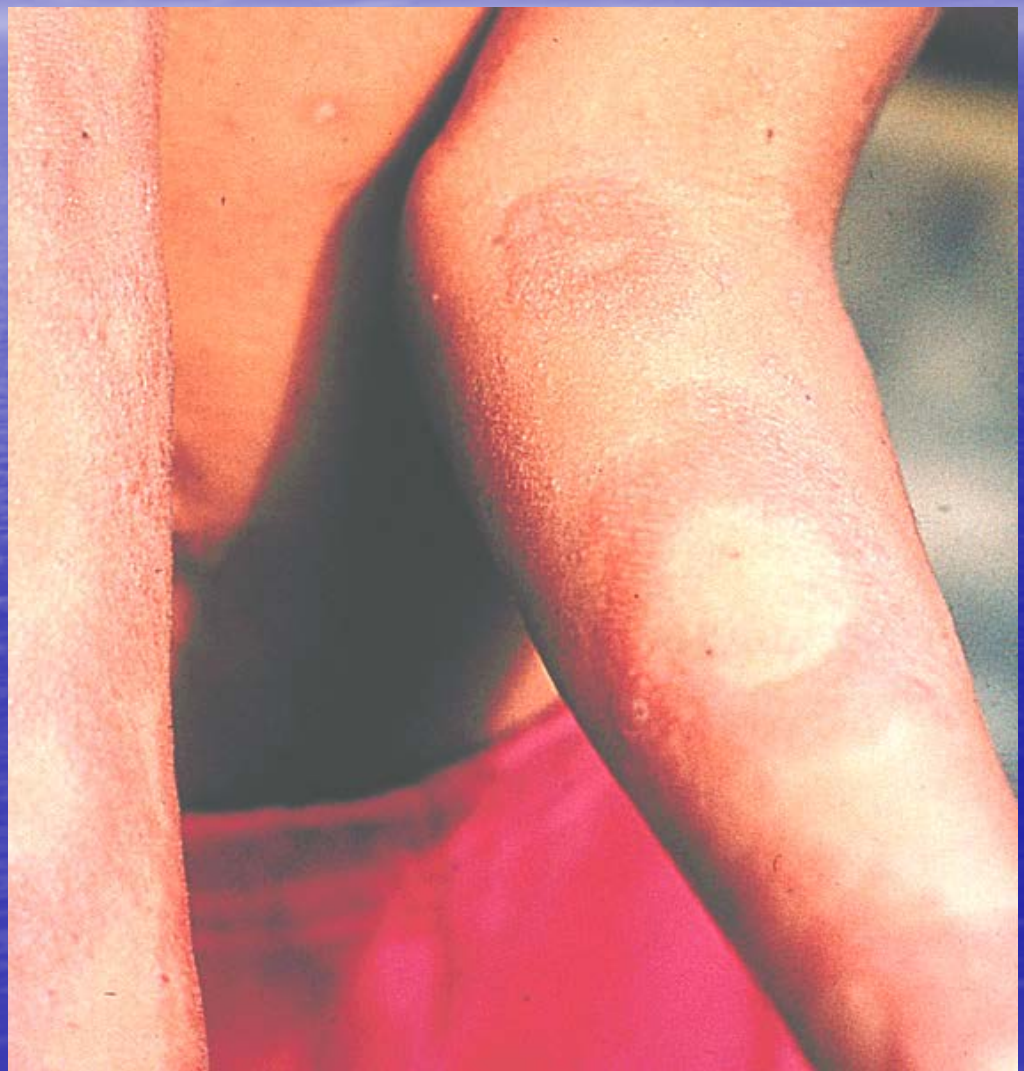
Borderline lepromatosus leprában kialakult talpi fekély.



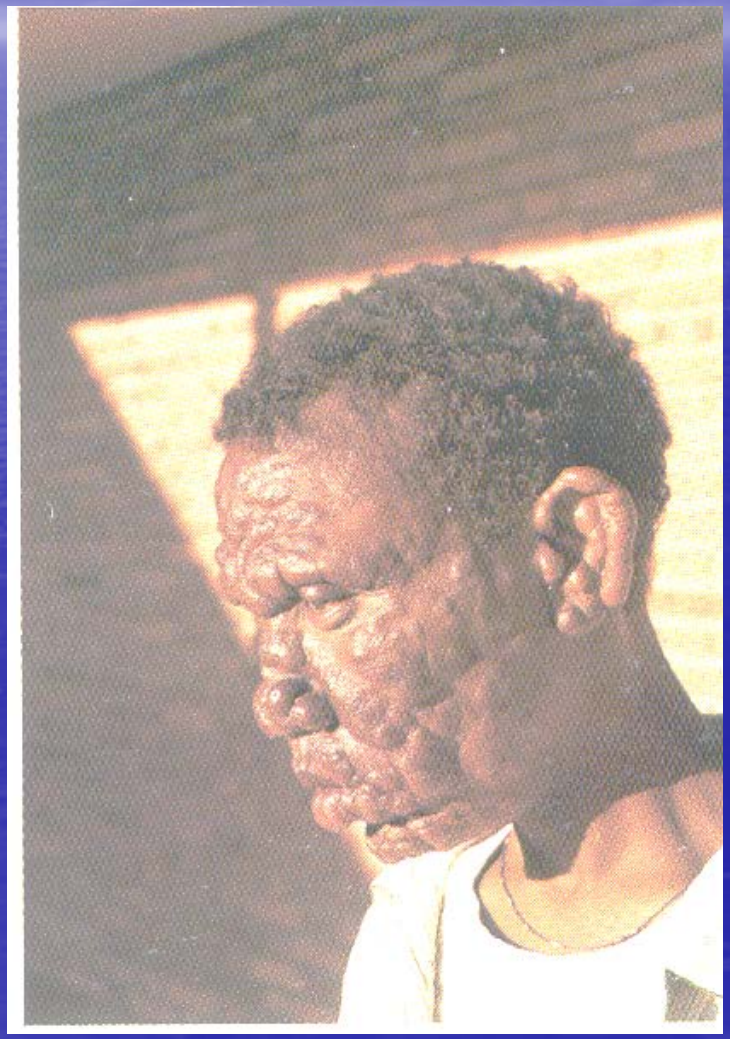
Borderline-tuberculoid lepra



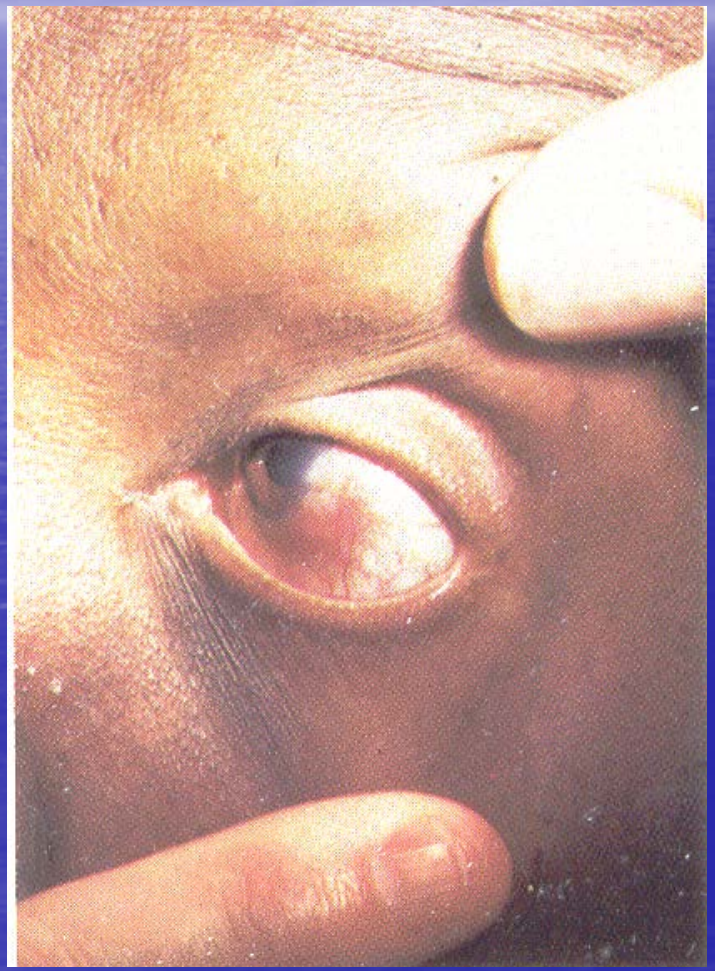
Mid-borderline lepra



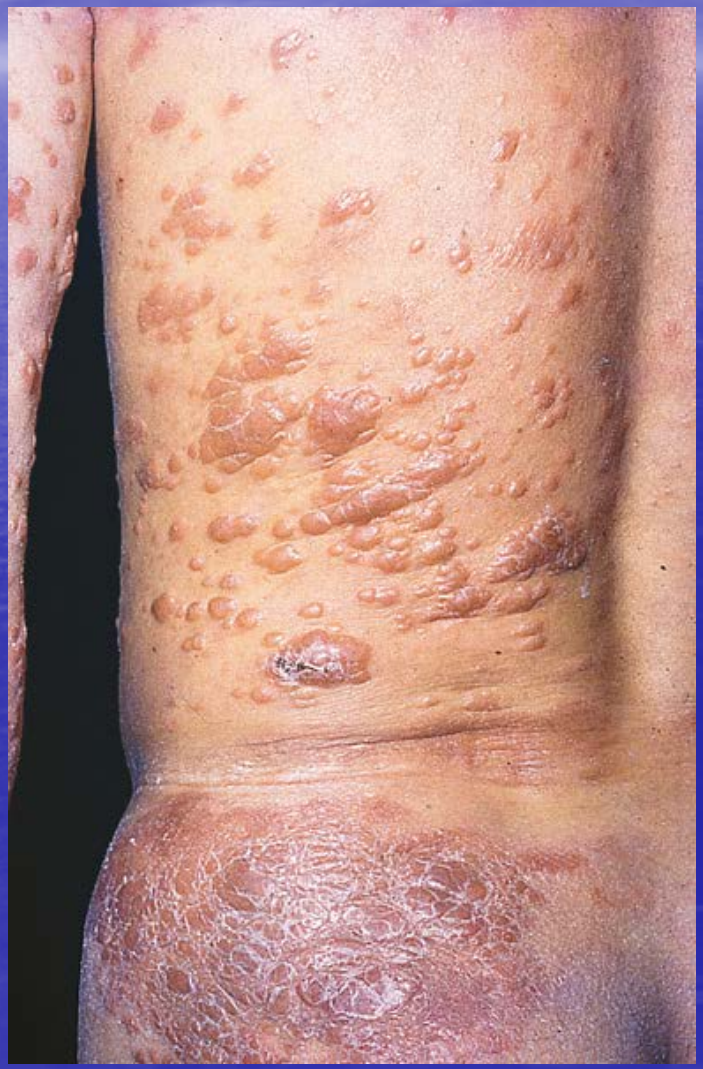
Lepromatosus lepra



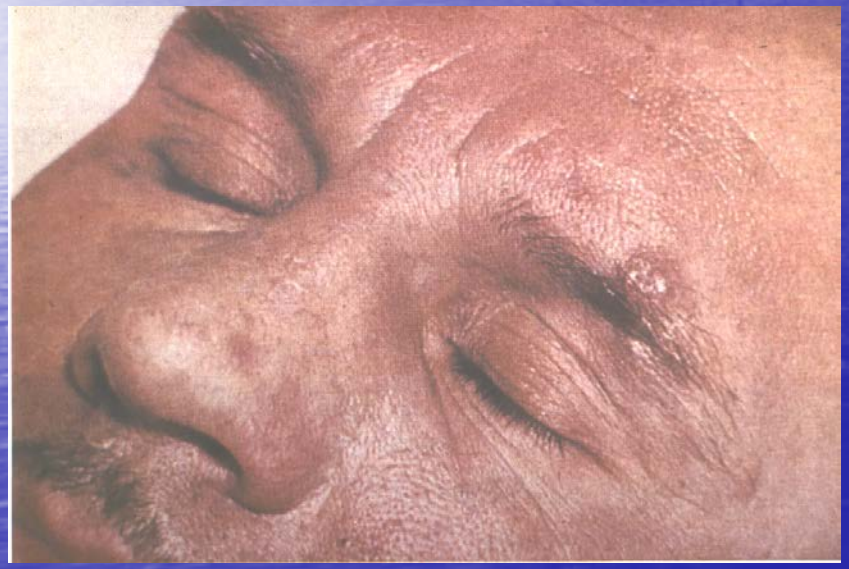
Lepromatosus nodula a szemben

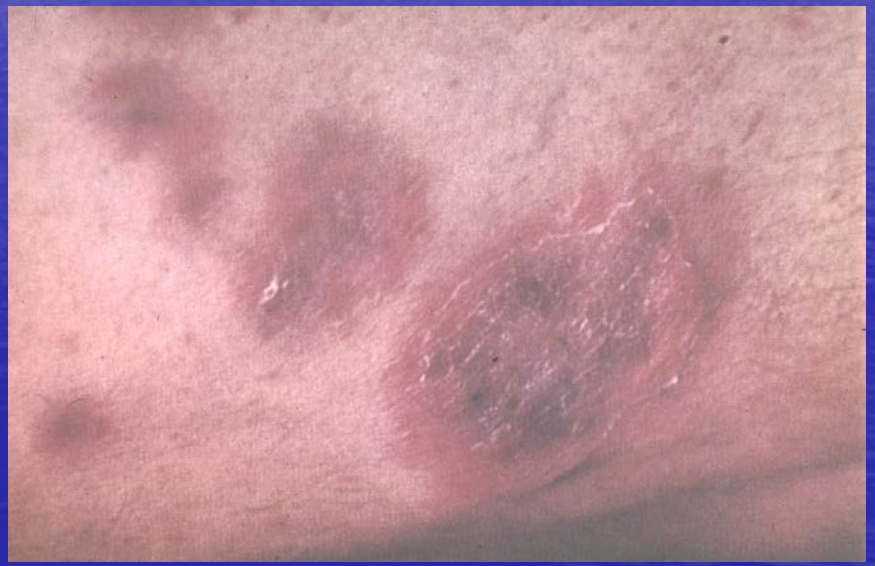


Noduláris lepromatosus lepra

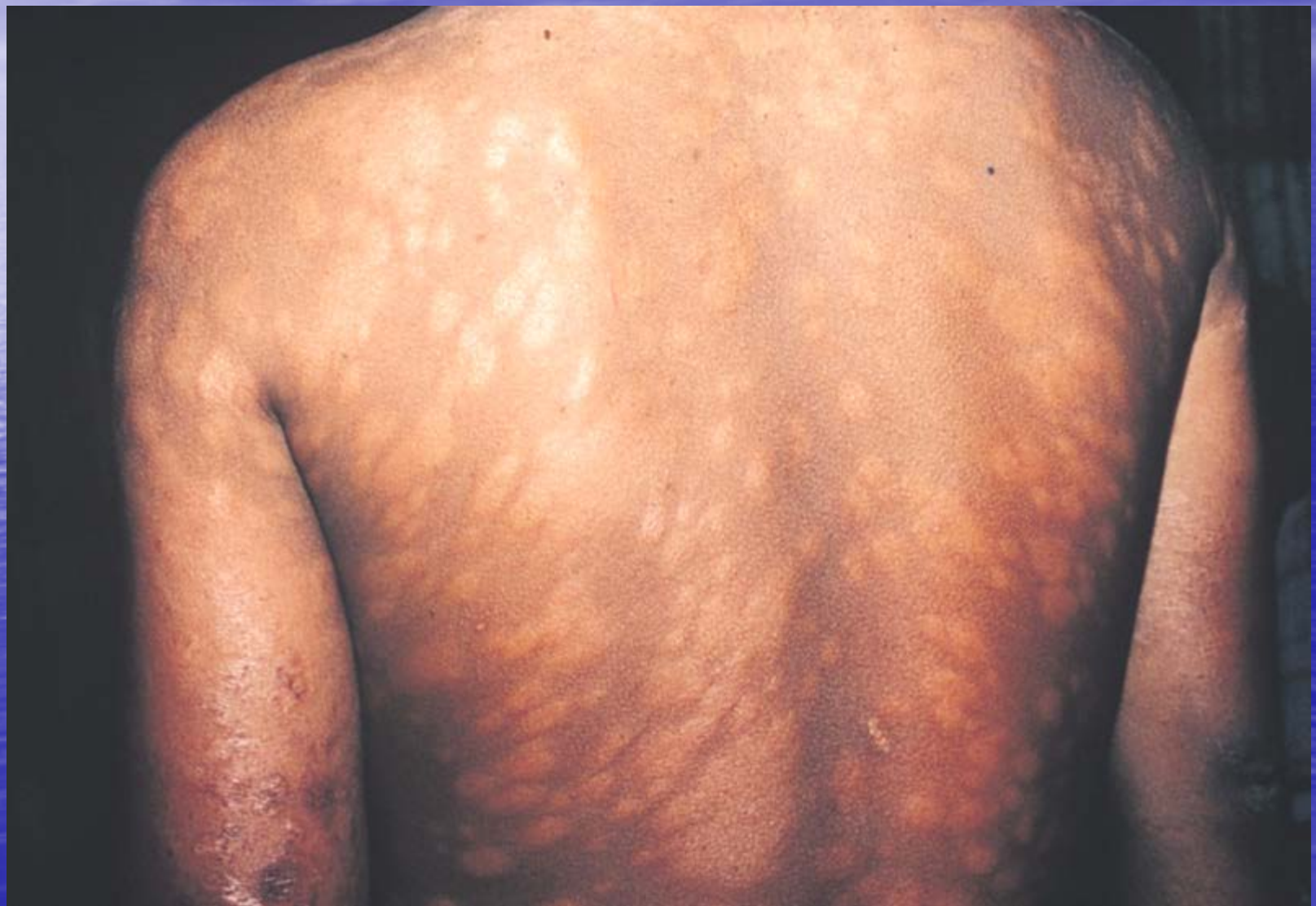


Lepromatosus leprában kialakult bőrelváltozás.

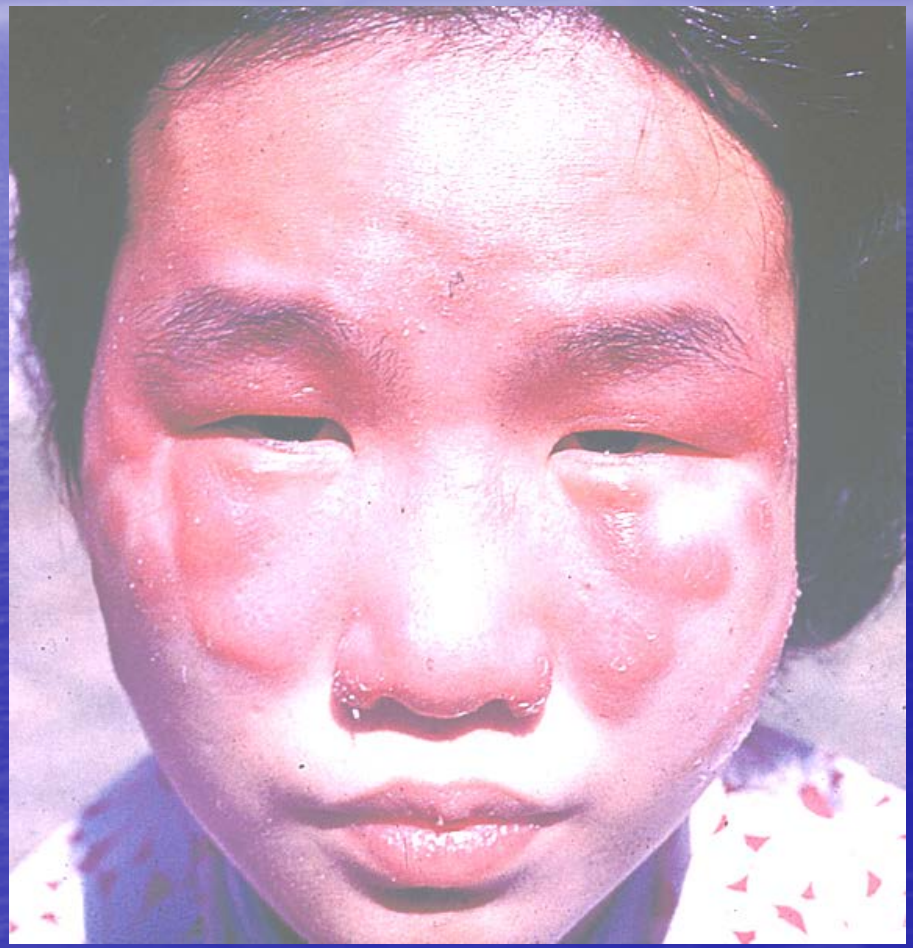




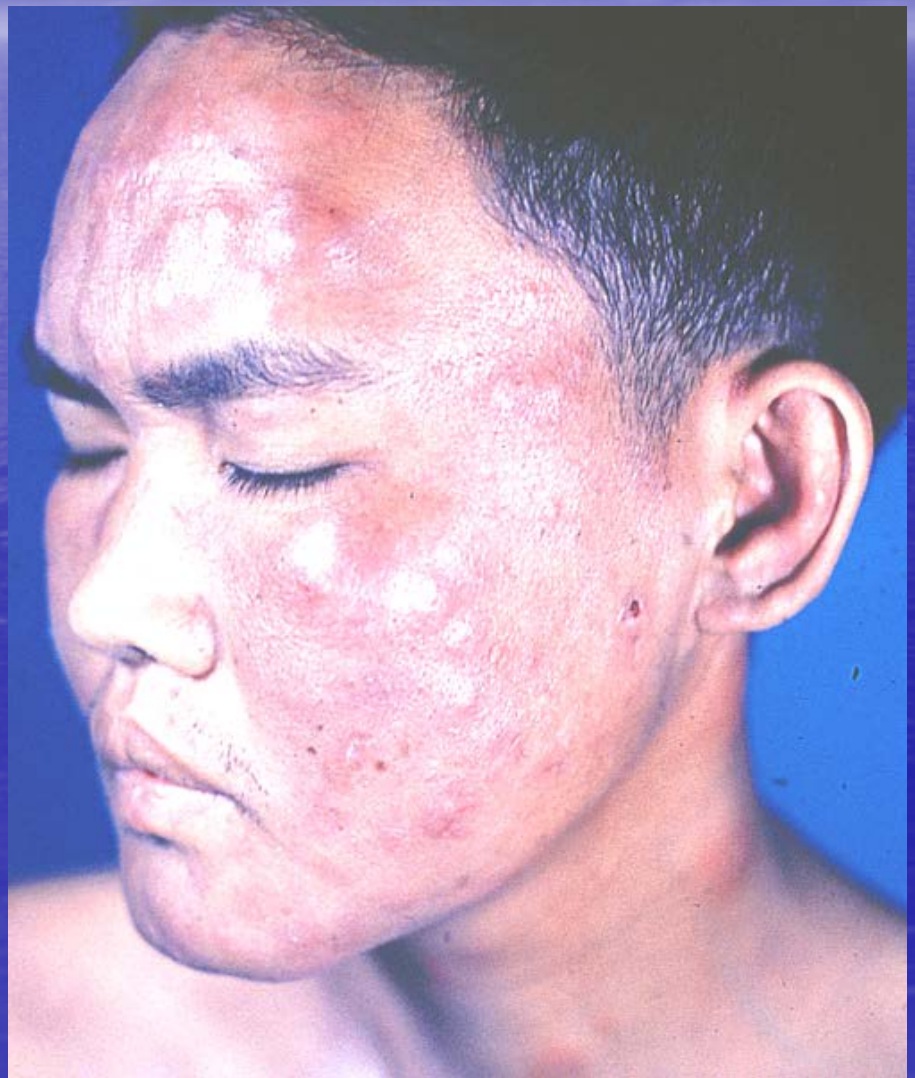
Lepromatosus lepra



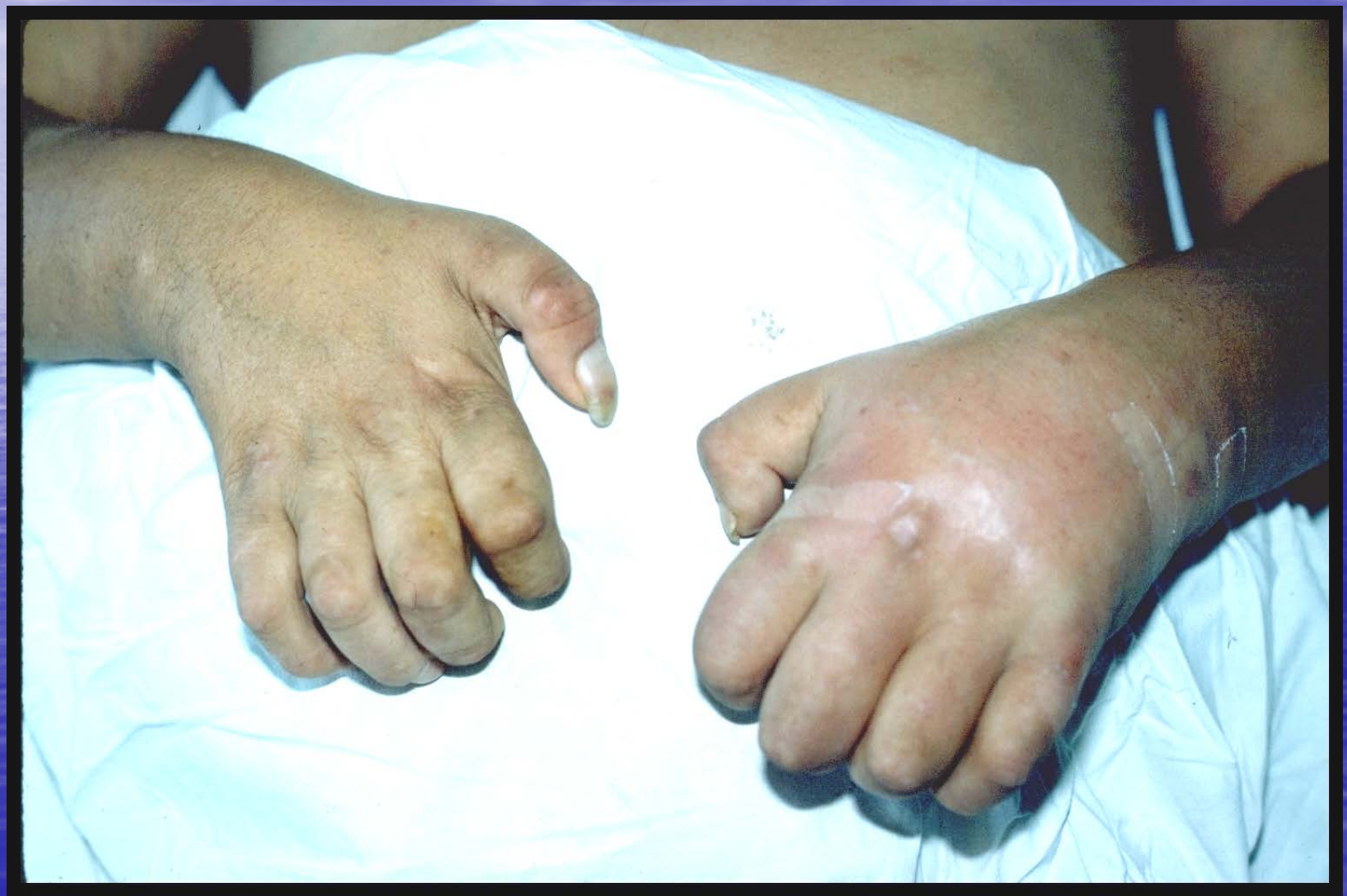
„Reversal-reaction”



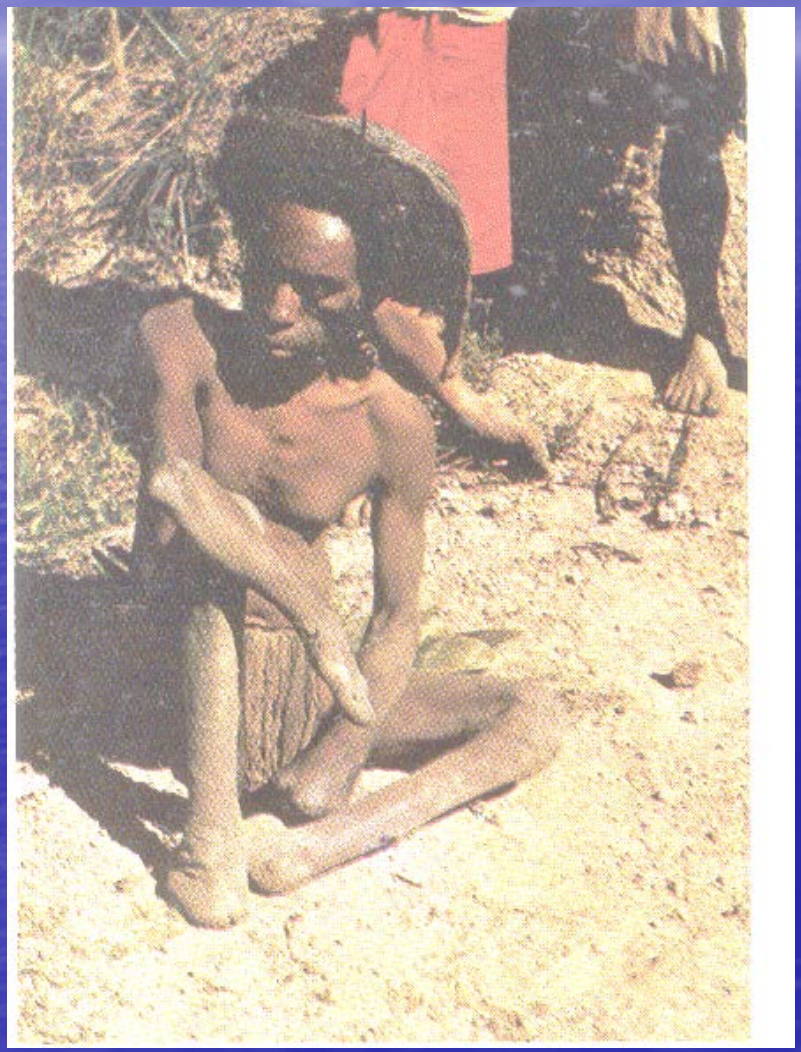
Erythema nodosum leprosum



Lepromatosus leprában szenvedő beteg kezén kialakult destructiv elváltozások.



Leprás beteg



The endemic treponematoses

- As in venereal syphilis the clinical manifestations of endemic treponematoses are divided into early (which includes primary and secondary lesions) and late stages of the disease.
- Lesions of the early stage are regarded as infectious or potentially infectious.
- This early stage usually lasts up to 5 years from the time of infection, with periods of latency in between symptomatic episodes.
- A period of latency often precedes the late-stage disease.

The endemic treponematoses

- All treponemal diseases have a relapsing clinical course and have prominent cutaneous manifestations, which in the case of pinta are the only clinical expression.
- In yaws and endemic syphilis the disease process also involves the mucous membranes and the bones.
- In some endemic foci of non-venereal syphilis cardiovascular and neurological lesions have been observed, but are in general extremely rare.

The endemic treponematoses

- The endemic treponematoses predominantly affect children under 15 years of age in the most underprivileged remote rural communities in the tropical belt, with endemic syphilis (bejel) extending to adjacent arid areas and some temperate zones.
- The diseases are transmitted from person to person by skin and mucous membrane contact or perhaps, through drinking vessels (predominant in bejel); the role of non-biting flies (*Hippelates pallipes*) in the transmission of yaws has been suggested.

The endemic treponematoses

- The known distribution of endemic treponematoses is closely related to poverty and isolation from organised social and health services (‘diseases at the end of the road’).
- The diseases tend to affect rural communities in developing countries.
- Climatic conditions appear to be especially important in yaws; humidity and a constant warm temperature are necessary for yaws to flourish.
- Few clothes are worn in humid and hot climates: opportunities for direct spread of infection between the uncovered skins of contacts are thereby increased.
- Lesions of the mouth are also responsible for transmission by indirect contact through drinking vessels, particularly for bejel in arid regions.
- The fact that so many factors influence the transmission and the natural course of the diseases may explain that a patchy distribution of these diseases in the population is a characteristic feature of their epidemiology.

Aetiological agents

- The pathogenic members of the genus *Treponema* include four human pathogens.
- Because of the distinctive clinical manifestations of infection with each, these organisms were initially classified as separate species.
- Saturation reassociation kinetic studies of the causative agents of syphilis and yaws however, resulted in the current classification scheme, in which three of the human pathogens are subspecies of *Treponema pallidum*: *T. pallidum* subsp*. pallidum*, *T. pallidum* subsp. *pertenue*, and *T. pallidum* subsp. *endemicum*.
- The fourth human pathogen, *Treponema carateum*, can be propagated only in primates and no isolates are known to exist.

Aetiological agents

Characteristics of the pathogenic *Treponema*

Treponema	Disease
T. pallidum subsp. *pallidum*	Venereal syphilis
T. pallidum subsp. *pertenue*	Yaws
T. pallidum subsp. *endemicum*	Endemic syphilis (bejel)
T. carateum	Pinta

The diseases

- *T. pallidum* subsp. *pertenue*, *T. pallidum* subsp. *endemicum*, and *T. carateum* are transmitted by non-venereal routes, usually by direct contact during childhood.
- Similarly to syphilis, infection with these organisms causes localised primary lesions, which are sometimes ulcerative, and disseminated skin or mucous membrane lesions; the nature and location of the lesions vary by aetiology.

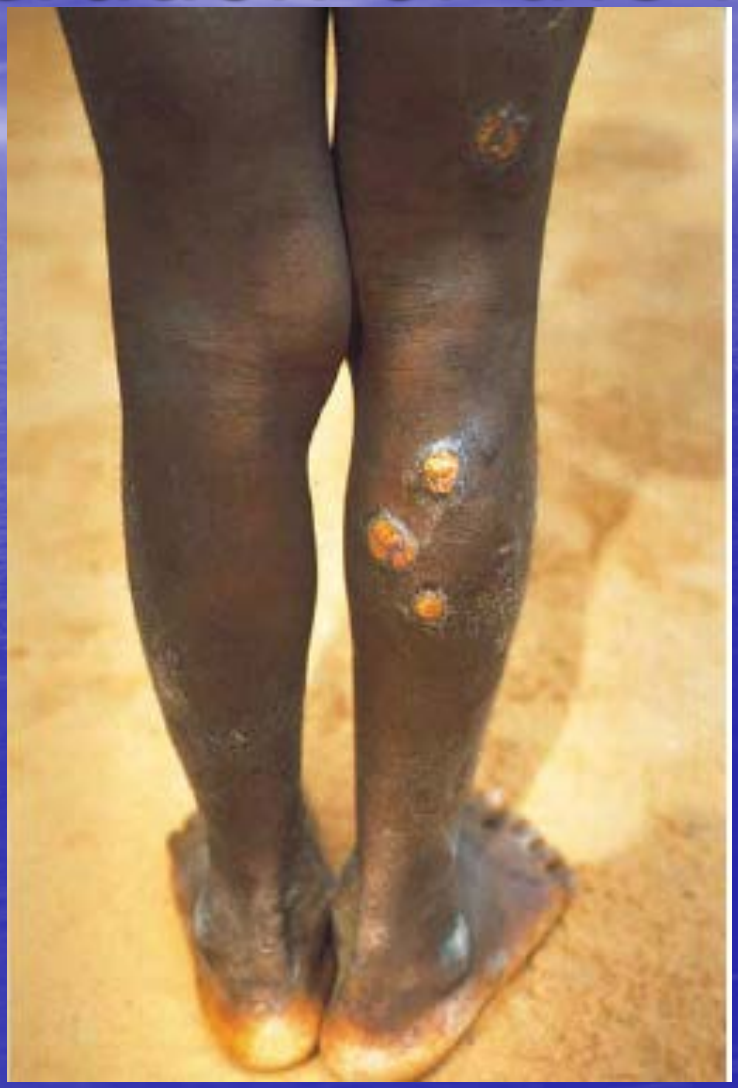
Yaws 1.

- Yaws is a contagious, chronic, relapsing treponematosis caused by *T. pallidum* subsp. *pertenue*.
- Like the other endemic treponematoses, yaws is transmitted by direct skin contact with the exudate or serum from an infectious lesion; the entry of treponemes is facilitated by breaks in the skin
- from scratches, scabies, etc.
- The disease, which is known under many different names [e.g. *pian* (French), *Frambösie* (German), *buba* (Spanish), *parangi* (Malay)], is the most prevalent endemic treponematosis affecting the rural populations in the rain forest areas of the world where high levels of humidity and rainfall prevail.
- It is endemic in rural populations with low levels of individual and collective hygiene, scanty clothing and minimal access to health services.

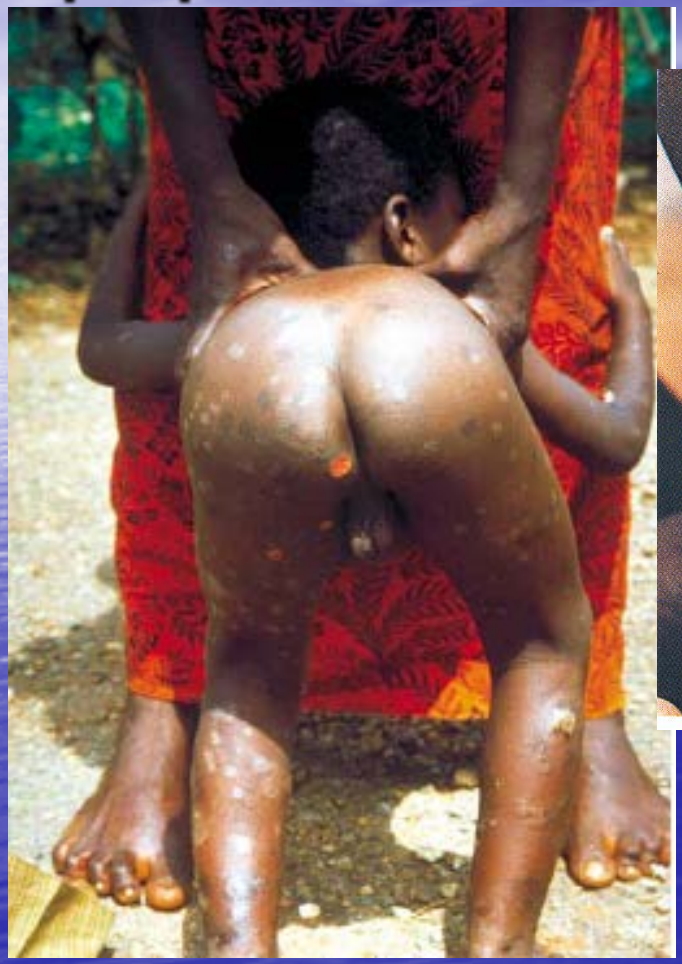
Yaws 2.

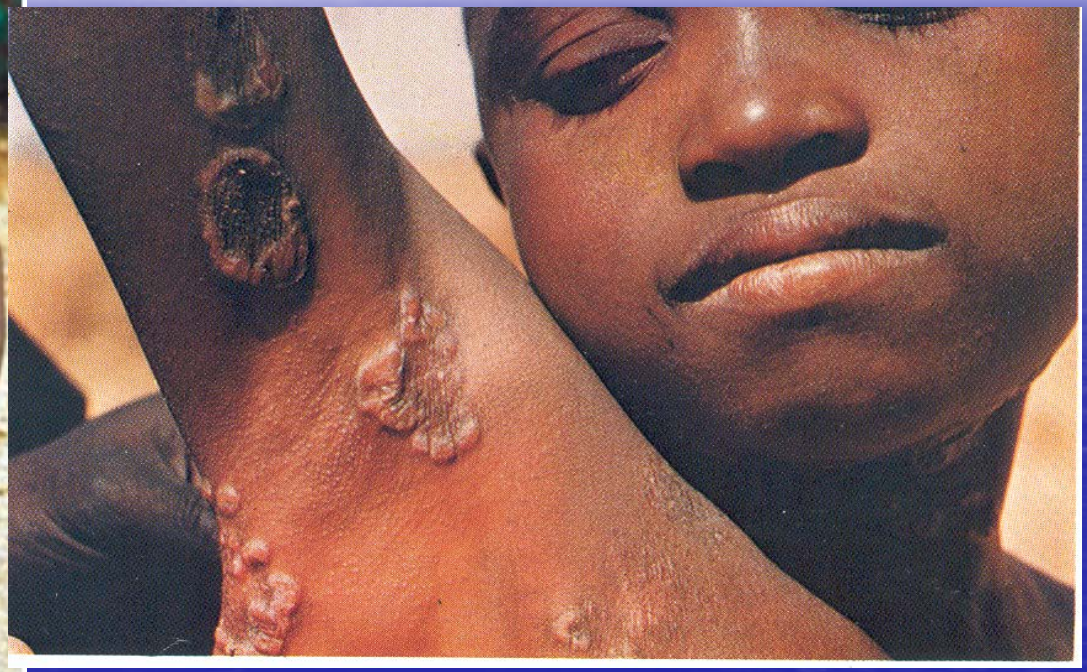
- In the early-stage disease, after an incubation period of 10 days to 3 months an initial lesion (‘mother yaw’), a small papule, arises at the site of entry of the organism at the legs, feet or buttocks. It is an itchy erythematous, scaly papule which proliferates into a papilloma.
- The lesion is very rich in treponemes and may persist for 3–6 months.
- A regional lymphadenitis may be observed.
- The first crop of secondary lesions may develop before the initial lesion has healed, but may not appear for 1–2 years.
- The characteristic secondary lesions are the large raised papillomas and papules in which exudation of highly infectious serum is a feature in addition a wide variety of squamous macular lesions may appear on the skin and mucous plaques in the oral cavity.
- At this stage hyperkeratotic changes of the palms and soles are common.

Early ulceration of the leg

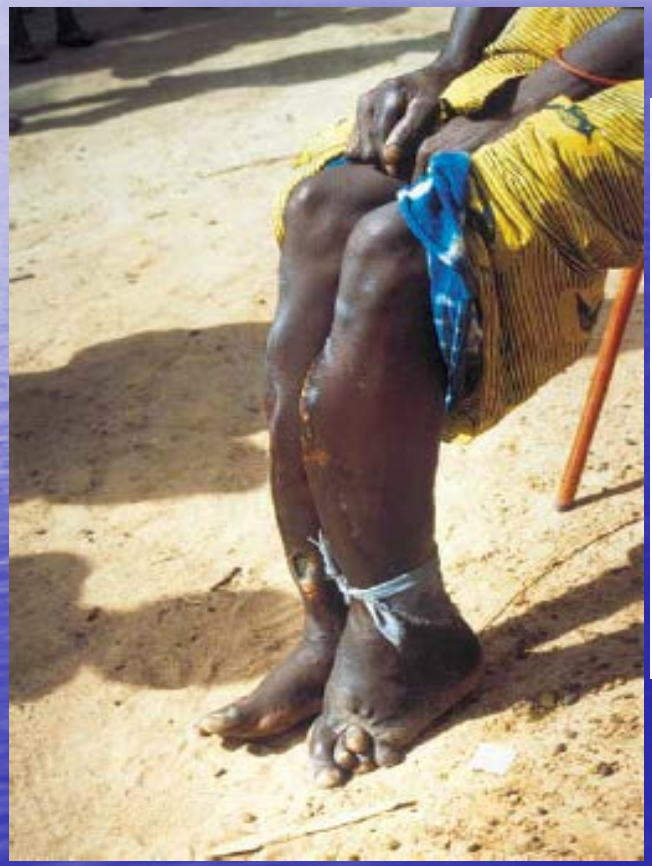


Polymorphous early yaws and late papillomatosis (right side)





Sabre tibia and plantar hyperkeratosis



Secondary framboesiform yaws (*T. pertenue),* and late manifestation (gangosa)

Bone lesions

- Early bone lesions commonly consist of painful osteoperiostitis of forearm or leg, and polydactylitis of the hand or foot.
- The secondary lesions resolve spontaneously after a period of weeks or months.
- One or two relapses occur, especially of the skin lesions.
- The subsequent eruption may appear before the previous lesions have resolved, or there may be an intervening period of latency.
- Ultimately, secondary lesions cease to recur and, after a further period of latency, late lesions may appear in about 10% of cases.

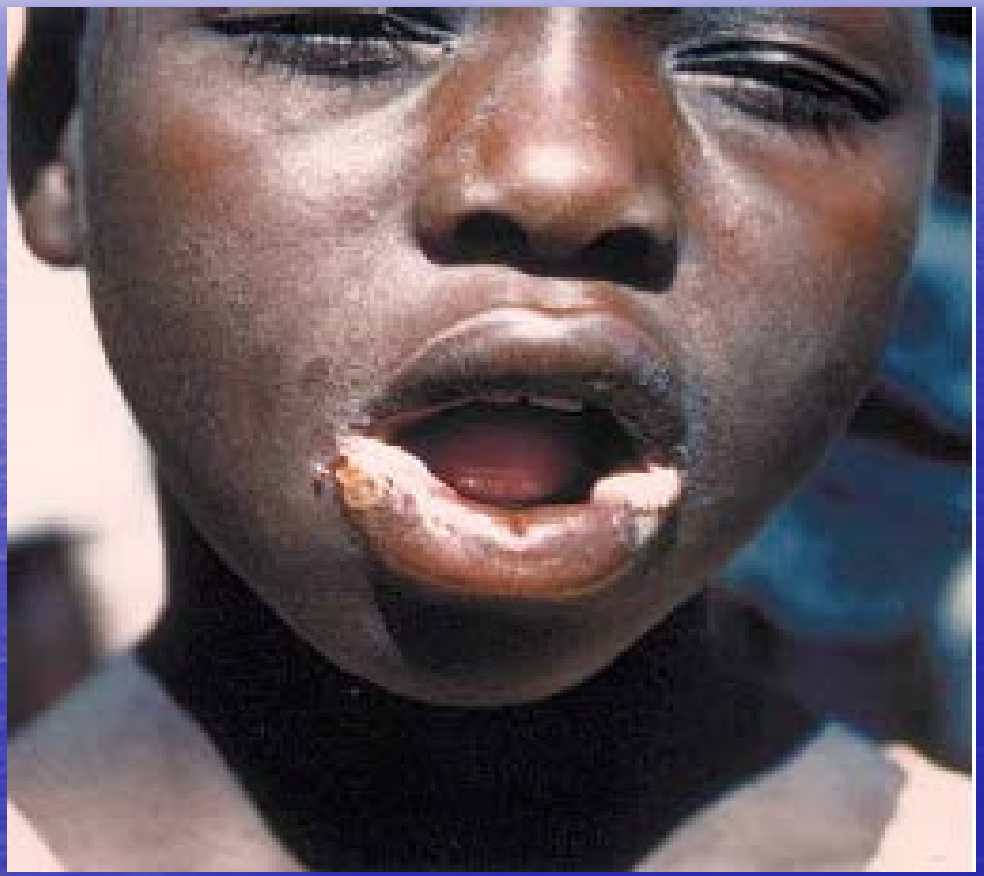
Endemic syphilis (bejel)

- *T. pallidum* subsp. *endemicum* is the organism responsible for bejel.
- The transmission of this 'pre-pubertal' syphilis occurs via infectious lesions on the skin and mucous membranes, often through the use of common feeding utensils.
- The main reservoir is in children 2–15 years of age.
- In contrast to yaws, endemic syphilis is prevalent in dry, hot and temperate climates and is endemic in rural and semi-urban communities living in low hygienic conditions.
- It used to be endemic in northern Europe (*Sibbins* of Scotland, the *Radesyge* of the Scandinavian countries), in the Balkans (*Sklerjevo*), Russia, Mongolia, the Near East and eastern Mediterranean (*Bejel*), southern Africa (*Njovera* or *Dichuchwa*), and among the nomadic and semi-nomadic rural populations in northern Africa.

Endemic syphilis (bejel)

- In the early-stage disease, primary lesions are rarely seen, but have been found in the mouth and lips, and the nipples of breastfeeding women.
- Characteristic secondary lesions include the mucous patches on the lips and oral mucosa.
- Papilloma favour warm and moist areas of the body and occur as split papules or angular stomatitis at the labial commissures.
- A generalised lymphadenopathy is common at this stage.
- As in yaws, a periostitis involving the long bones or hand can be observed.
- A crop of untreated secondary lesions lasts for approximately 6–9 months.

Angular stomatitis of endemic syphilis (also called split papules)



Gangosa of late endemic syphilis

Pinta

- *T. carateum* is the organism responsible for pinta.
- The precise mode of transmission is not known, but repeated direct lesion-to-skin contact is the likely mechanism.
- Scanty clothing promotes disease transmission.
- Transmission through insects does not seem to occur.
- Treponemes are abundant in early lesions and persist through the late dyschromic stage, i.e. up to 40 years after infection.
- The disease used to be prevalent in forest and rural populations living in poor and unhygienic conditions in the arid and semi-arid areas in the northern part of South America and in Central America, including Cuba.
- The disease was observed by the first Spanish explorers in certain Caribbean and Aztec communities.
- It was given many curious names referring to the colour changes in
- persons suffering from the disease.
- The most current names are ‘pinta’, ‘mal de pinto’, and ‘carate’.

Pinta

- In pinta, as in the other treponematoses, an early and late stage are recognised; also, reagin and treponemal antibodies develop in the course of the infection, but may not yet be demonstrable at the time of the initial lesion.
- As in the other endemic treponematoses a large proportion of infected individuals remain asymptomatic (latent).

Pinta

- In the early-stage disease, after an incubation period of 15 days to 1 month, an initial lesion, a papule or an erythemato-squamous plaque, appears on the uncovered part of the body.
- This lesion may be single, but more commonly there are two or three.
- After a few weeks or months, the papules increase in size or merge with satellite lesions and become small patches; the centre becomes paler and the infiltration outwards continues.
- This is accompanied by an enlargement of regional lymph nodes.

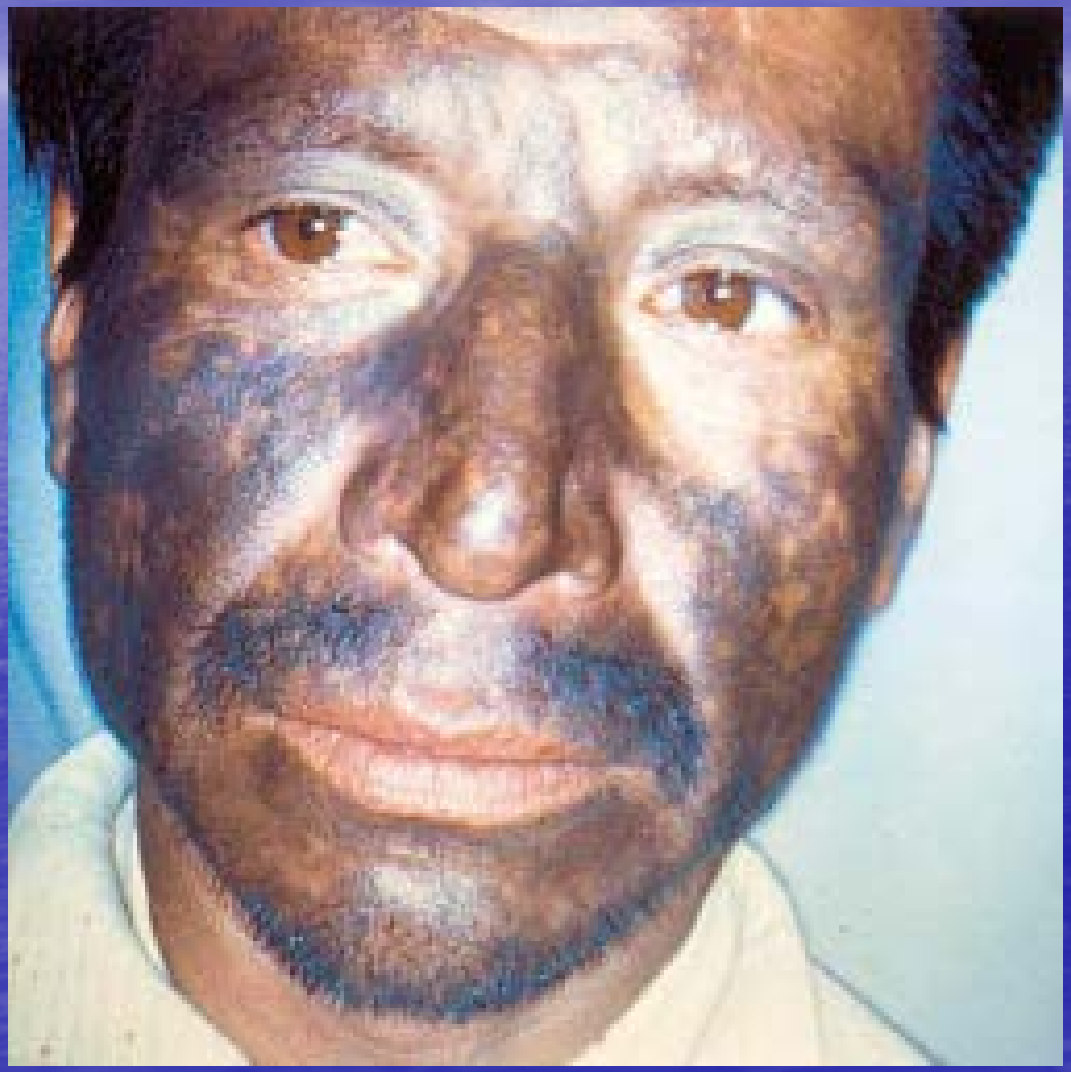
Pinta

- After some months many of the patches become hypochromic.
- In others a greyish, light-blue or pale-mauve pigmentation appears, the colour being more marked in the centre of the lesions.
- Subsequently, the initial lesions may gradually extend to form a larger patch with an irregular outline, which may either disappear, leaving a very slightly pigmented or hypochromic patch or may persist for years.

Pinta

- The late stage generally develops 2–4 years after the onset of the disease and is characterised by the development of depigmented lesions.
- Symmetric lesions tend to develop from 3 months to 10 years after the appearance of pintids, creating a mottled appearance.
- Cutaneous atrophy or hyperkeratosis may also be present.
- There is no evidence of involvement of other organs nor congenital transmission.

Hyperpigmented lesion of pinta



Diagnosis

- Careful assessment of the clinical manifestations in patients together with the epidemiological context for each of the diseases usually allows a presumptive diagnosis of yaws, endemic syphilis, or pinta.
- But in areas of low endemicity, where cases are sporadic and health care workers may be less familiar with the diseases, the diagnosis on clinical grounds is not easy and confusion can arise with other conditions affecting the skin or mucosa (e.g. impetigo, psoriasis, tropical ulcer, tungiasis, etc.)

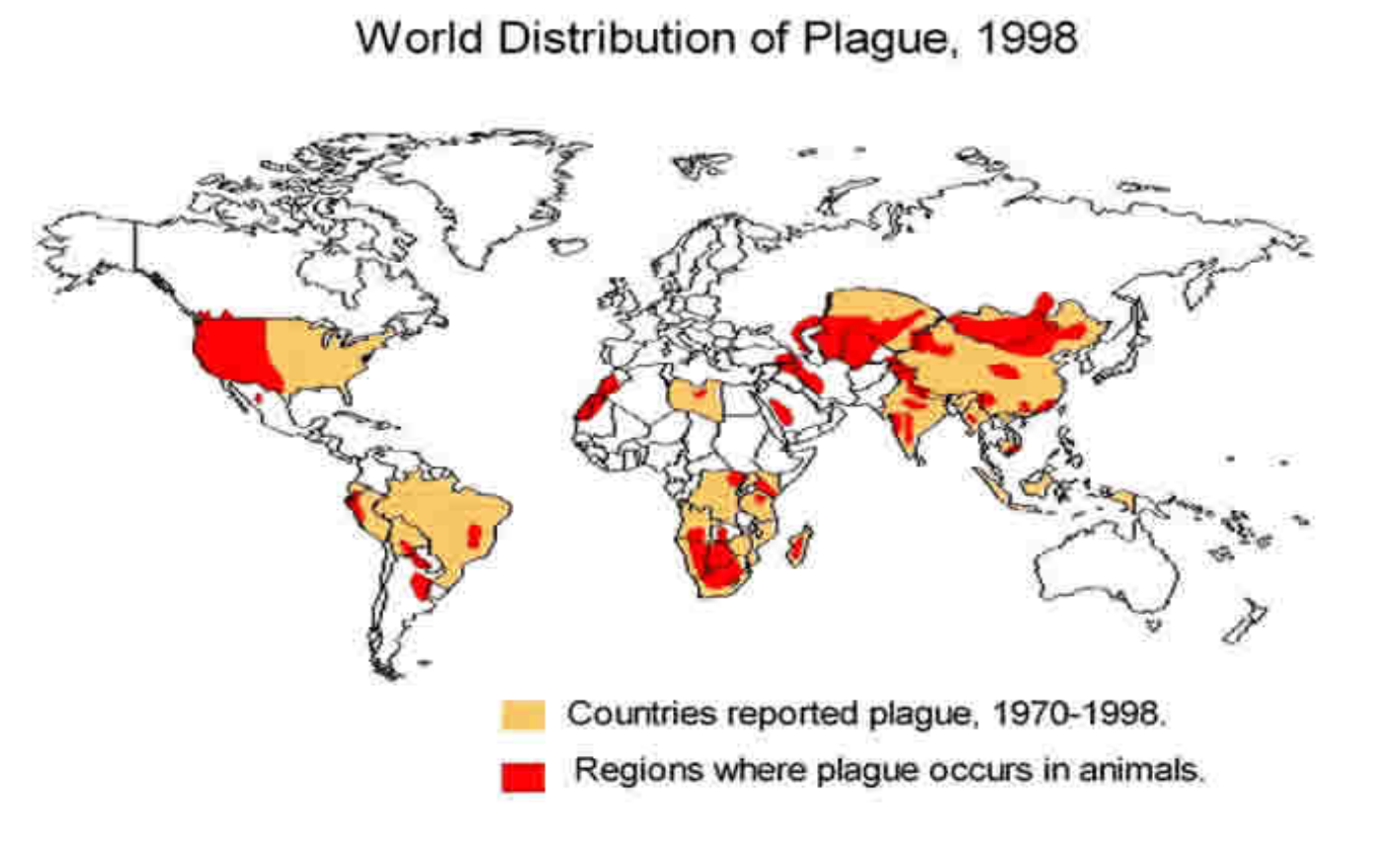
Treatment

- Penicillin remains the drug of choice.
- Current treatment recommendations for endemic treponematoses were formulated by a WHO Scientific Group in 1980 and include a single dose of 1.2 million units of benzathine penicillin for early and late active cases.
- For patients under 10 years of age, the recommendation is half that dose (0.6 million units).
- Cases in latency and contacts should receive the same dose according to their age.
- Tetracycline, doxycycline and erythromycin, at doses appropriate for venereal syphilis, are alternatives in patients allergic to penicillin.
- At the recommended dose, penicillin will cure active lesions and prevent the development of destructive late lesions, but often does not lead to seroreversal.

Plague

- The Black Death
  - The second pandemic of plague, known as the Black Death, brought plague into the collective Western memory.
  - It is considered one of the great epidemic scourges of humankind.
  - Between the years 1346 and 1352, it caused the death of some 25 million people, one-third of the world's population at that time.
  - Another 20 million are thought to have died by the end of the century.
  - During the 15th to the 18th centuries, an estimated 30 percent to 60 percent of the populations of large cities, including Genoa, Milan, Lyons, and Venice, died from the disease. It continued into the 18th century, when a final "foray" occurred in Marseilles in 1720.

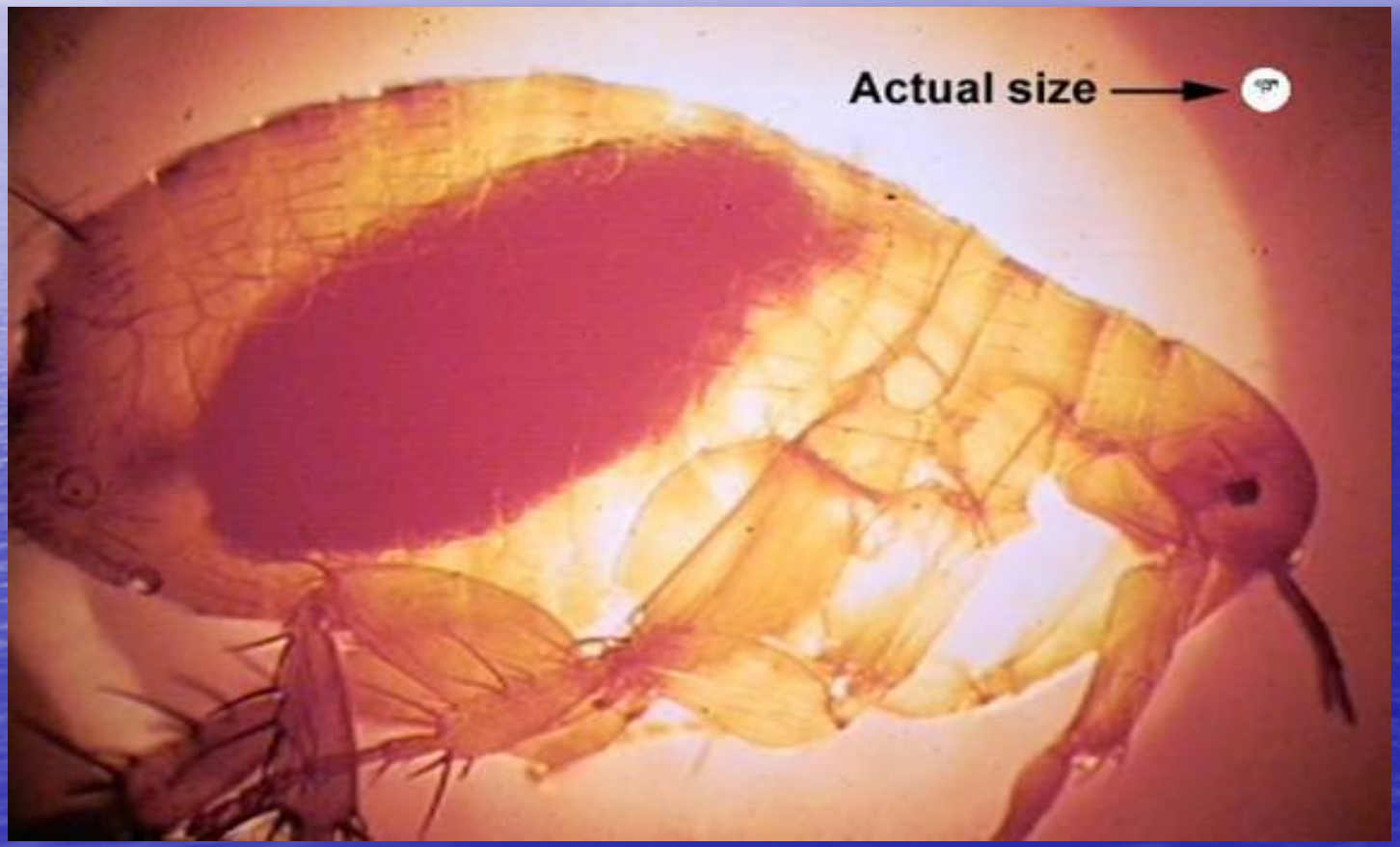
Distribution of plague



Plague

- Plague is a zoonotic disease circulating mainly among small animals and their fleas.
- The bacteria *Yersinia pestis* can also infect humans.
- It is transmitted between animals and humans by the bite of infected fleas, direct contact, inhalation and rarely, ingestion of infective materials.
- Plague can be a very severe disease in people, with a case-fatality ratio of 30%-60% if left untreated.
- Infected persons usually start with “flu-like” symptoms after an incubation period of 3-7 days.
- Patients typically experience the sudden onset of fever, chills, head and body-aches and weakness, vomiting and nausea.
- Clinical plague infection manifests itself in three forms depending on the route of infection: bubonic, septicaemic and pneumonic.

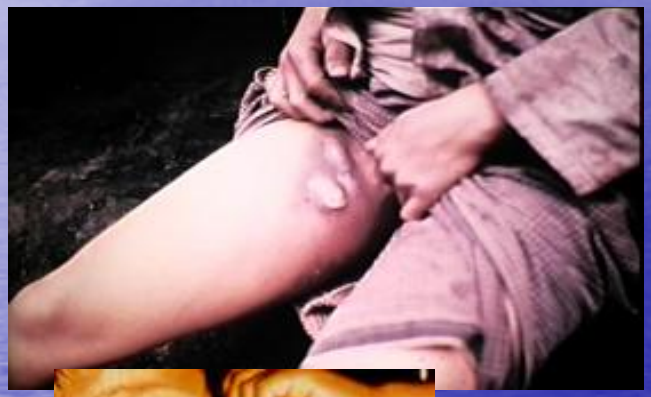
Flea



Plague

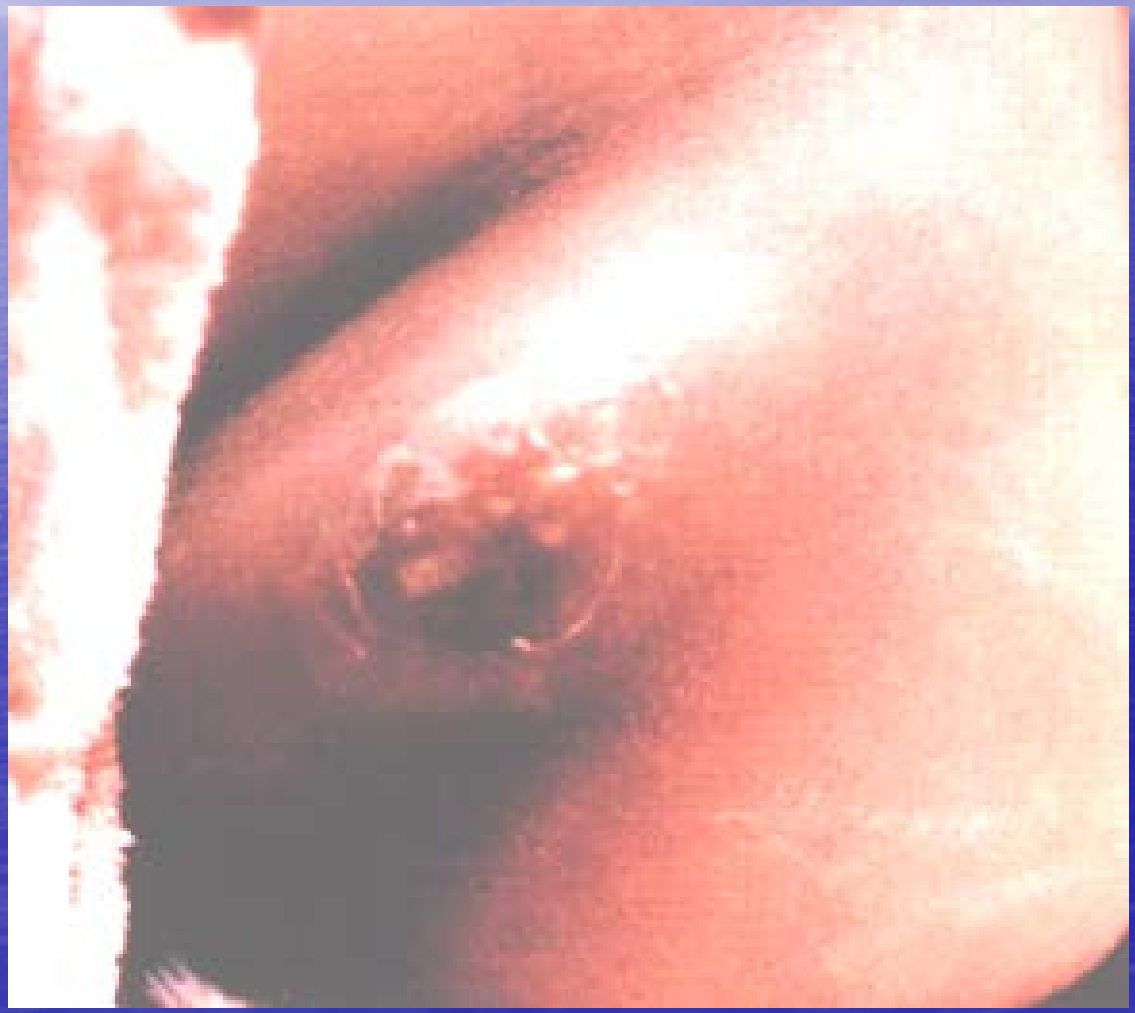
- Bubonic form is the most common form of plague resulting from the bite of an infective flea.
- Plague bacillus enters the skin from the site of the bite and travels through the lymphatic system to the nearest lymph node.
- The lymph node then becomes inflamed because the plague bacteria, *Yersinia pestis* or *Y. pestis*, will replicate here in high numbers.
- The swollen lymph node is called a "bubo" which is very painful and can become suppurated as an open sore in advanced stage of infection;

Bubonic and septic plague

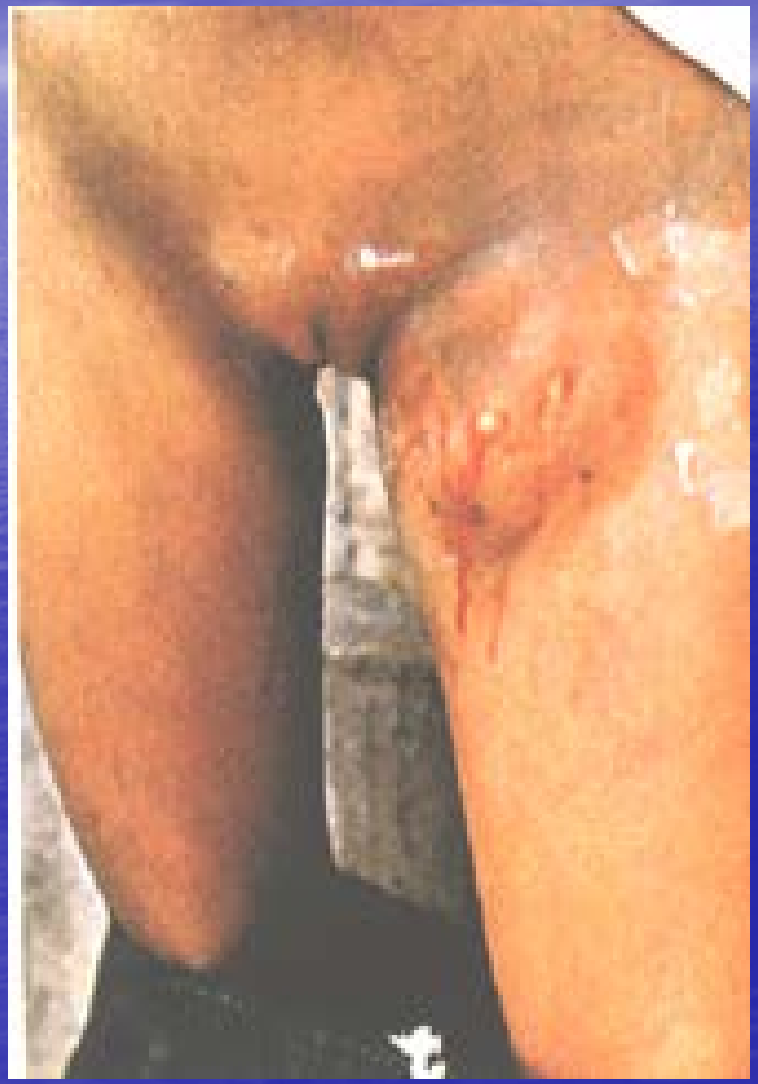


Developing bubonic plague 1.

Ugyanaz későbbi fázisban



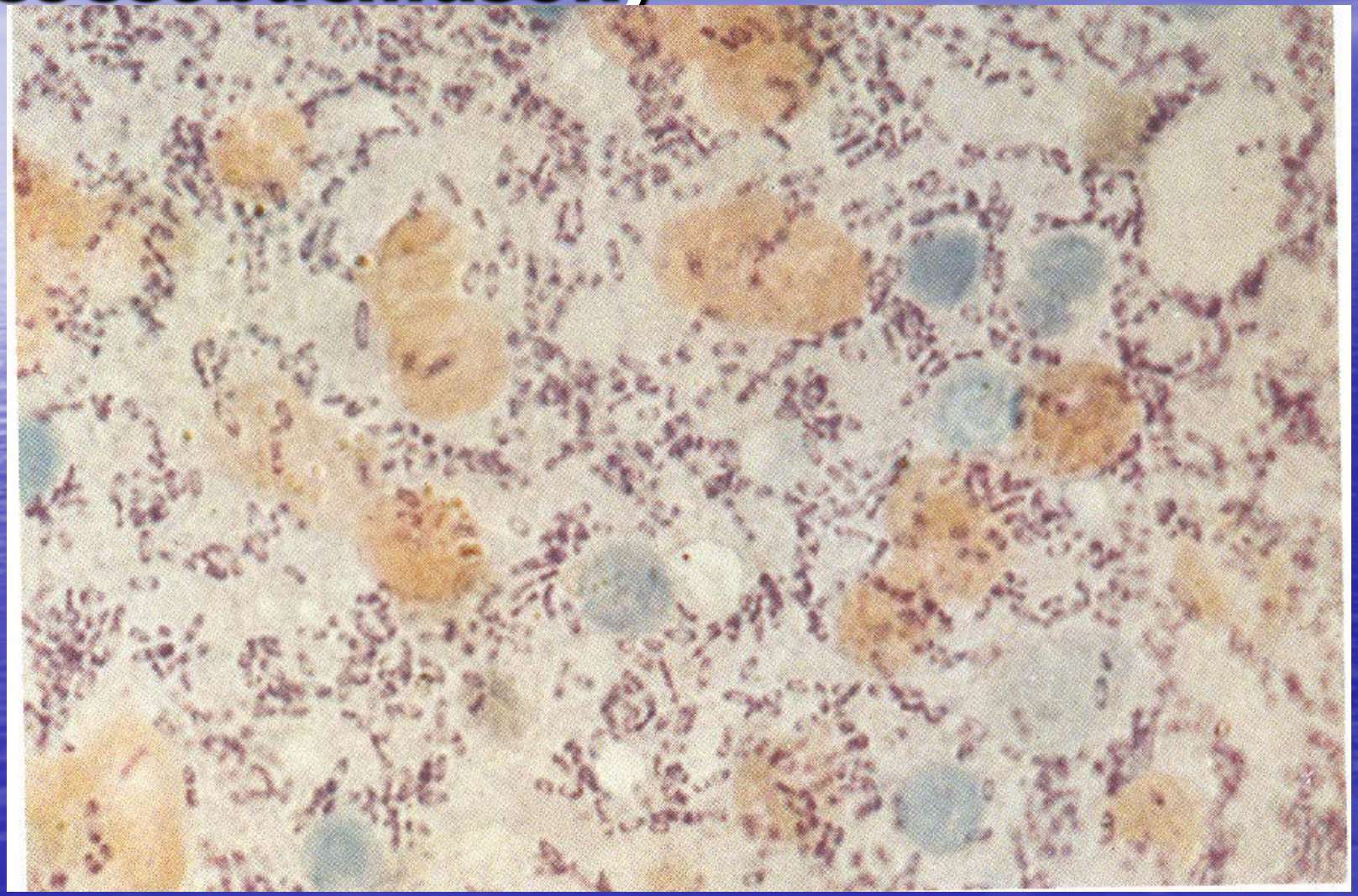
Bubopestis kialakulása. Jól látható az érintett nyirokcsomó beolvadása és a genny kiürülése.



Septicaemic form of plague

- Septicaemic form of plague occurs when infection spreads directly through the bloodstream without evidence of a "bubo".
- More commonly advanced stages of bubonic plague will result in the presence of *Y. pestis* in the blood.
- Septicaemic plague may result from flea bites and from direct contact with infective materials through cracks in the skin.

Y. pestis baktériumok májszövetben (Gram-negatív coccobacillusok)



Pneumonic form of plague

- Pneumonic form of plague is the most virulent and least common form of plague. Typically, pneumonic form is due to a secondary spread from advanced infection of an initial bubonic form. Primary pneumonic plague results from inhalation of aerosolized infective droplets and can be transmitted from human to human without involvement of fleas or animals. Untreated pneumonic plague has a very high case-fatality ratio.

Treatment

-