AZERBAIJAN MEDICAL UNIVERSITY
DEPARTMENT OF MEDICAL MICROBIOLOGY and IMMUNOLOGY

LESSON 19.

Latent virus infections. Microbiology diagnosis of HIV infection (Human Immunodeficiency Virus). Oncogenic viruses. Prion infections

FACULTY: ***General Medicine***
SUBJECT: ***Medical microbiology - 2***

Discussed questions:

1. Retroviruses.
- Human immunodeficiency viruses, classification. Virion structural features, structural and non-structural genes. Virus reproduction, variability, persistence, ways of infection. Pathogenesis of the disease. Clinical course, opportunistic infections.
- Microbiological diagnosis of HIV infection (serological, molecular-genetic and immunological methods).
- Specific prevention problem and treatment principles.
2. Oncogenic viruses. Human tumor-causing oncogenic viruses:
 DNA-containing oncogenic viruses:
- Herpesviridae family (cytomegalovirus (SMV), Epstein-Barr virus (Burkitt's lymphoma), human herpesvirus type 8 (Kaposh's sarcoma)
- Family Hepadnaviridae. Genus Orthohepadnavirus (hepatitis B virus)
- Papillomaviruses, general characteristics, types, pathogenetic characteristics of the diseases caused by them.
- Polyomaviruses. Merkel polyomavirus.
 RNA-containing oncogenic viruses:
• Family Retroviridae:
- Human T-lymphotropic viruses (Human T-lymphotropic virus, HTLV). HTLV-1 – T-cell leukemia, HTLV-2 – hairy-cell leukemia
- Family Flaviviridae Genus Hepacivirus (hepatitis C virus)
3. Prion infections, pathogenesis, diagnostic problems

Purpose of the lesson:

- To provide students with information about the causative agents of slow viral infections (human immunodeficiency virus), their characteristics, the pathogenesis of the diseases they cause, the main clinical signs, microbiological diagnosis, treatment and prevention principles. To teach students about oncogenic viruses and prion infections

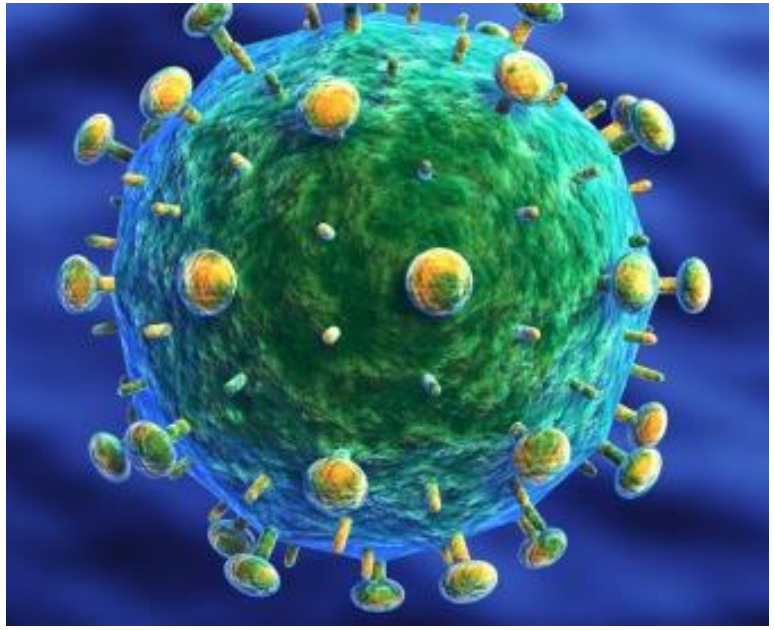
Retroviridae family (retroviruses)

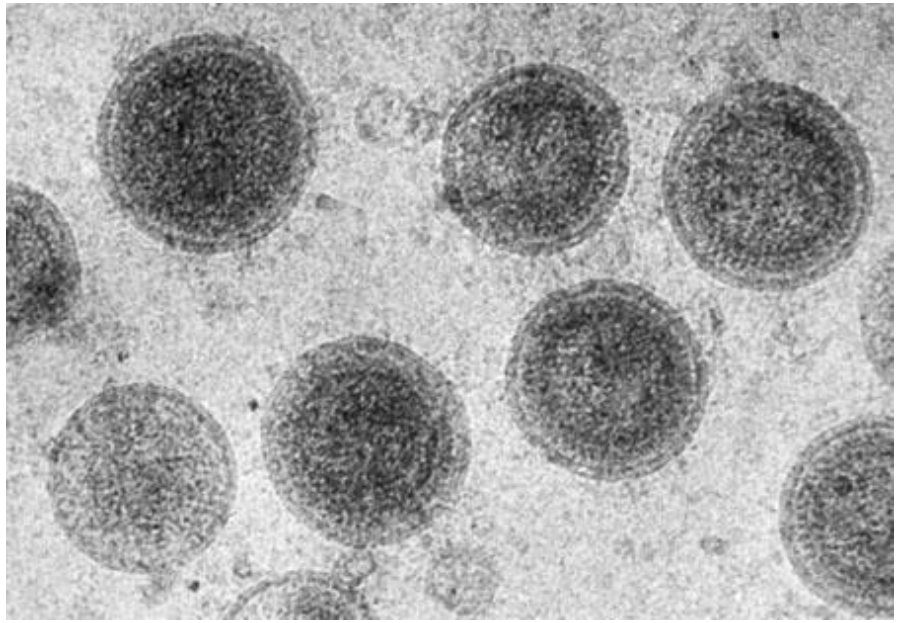
- The retroviridae family consists of single-stranded RNA viruses. The family is named after an enzyme that enables the synthesis of DNA from RNA in virions (RNA-dependent DNA polymerase, or reverse transcriptase).
- Retroviruses are spherical in shape and measure 80-110 nm. The core of the virion consists of a helical nucleoprotein surrounded by an icosahedral capsid, surrounded on the outside by a lipid-like membrane. There are glycoprotein spikes on the surface of the outer membrane.
- At the center of the central part is the presence of the viral genome and the complex reverse transcriptase associated with it.
- The genome consists of two identical positive-stranded, linear RNAs

Classification of retroviruses

- The Retroviridae family consists of 7 genera with many representatives. Most of them cause malignant tumors (cancer, sarcoma, leukemia, etc.) in various animals.
- Human immunodeficiency virus (IIV-1, IIV-2) and human T-lymphotropic viruses (HTLV-1 and HTLV-2) are more important in human pathology.

Human immunodeficiency virus





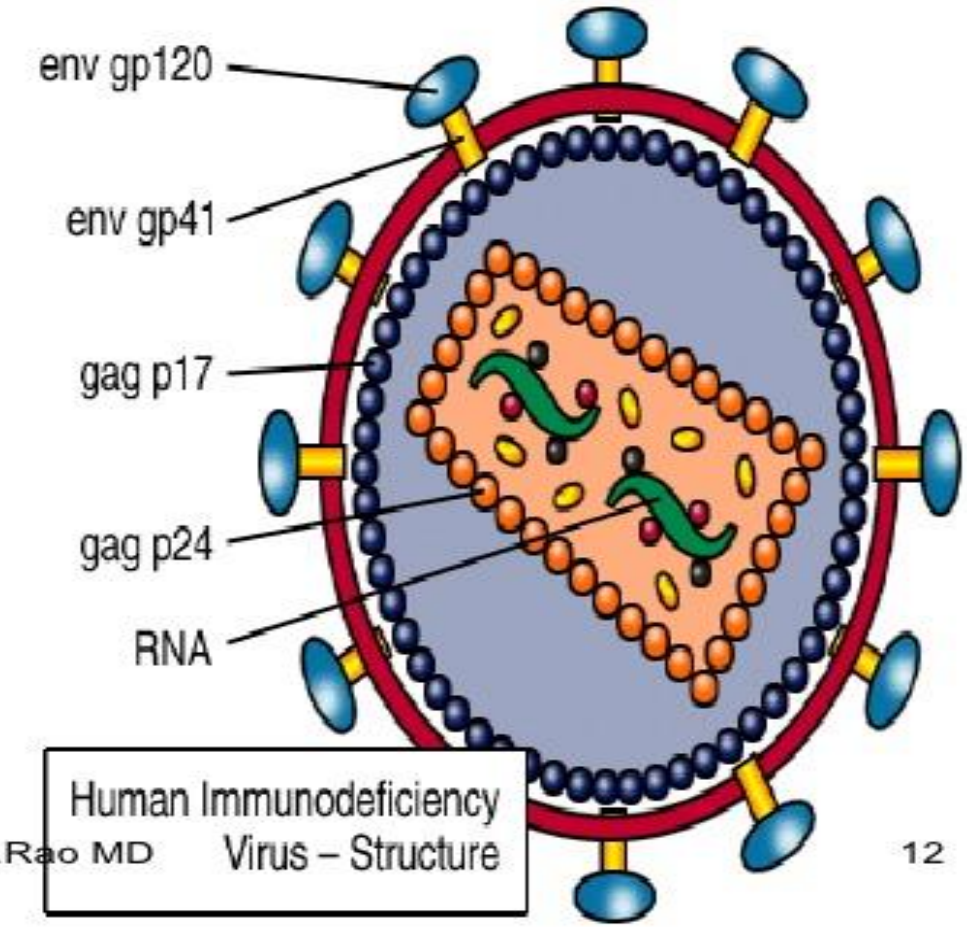
Introduction

- HIV was first Identified in 1981 in USA among homosexuals
- In 1983, French investigator named Lymphadenopathy associated virus (LAV).
- In 1984 virus was isolated by Gallo and co-workers from national institute of health in United States.

They named Human T-cell Lymphotropic virus III (HTLV-III).

Family : Retroviridae
Subfamily : Lentivirus

- RNA virus, 120nm in diameter
- Envelope gp160; gp120 & gp41
- Icosahedral symmetry
- Nucelocapsid
  - Outer matrix protein (p17)
  - Major capsid protein (p24)
  - Nuclear protein (p7)
- Diploid RNA with several copies of reverse transcriptase



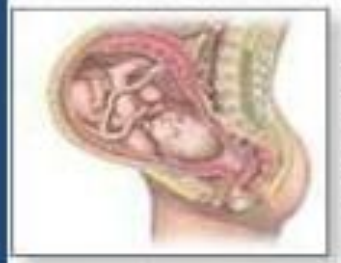
Human Immunodeficiency Virus – Structure

HIV Modes of Transmission

Unprotected sex with an infected partner

Sharing needles with infected person

Almost eliminated as risk factors for HIV transmission are:



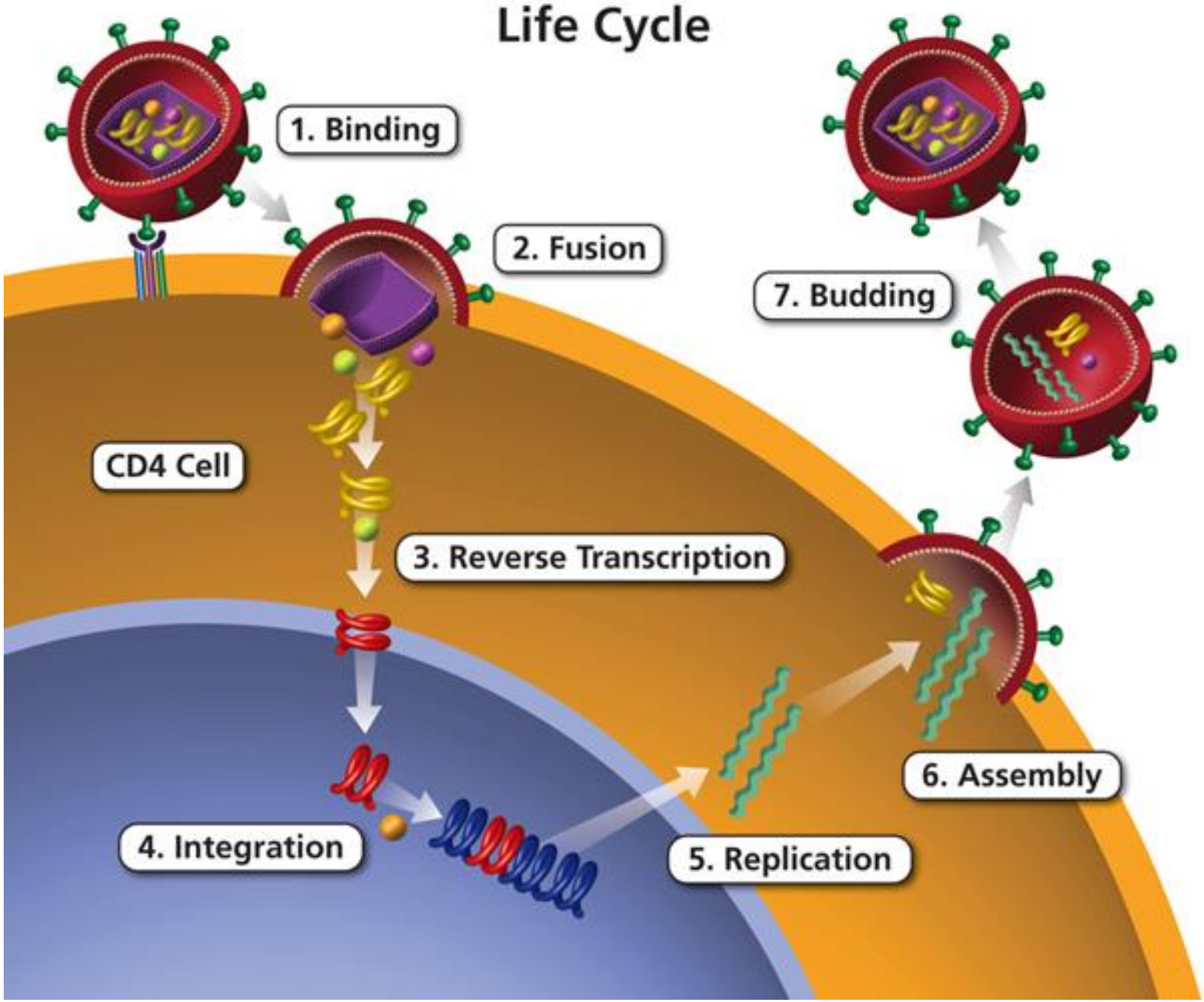
Transmission from infected mother to fetus

Infection from blood products

- vertical transmission of HIV from mother to child is the main route by which childhood HIV infection is acquired
- the risk of perinatal acquisition is 25-40% without intervention

- *The body fluids have been proven to spread HIV:*

- *blood*
- *semen*
- *vaginal fluid*
- *breast milk*
- *other body fluids containing blood*
- *cerebrospinal fluid surrounding the brain and the spinal cord*
- *synovial fluid surrounding bone joints*


Life Cycle
1. Binding
2. Fusion
CD4 Cell
3. Reverse Transcription
4. Integration
5. Replication
6. Assembly
7. Budding

PATHOGENESIS :

- *Attachment of virus at the CD4 receptor and chemokine co-receptors .*
- *viral fusion and uncoating*
- *Reverse transcriptase .*
- *Migration to nucleus*
- *Integration of the viral DNA into cellular DNA by the enzyme integrase*
- *Transcription and RNA processing*
- *Protein synthesis.*
- *protease cleaves polypeptides into functional HIV proteins and the virion assembles*
- *virion budding*
- *Virion maturation*

FOUR STAGES OF HIV

STAGE 1 – PRIMARY :

- *flu like illness - occurs two to six weeks after infection or there may be*
- *no symptoms at all*
- *Infected person can infect other people*

Stage 2 - Asymptomatic

- *This stage is free from symptoms*
- *There may be swollen glands.*
- *HIV antibodies are detectable in the blood*
- *This stage is last for about ten years*

STAGE 3 – SYMPTOMATIC :

The person starts showing symptoms like fever, skin disease.

The immune system deteriorates emergence of opportunistic infections and cancers

STAGE 4 - HIV ⇨ AIDS :

- *The immune system weakens*
- *The illnesses become more severe leading to AIDS*
- *The illnesses become more severe leading to emergence of opportunistic infections and cancers*

SYMPTOMS :

The symptoms of this :

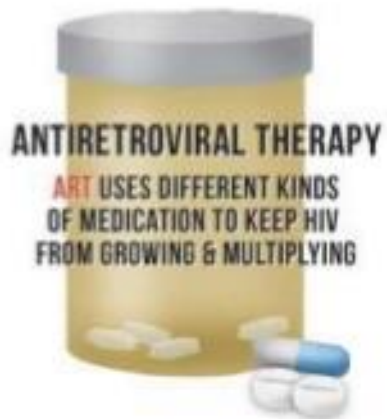
- *diarrhea*
- *fatigue or weakness*
- *fever*
- *headache*
- *joint pain*
- *night sweats*
- *rash*
- *swollen glands*
- *weight loss*
- *yeast infections (of the mouth or vagina) that last a long time or occur frequently*

Diagnostic Tests for HIV Infection

- Serological methods for detection of antibody
  - Rapid tests
  - ELISA
  - Western blot
- Antigen detection methods
  - P24 antigen capture test
  - Polymerase Chain Reaction (also known as PCR or viral load)

HIGHLY ACTIVE ANTIRETROVIRAL DRUGS

- NUCLEOSIDE REVERSE TRANSCRIPTASE
  - *Zidovudine*
  - *Stavudine*
- NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR
  - *Efavirenz*
  - *Nevirapine*
- PROTEASE INHIBITOR
  - *Atazanavir*
  - *Darunavir*



PREVENTION

There's no vaccine to prevent HIV infection and no cure for AIDS. But it's possible to protect yourself and others from infection. That means educating yourself about HIV and avoiding any behavior that allows HIV-infected fluids — blood, semen, vaginal secretions and breast milk — into your body.

ONCOGENIC VIRUS

Introduction

- **Oncogenesis** -An abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function. Result of genetic changes that alter the expression or function of proteins that play critical roles in the control of cell growth and division.
- **Proto-oncogenes** - normal gene,present in normal cells, conserved in their genomes, code for proteins which regulate cell growth and differentiation.
- **Oncogenes** - mutated versions of proto-oncogenes that contribute to cancer development by disrupting a cell's ability to control its own growth.

ONCOGENIC VIRUSES

- Viruses that produce tumours in their natural host/experimental animals or which induce malignant transformation of cells on culture.

TYPES:

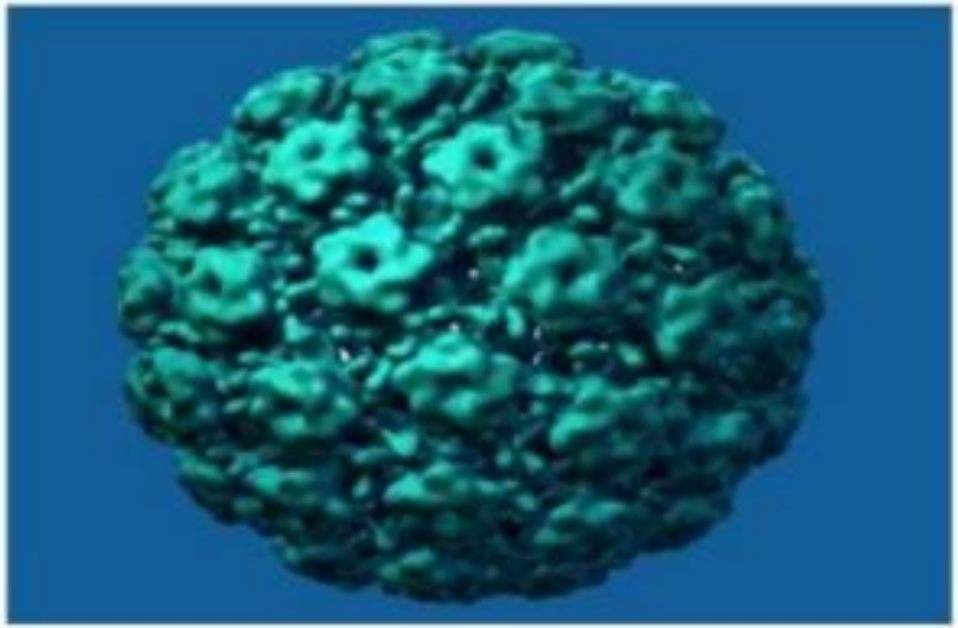
- Oncogenic RNA Viruses

  Retroviruses are divided into oncoviruses, lentiviruses, and spumaviruses.

- Oncogenic DNA Viruses

  Oncogenic human DNA viruses include hepatitis B viruses, herpesviruses, and papillomaviruses.

Human Papillomavirus (HPV)



Double-stranded DNA virus

Infects human epithelial cells

>200 different strains of the virus

- 30-40 anogenital
- 15-20 oncogenic

Genital warts, cervical dysplasia not-reportable, so prevalence data incomplete

Considered the most common sexually transmitted infection in the United States

HPV

- Small
- Non-enveloped
- Virion –Icosahedral
- Genome – double stranded ,circular DNA (8000bp)
- 16 genera (5 – human infections)

Epidemiology:

- HPV induced cervical cancer is 2nd most common cancer worldwide
- 16% of all female cancers are linked to HPV
- Papilloma virus is found in 90% of women with cervical cancers

HPV DISEASES

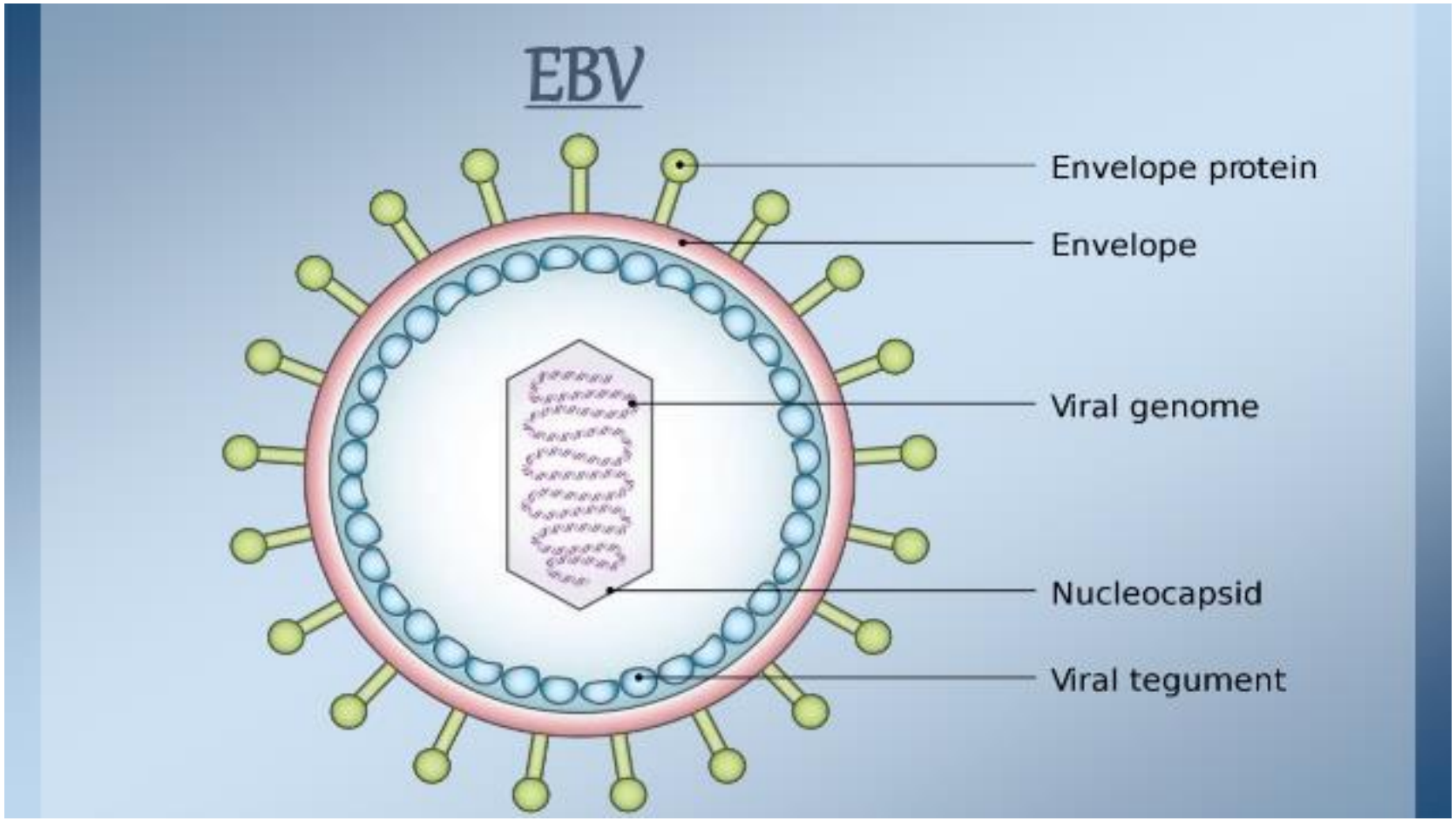
- Genital HPV is a very common sexually transmitted infection which usually causes no symptoms and goes away by itself, but can sometimes cause serious illness. HPV is responsible for:
- almost all cases of genital warts and cervical cancer
- 90% of anal cancers
- 65% of vaginal cancers
- 50% of vulva cancers
- 35% of penile cancers
- 60% of oropharyngeal cancers (cancers of the back of the throat, including the base of the tongue and tonsils).
- Four out of five people have at least one type of HPV at some time in their lives. It is sometimes called the 'common cold' of sexual activity. HPV infects both men and women.

Diagnosis

- The **Pap test** can find abnormal cells on the cervix so that they can be removed before cancer develops. Abnormal cells often become normal over time, but can sometimes turn into cancer. These cells can usually be treated, depending on their severity and on the woman's age, past medical history, and other test results.
- An **HPV DNA test**, which can find certain HPV types on a woman's cervix, may also be used with a Pap test in certain cases (called co-testing). Even women who were vaccinated when they were younger need regular cervical cancer screening because the vaccines do not protect against all cervical cancers.

Treating HPV

- **HPV vaccination** could prevent most cancers and other diseases caused by HPV. There is **no treatment** for the virus itself, but there are treatments for the problems that HPV can cause.
- ✓ In most cases the immune system clears HPV from the body naturally over time and has no long-lasting effects. Most people with HPV have **no symptoms** and will never know they have it.
- ✓ For women, having regular **Pap tests** once they become sexually active is the only way to detect abnormal cells on the cervix caused by HPV.
- ✓ **Genital warts** can be treated by doctors or at sexual health clinics.
- ✓ **Recurrent Respiratory Papillomatosis (RRP)**, a rare condition in which warts grow in the throat, can be treated with surgery or medicines.


EBV
Envelope protein
Envelope
Viral genome
Nucleocapsid
Viral tegument

EBV

- Infectious mononucleosis
- Burkitt's lymphoma
- Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family. It is one of the most common human viruses. EBV is found all over the world.
- **Epidemiology**
  - Ubiquitous
  - Burkitt's lymphoma – children in Central Africa
  - Nasopharyngeal carcinoma – Cantonese China , Alaskan eskimos.

- Malaria - cofactor

Symptoms

- Once you're infected with EBV, symptoms can take 4 to 6 weeks to show up. When they do, they're often mild, especially in young children. Kids' symptoms may be more like those of a cold or flu. Teens often have more obvious symptoms of mononucleosis. If you do get symptoms, most likely you'll have:

- Fatigue
- Fever
- Lack of appetite
- Rash
- Sore throat
- Swollen glands in the neck
- Weakness and sore muscles

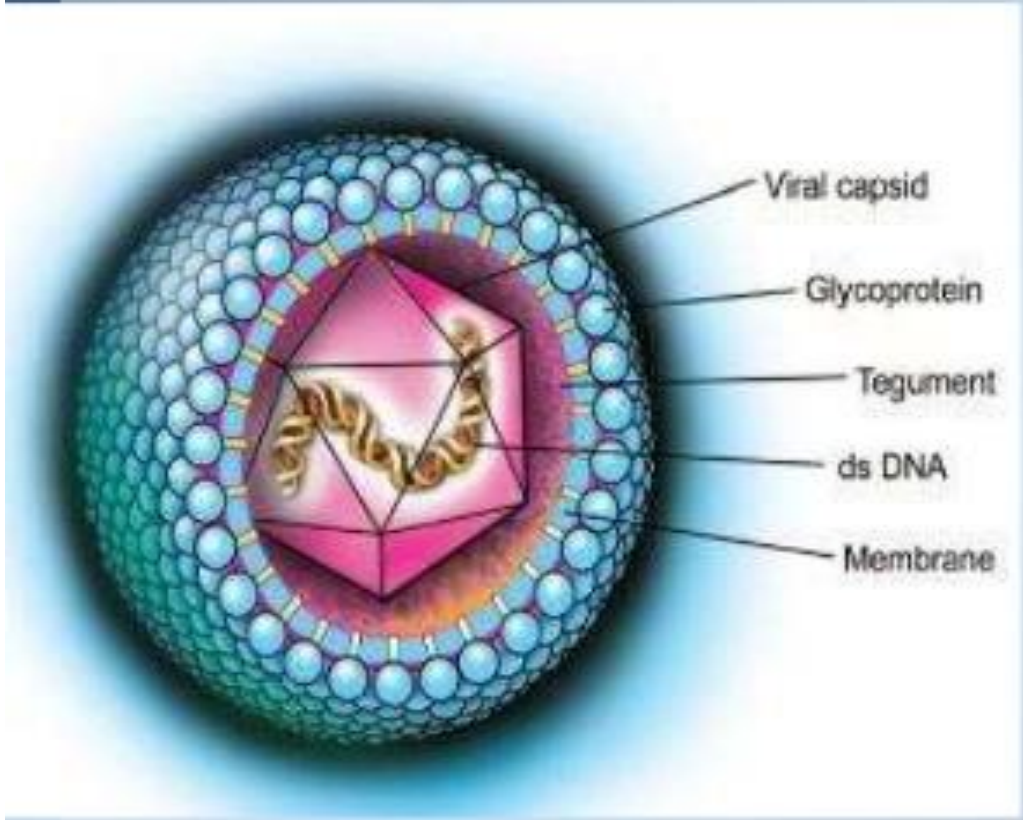
Symptoms of Burkitt's Lumphoma

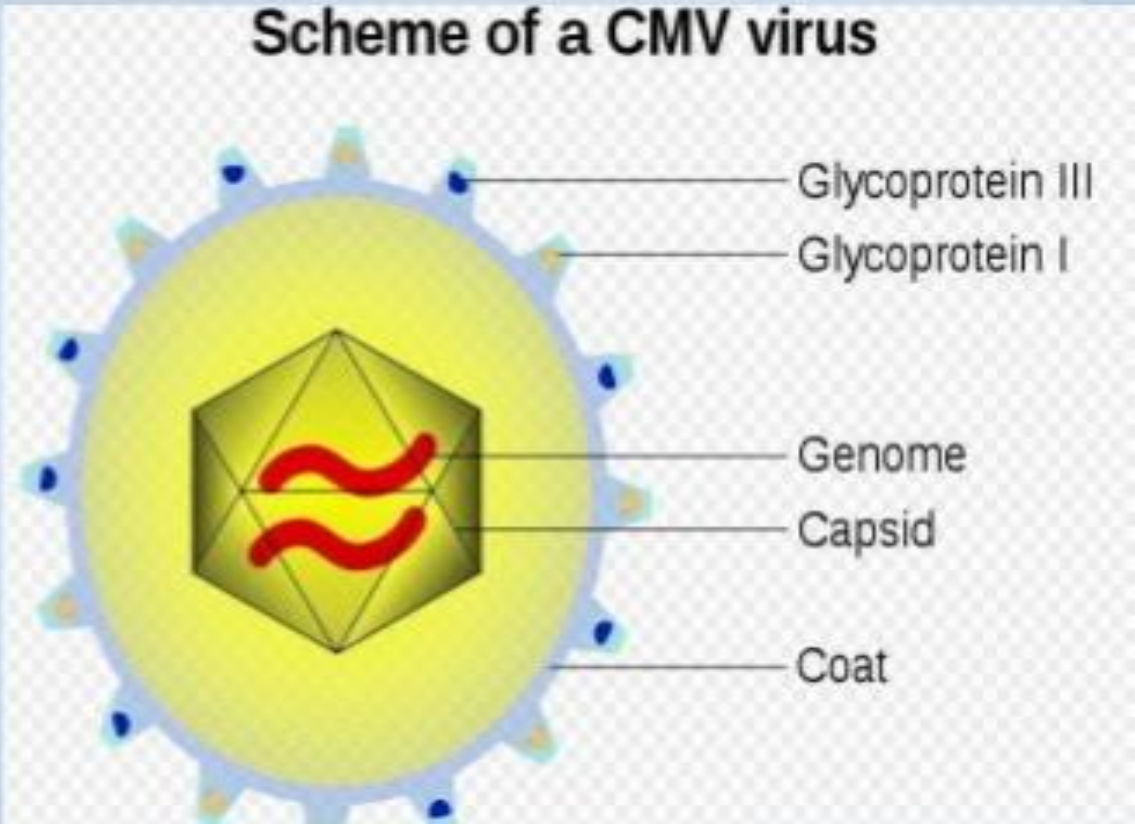
- The symptoms depend on the type.
- The endemic (African) variant usually starts as tumors of the jaw or other facial bones. It also can affect the gastrointestinal tract, ovaries, and breasts and can spread to the central nervous system, causing nerve damage, weakness, and paralysis.
- The sporadic and immunodeficiency-associated types usually start in the bowel and form a bulky tumor mass in the abdomen, often with massive involvement of the liver, spleen, and bone marrow. These variants also can start in the ovaries, testes, or other organs, and spread to the brain and spinal fluid.

TREATMENT

- Treatments for Burkitt lymphoma may include intensive chemotherapy in combination with:
- **Rituximab (Rituxan),** a monoclonal antibody that sticks to proteins on cancer cells and stimulates the immune system to attack cancer cells
- **Autologous stem cell transplantation**, in which the patient's stem cells are removed, stored, and returned to the body
- Radiation therapy
- Steroid therapy
- In some cases, surgery may be needed to remove parts of the intestine that are blocked, bleeding, or have ruptured

CMV


Viral capsid
Glycoprotein
Tegument
ds DNA
Membrane


Scheme of a CMV virus
Glycoprotein III
Glycoprotein I
Genome
Capsid
Coat

CMV

- Cytomegalovirus or CMV, is a common virus that infects people of all ages. In the United States, nearly one in three children are already infected with CMV by age 5 years. Over half of adults by age 40 have been infected with CMV. Once CMV is in a person's body, it stays there for life and can reactivate. A person can also be reinfected with a different strain of the virus.
- Most people infected with CMV show no signs or symptoms. That's because a healthy person's immune system usually keeps the virus from causing illness. However, CMV infection can cause serious health problems for people with weakened immune systems, as well as babies infected with the virus before they are born (Congenital CMV).

Signs & Symptoms

- Most people with CMV infection have no symptoms and aren't aware that they have been infected. In some cases, infection in healthy people can cause mild illness that may include

•Fever,
•Sore throat,
•Fatigue, and
•Swollen glands.
•Occasionally, CMV can cause mononucleosis or hepatitis

- People with weakened immune systems who get CMV can have more serious symptoms affecting the eyes, lungs, liver, esophagus, stomach, and intestines. Babies born with CMV can have brain, liver, spleen, lung, and growth problems. Hearing loss is the most common health problem in babies born with congenital CMV infection.

Diagnosis

- **Blood tests** can be used to diagnose CMV infections in people who have symptoms.
- A person who has been infected with cytomegalovirus (CMV) will develop **antibodies** to the virus that will stay in the body for the rest of that person's life. A blood test for these antibodies can tell whether a person has ever been infected with CMV.
- Tests that can indicate when a person was infected are **not** widely available commercially.
- If the virus is detected in the blood, saliva, urine or other body tissues, it means that the person has an active infection.

Treatment

- Healthy people who are infected with CMV usually **do not** require medical treatment.
- **Medications** are available to treat CMV infection in people who have weakened immune systems and babies who show symptoms of congenital CMV infection.
- If treatment is needed, it's most often in the form of **antiviral drugs**. Antiviral drugs slow the virus reproduction, but can't cure it.
- The antiviral medications against CMV include the following:
  - Ganciclovir (Cytovene)
  - Valganciclovir (Valcyte)
  - Foscarnet (Foscavir)
  - Cidofovir (Vistide)

The causative agents of slow viral infections

- In humans, slow viral infections include measles, mumps, poliomaviridae, JC-virus, and others.
- Typical slow viral infections in animals include Visna and Maedi viruses of the genus Lentivirus of the family Retroviridae.
- Visna virus infects in the form of DNA-virus integration with the genome of cells. The disease affects all internal organs of sheep, pathological changes occur, especially in the brain, lungs and reticuloendothelial system.
- Diseases similar to slow viral infections are also caused by prions.

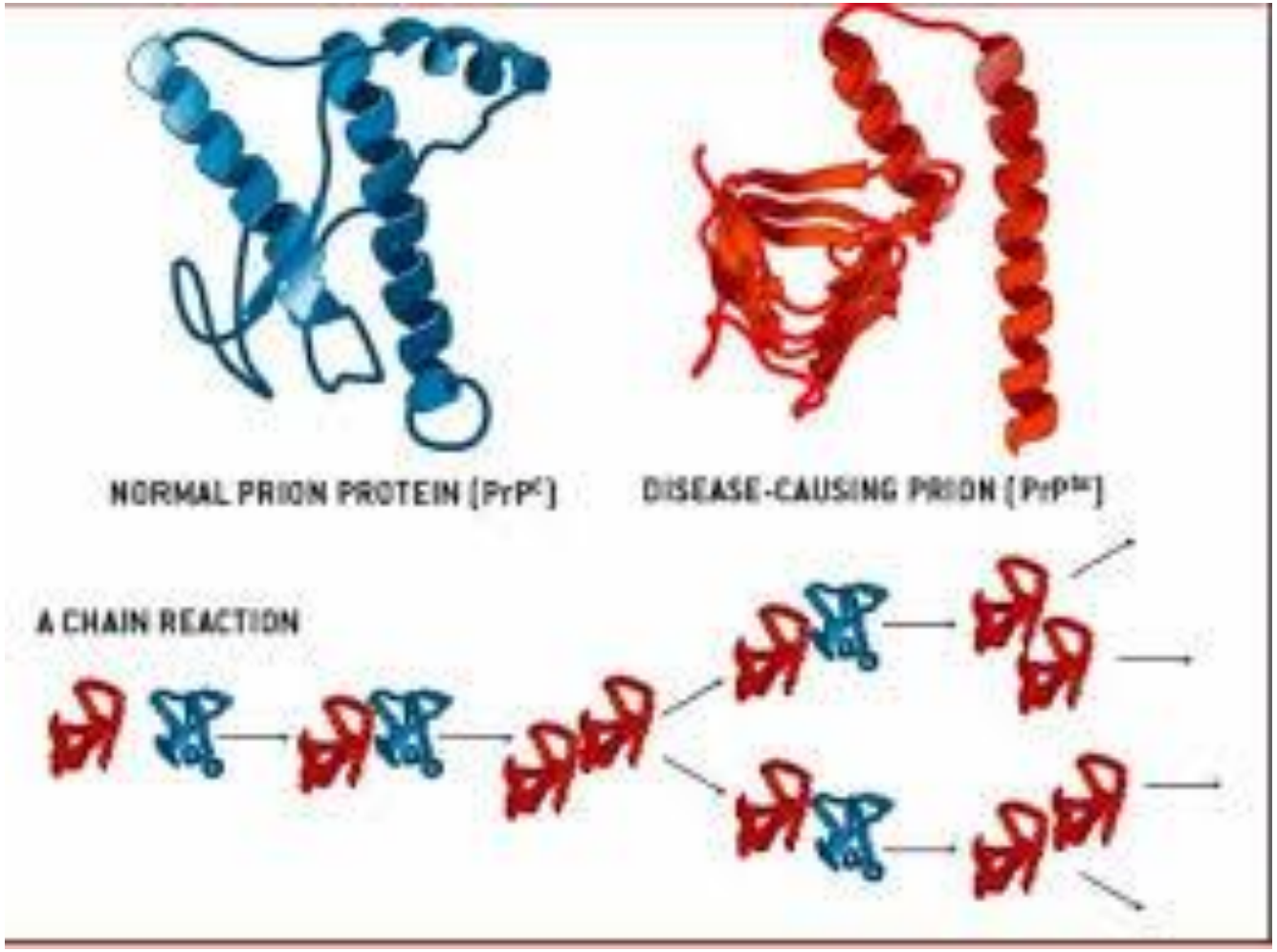
Prions

- The term prion, proposed by the American scientist S.Pruziner, is derived from the English word "proteinaceous infectious particle", which means "infectious protein particle". Prion protein (PrP - prion protein) can be in two forms - cellular, normal (PrPC) and altered, pathological (PrPSC).
- Normal prion protein (Prc) is present in both animal and human organisms. Found on the surface of cells anchored to the membrane by the glycoprotein of the molecule, this protein performs a number of regulatory functions - it is involved in the transmission of nerve impulses, the regulation of diurnal biorhythms.

Infectious prion protein

- In prion diseases, the normal prion protein becomes an infectious form. It is referred to as PrPSc (Sc - from the English word "scrape", which is a prion disease of sheep and goats).
- **Infectious prion protein** differs from normal prion protein in its tertiary and quaternary structure. PrPSC has a molecular weight of 27-30 kDa and is a pathological, posttranslated altered form of the prion protein.
- These prions are resistant to proteases, boiling, high temperature, ionizing radiation, 50% ethyl alcohol, 3.7% formaldehyde, glutaric aldehyde, beta-propionate.
- They can be inactivated by 90% ethyl alcohol, ether, strong detergents, as well as autoclaving at 121C for 1 hour. Quanidine thiocyanate is very effective in neutralizing medical instruments and accessories.

PrP^{c} və PrP^{Sc}

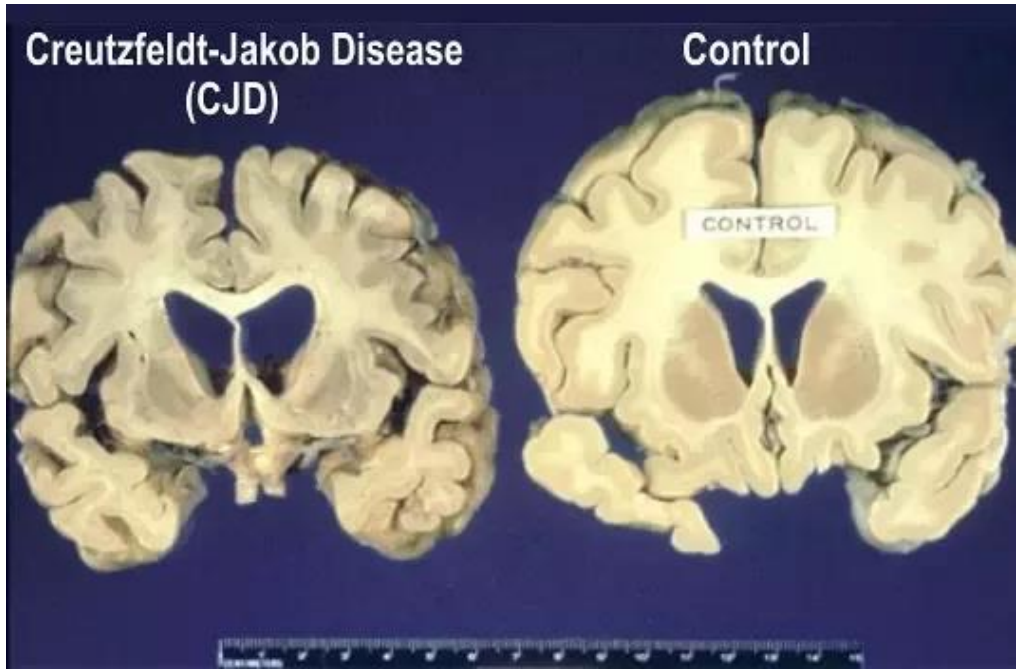


Prion diseases

- Prions are unusual pathogens that cause transmissible spontaneous encephalopathy.
- In humans (kuru, Kreitsfeldt-Jacob disease);
- in animals (scrap in sheep and goats, sponge-like encephalopathy in cattle, etc.)

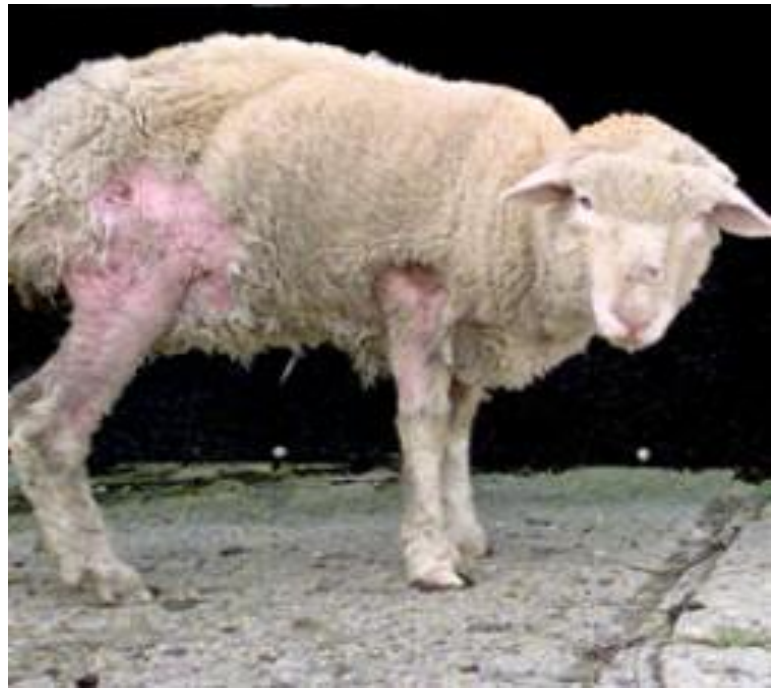
Clinical forms of prion diseases

- **Kreitsfeldt-Jacob's disease** is infected by the use of undercooked animal products, such as beef from the brain of cattle with spongiform encephalopathy, and by the use of other substances in the transplantation of tissues, such as the cornea and meninges.



Clinical forms of prion diseases

- **Scraping** - severe itching of the skin in various animals, especially sheep and goats, hair loss ("sheep disease"), damage to the central nervous system, progressive impairment of coordination of movements with the inevitable death of the animal.



Clinical forms of prion diseases

- **Spongeal encephalopathy of cattle** ("mad cow disease", "cattle rabies") is a scrapie-like disease associated with the addition of bone meal made from the bones of sick sheep to the feed of animals as a feed additive.
- The disease is accompanied by damage to the central nervous system, impaired coordination of movements, ataxia and eventually death.

Diagnosis of prion diseases

- Diagnosis of prion diseases is based on histological examination of sections of the brain.
- Spongeal changes in the brain, astrocytosis (gliosis), amyloidosis are detected in prion pathology.
- Amyloid areas are detected by staining with Congo red.
- Inflammatory changes are not characteristic.