RNA viruses

RNA VIRUSES

- **(+) RNA -** resembles mRNA - binds to ribosomes - polyprotein - cleaved into individual proteins. One of the viral proteins - RNA polymerase - makes a (–) RNA template - then more (+) RNA genome progeny and mRNAs
- **(–) RNA -** transcribed into mRNAs and a full-length (+) RNA template by the RNA polymerase carried in the virion. (+) RNA template is used to make (–) RNA genome progeny.
- **DS RNA** - acts like (–) RNA. (–) strands - transcribed into mRNAs (by RNA polymerase) New (+) RNAs get encapsidated and (–) RNAs are made in the inner capsid.
- **Retroviruses** have (+) RNA that is converted to complementary DNA (cDNA) by reverse transcriptase carried in the virion **(SEPARATE LECTURE)**

Family*	Members†
PARAMYXOVIRIDAE	Parainfluenza virus, Sendai virus, *measles virus,* mumps virus, respiratory syncytial virus, metapneumovirus
ORTHOMYXOVIRIDAE	*Influenza virus* types A, B, C and thogotoviruses
CORONAVIRIDAE	*Coronavirus,* severe acute respiratory syndrome (SARS) virus, Middle East respiratory syndrome (MERS) virus
Arenaviridae	*Lassa fever virus,* Tacaribe virus complex (Junin and Machupo viruses), lymphocytic choriomeningitis virus
Rhabdoviridae	*Rabies virus,* vesicular stomatitis virus
Filoviridae	*Ebola virus,* Marburg virus
Bunyaviridae	*California encephalitis virus,* La Crosse virus, sandfly fever virus, hemorrhagic fever virus, Hanta virus
Retroviridae	Human T-cell leukemia virus types I and II, *human immunodeficiency virus,* animal oncoviruses
Reoviridae	*Rotavirus,* Colorado tick fever virus
Togaviridae	Rubella virus; *western, eastern, and Venezuelan equine encephalitis virus;* Ross River virus; Sindbis virus; Semliki Forest virus chikungunya virus
Flaviviridae	*Yellow fever virus,* dengue virus, St. Louis encephalitis virus, West Nile virus, hepatitis C virus
Caliciviridae	*Norwalk virus,* calicivirus
Picornaviridae	Rhinoviruses, *poliovirus,* echoviruses, coxsackievirus, hepatitis A virus
Delta	Delta agent

*The size of the type is indicative of the relative size of the virus.

†The italicized virus is the prototype virus for the family.

Properties of RNA viruses

RNA is labile and transient.

Most RNA viruses replicate in the cytoplasm.

Cells cannot replicate RNA. RNA viruses must encode an RNA-dependent RNA polymerase.

The genome structure determines the mechanism of transcription and replication.

RNA viruses are prone to mutation.

The genome structure and polarity determine how viral messenger RNA (mRNA) is generated and proteins are processed.

RNA viruses, except for (+) RNA genome, must carry polymerases.

All (–) RNA viruses are enveloped.

Picornaviruses, Togaviruses, Flaviviruses, Caliciviruses, and Coronaviruses

(+) RNA genome resembles mRNA and is translated into a polyprotein, which is proteolyzed. A (–) RNA template is used for replication. For togaviruses, coronaviruses, and caliciviruses, early proteins are translated from the genome and late proteins from smaller mRNAs transcribed from template.

Orthomyxoviruses, Paramyxoviruses, Rhabdoviruses, Filoviruses, and Bunyaviruses

(–) RNA genome is a template for individual mRNAs, but full-length (+) RNA template is required for replication. Orthomyxoviruses replicate and transcribe in the nucleus, and each segment of the genome encodes one mRNA and is a template.

Reoviruses

(+/–) Segmented RNA genome is a template for mRNA (+RNA). (+) RNA may also be encapsidated to generate the (+/–) RNA and then more mRNA.

Retroviruses

(+) Retrovirus RNA genome is converted into DNA, which is integrated into the host chromatin and transcribed as a cellular gene

Non enveloped single-stranded RNA viruses

Picornaviruses

- **small *(pico)*** ribonucleic acid **(RNA)** viruses that have a **naked capsid** structure
- **Genera**:

Enterovirus,

Rhinovirus,

Hepatovirus (hepatitis A virus; discussed in separate lecture),

Cardiovirus,

Aphthovirus

Virion is a **naked, small** (25 to 30 nm), **icosahedral** capsid enclosing a single-stranded positive RNA genome.

Enteroviruses are resistant to pH 3 to pH 9, detergents, mild sewage treatment, and heat.

Rhinoviruses are labile at acidic pH; optimum growth temperature is 33° C.

Genome is a messenger ribonucleic acid (mRNA).

Naked genome is sufficient for infection.

Virus replicates in cytoplasm.

Viral RNA is translated into **polyprotein,** which is then cleaved into enzymatic and structural proteins.

Most viruses are **cytolytic.**

Picornaviruses – disease mechanism

Enteroviruses enter via the oropharynx, intestinal mucosa, or upper respiratory tract and infect the underlying lymphatic tissue; rhinoviruses are restricted to the upper respiratory tract.

In the absence of serum antibody, enterovirus spreads by viremia to cells of a receptor-bearing target tissue.

Different picornaviruses bind to different receptors, many of which are members of the immunoglobulin superfamily (i.e., intercellular adhesion molecule-1).

The infected target tissue determines the subsequent disease.

Viral, rather than immune, pathologic effects are usually responsible for causing disease.

The secretory antibody response is transitory but can prevent the initiation of infection.

Serum antibody blocks viremic spread to target tissue, preventing disease.

Enterovirus is shed in feces for long periods.

Infection is often asymptomatic or causes mild, flulike, or upper respiratory tract disease.

- Enterovirus
  - Poliovirus types 1, 2, and 3
  - Coxsackievirus A types 1 to 22 and 24
  - Coxsackievirus B types 1 to 6
  - Echovirus* types 1 to 9, 11 to 27, and 29 to 34
  - Enterovirus 68 to 71+
- Rhinovirus types 1 to 100+
- Cardiovirus
- Aphthovirus
- Hepatovirus
  - Hepatitis A virus

*Enteric, cytopathic, human, orphan + virus.

Polioviruses

- Enterovirus
  - Poliovirus types 1, 2, and 3
  - Coxsackievirus A types 1 to 22 and 24
  - Coxsackievirus B types 1 to 6
  - Echovirus* types 1 to 9, 11 to 27, and 29 to 34
  - Enterovirus 68 to 71+
- Rhinovirus types 1 to 100+
- Cardiovirus
- Aphthovirus
- Hepatovirus
  - Hepatitis A virus

*Enteric, cytopathic, human, orphan + virus.

- **1. Asymptomatic illness -** oropharynx and gut
- **2. Abortive poliomyelitis, the minor illness,** nonspecific febrile in such persons within 3 to 4 days of exposure.
- **3. Nonparalytic poliomyelitis or aseptic meningitis** virus progresses into the central nervous system and the meninges
- **4. Paralytic polio, the major illness,** virus spreads from the blood to the anterior horn cells of the spinal cord and to the motor cortex of the brain

Polioviruses

- Enterovirus
  - Poliovirus types 1, 2, and 3
  - Coxsackievirus A types 1 to 22 and 24
  - Coxsackievirus B types 1 to 6
  - Echovirus* types 1 to 9, 11 to 27, and 29 to 34
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- Cardiovirus
- Aphthovirus
- Hepatovirus
  - Hepatitis A virus

*Enteric, cytopathic, human, orphan + virus.

Paralytic poliomyelitis

- asymmetric flaccid paralysis
- no sensory loss.
- paralysis may involve only a few muscle groups (e.g., one leg) or - complete flaccid paralysis of all four extremities
- paralysis - may result in complete recovery, residual paralysis, or death
- most recoveries -within 6 months, but as long as 2 years may be required for complete remission.
- neurons in the initially affected nerves.

Bulbar poliomyelitis

- severe
- involve the muscles of the pharynx, vocal cords, and respiration (death in 75%)
- Iron lungs, - provided external respiratory compression, were used during the 1950s to assist the breathing of patients

Postpolio syndrome

- sequela of poliomyelitis
- occur 30 to 40 years later
- 20% to 80% of patients
- deterioration of the originally affected muscles
- poliovirus is not present
- result from a loss of neurons in the initially affected nerves

Polioviruses - vaccination

Vaccine	Advantages	Disadvantages
Live oral polio vaccine (OPV)	Effective Lifelong immunity Induction of secretory antibody response similar to that of natural infection Prevents spread of virus in feces Spread of attenuated virus to contacts promotes indirect immunization Inexpensive and easy to administer No need for repeated booster vaccine Herd immunity	Risk of vaccine-associated poliomyelitis in vaccine recipients or contacts; spread of vaccine to contacts without their consent Not safe for administration to immunodeficient patients
Inactivated polio vaccine (IPV)	Effective Good stability during transport and in storage Safe administration in immunodeficient patients No risk of vaccine-related disease	Lack of induction of secretory antibody Booster vaccine needed for lifelong immunity Requires sterile syringes and needles Injection more painful than oral administration Higher community immunization levels needed than with live vaccine Does not prevent replication and spread of virus from

Enterovirus
- Poliovirus types 1, 2, and 3
- Coxsackievirus A types 1 to 22 and 24
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- Echovirus* types 1 to 9, 11 to 27, and 29 to 34
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Rhinovirus types 1 to 100+
Cardiovirus
Aphthovirus
Hepatovirus
- Hepatitis A virus

*Enteric, cytopathic, human, orphan + virus.

- (1) **inactivated polio vaccine (IPV),** developed by Jonas Salk,
- (2) **live attenuated oral polio vaccine (OPV),** developed by Albert Sabin.
- Both - incorporate the three strains of polio, are stable, are relatively inexpensive, and induce a protective antibody response (Figure 46-10).
- oral vaccine -less expensive, easy to administer, limits production of virus and virus transmission, and elicits lifelong and mucosal immunity

Coxsackievirus and Echovirus Infections

- Enterovirus
  - Poliovirus types 1, 2, and 3
  - Coxsackievirus A types 1 to 22 and 24
  - Coxsackievirus B types 1 to 6
  - Echovirus* types 1 to 9, 11 to 27, and 29 to 34
  - Enterovirus 68 to 71+
- Rhinovirus types 1 to 100+
- Cardiovirus
- Aphthovirus
- Hepatovirus
  - Hepatitis A virus

*Enteric, cytopathic, human, orphan + virus.

- Coxsackievirus A, echovirus - vesicular lesions (heparangina)
- coxsackievirus B, echovirus – myocarditis, pleurodynia - **(Bornholm disease),** also known as the **devil's grip -** sudden onset of fever and unilateral low thoracic, pleuritic chest pain
- Coxsackieviruses and enterovirus 68 - polio-like paralytic disease
- **Herpangina** -fever, sore throat, pain on swallowing, anorexia, vomiting
- vesicular ulcerated lesions around the soft palate and uvula
- coxsackievirus A16 - **Hand-foot-and-mouth disease-** vesicular lesions on the hands, feet, mouth, and tongue
- **Viral (aseptic) meningitis** -acute febrile illness, headache, meningeal irritation, , petechiae, rash

Rhinoviruses – epidemiology, clinical manifeststion, diagnosis, treatment

- Enterovirus
  - Poliovirus types 1, 2, and 3
  - Coxsackievirus A types 1 to 22 and 24
  - Coxsackievirus B types 1 to 6
  - Echovirus* types 1 to 9, 11 to 27, and 29 to 34
  - Enterovirus 68 to 71+
- Rhinovirus types 1 to 100+
- Cardiovirus
- Aphthovirus
- Hepatovirus
  - Hepatitis A virus

*Enteric, cytopathic, human, orphan + virus.

Box 46-5 Epidemiology of Rhinovirus Infections

Disease/Viral Factors

Virion is resistant to drying and detergents

Multiple serotypes preclude prior immunity

Replication occurs at optimum temperature of 33°C and cooler temperatures

Transmission

Direct contact via infected hands and fomites

Inhalation of infectious droplets

Who Is at Risk?

Persons of all ages

Geography/Season

Virus found worldwide

Disease more common in early autumn and late spring

Modes of Control

Washing hands and disinfecting contaminated objects help prevent spread

- **common cold,** upper respiratory tract infections - self-limited
- more than 100 serotypes
- rhinoviruses - **unable to replicate in the gastrointestinal tract labile to acidic pH, grow best at 33° C,** - preference for the cooler environment of the nasal mucosa
- Immunity – transient, unlikely to prevent subsequent infection (because of the numerous serotypes of the virus)
- nasal secretory IgA and serum IgG antibody - induced by a primary rhinovirus infection

- laboratory diagnosis is unnecessary. Virus can be obtained from nasal washings. Rhinoviruses are grown in human diploid fibroblast cells
- No antiviral drugs are effective.
- Nasal vasoconstrictors may provide relief, but their use may be followed by rebound congestion and a worsening of symptoms

Enveloped single-stranded segmentet RNA viruses

Influenza

The Biology of Orthomyxoviruses: Influenza

- 3 distinct influenza virus types: A, B, C; Type A causes most infections
- Viral infection
  - Virus attaches to, and multiplies in, the cells of the respiratory tract
  - Segments of RNA genome enter the nucleus (transcribed/translated)
  - Finished viruses are assembled and budded off the cell with an envelope

- Key to influenza are glycoprotein spikes –
  - **Hemagglutinin** (H) – 15 different subtypes; most important virulence factor; binds to host cells
  - **Neuraminidase** (N) – 9 subtypes – hydrolyzes mucus and assists viral budding and release

Influenza

- Both glycoproteins frequently undergo genetic changes
- decreasing the effectiveness of the host immune response
- Constant mutation is called **antigenic drift** – gradually change their amino acid composition
- **Antigenic shift** – one of the genes or RNA strands is substituted with a gene or strand from another influenza virus from a different animal host

Influenza B, C

Influenza B

- Only undergo antigenic drift
- Not known to undergo antigenic shift

Influenza C

- probably not involved in epidemics
- known to cause only minor respiratory disease

Influenza A

- Seasonal, pandemics;
- among top 10 causes of death in U.S. – most commonly among elderly and small children
- Binds to ciliated cells of respiratory mucosa
- Causes rapid shedding of cells, stripping the respiratory epithelium; severe inflammation
- Fever, headache, myalgia, pharyngeal pain, shortness of breath, coughing
- Weakened host defenses predispose patients to secondary bacterial infections, especially pneumonia

Influenza - Diagnosis, Treatment, Prevention

- Rapid immunofluorescence tests to detect antigens in a pharyngeal specimen;
- serological testing to screen for antibody titer

Treatment:

- control symptoms; amantadine, rimantadine, zanamivir (Relenza), and oseltamivir (Tamiflu)
- Flu virus has developed high rate of resistance to amantadine and rimantadine
- Annual trivalent vaccine recommended

Bunyaviruses

- spherical, enveloped particles
- Two external glycoproteins form surface projections
- virus-encoded transcriptase - in the virion
- replicate in the cytoplasm
- four genera— *Bunyaviruses, Phlebovirus, Nairovirus*, and *Hantavirus*
- cause fevers sometimes with rash.
- Hantaan virus - hemorrhage and renal failure, hantavirus pulmonary syndrome
- virus isolation, specific IgM, RT-PCR
- control of vector arthropods, vaccination
- The rodents are asymptomatic and transmit virus to other rodents and humans by way of infected urine and perhaps other body secretions

Arenaviruses

- round, oval, or pleomorphic
- five cause disease in humans:
  - Lassa virus, Junin virus, Machupo virus,
  - Guanarito virus, and **lymphocytic choriomeningitis virus (LCM)**
- Infection - invasion through broken skin or aerosol/respiratory route
- Interferon - induced -questionable benefit
- humoral response - exceptionally slow
- **Cell-mediated immunity - prime importance**
- LCM - headache, photophobia, apathy, memory defects, confusion, mental difficulties
- rarelyfatal - complete recovery is usually seen

Enveloped Single stranded non-segmented RNA viruses

Paramyxoviridae

Genus	Human Pathogen
Morbillivirus	Measles virus
Paramyxovirus	Parainfluenza viruses 1 to 4 Mumps virus
Pneumovirus	Respiratory syncytial virus Metapneumovirus

- genera *Morbillivirus, Paramyxovirus,* and *Pneumovirus*

Human pathogens:

- Morbilliviruses - **measles** virus;
- Paramyxoviruses - **parainfluenza** and **mumps** viruses;
- Pneumoviruses - **respiratory syncytial virus (RSV)** and **metapneumovirus**

Paramyxoviridae – characteristics, structure

- large viruses
- **negative-sense, single-stranded ribonucleic acid (RNA)-** helical nucleocapsid - **envelope**
- replicates in the cytoplasm
- exit by budding from the plasma membrane without killing the cell.
- induce cell-to-cell fusion, causing multinucleated giant cells **(syncytia)**
- **Cell-mediated immunity**
- transmitted in **respiratory droplets** in the respiratory tract.

Table 48-2 Major Viral-Encoded Proteins of Paramyxoviruses

Gene and Proteins*†	Virion Location	Protein Function
N: nucleoprotein	Major internal protein	Protection of viral RNA
P: phosphoprotein and C and V proteins	Association with nucleoprotein	Part of transcription complex; C and V are antagonists of innate responses
M: matrix	Inside virion envelope	Assembly of virions
F: fusion protein	Transmembranous envelope glycoprotein	Protein promotes fusion of cells, hemolysis, and viral entry
G: glycoprotein (HN, H, G)	Transmembranous envelope glycoprotein	Viral attachment protein
L: polymerase (large)	Association with nucleoprotein	Polymerase

*In order on the genome.

†Pneumoviruses also encode an SH and M2 protein.

Measles Caused by Morbillivirus

- **also known as red measles and rubeola**
- Different from German measles (Rubella)
- Very contagious;
- transmitted by respiratory aerosols
- Humans are the only reservoir
- Virus invades respiratory tract
- Sore throat, dry cough, headache, conjunctivitis, lymphadenitis, fever,
- Koplik spots – oral lesions
- Exanthem

Measles Caused by Morbillivirus

- Most serious complication - subacute sclerosing panencephalitis (SSPE
- progressive neurological degeneration of the cerebral cortex, white matter, and brain
- Involves a defective virus spreading through the brain by cell fusion and destroys cells
- Leads to coma and death in months or years
- Attenuated viral vaccine MMR

Parainfluenza

- **Widespread as influenza but more benign**
- Respiratory transmission
- mostly in children
- Minor cold, bronchitis, bronchopneumonia, croup
- No specific treatment available;
- supportive therapy

Mumps

- Epidemic parotitis; self-limited,
- painful swelling of parotid salivary glands
- Humans are the only reservoir - 40% of infections are subclinical;
- long-term immunity
- Incubation - 2-3 weeks
- fever, muscle pain and malaise,
- swelling of one or both cheeks
- uncomplicated invasion of other organs - but in 20-30% of infected adult males - epididymis and testes become infected - sterility (rare)
- Symptomatic treatment
- Live attenuated vaccine MMR

Rabies - Rhabdovirus family; genus Lyssavirus

- Enveloped, bullet-shaped virions
- Slow, progressive zoonotic disease
- Primary reservoirs are wild mammals
- can be spread by both wild and domestic mammals
- bites, scratches, inhalation of droplets

Rabies

- Virus grows at trauma site
- Enters nerve endings, ganglia, spinal cord, brain
- Infection cycle completed when virus replicates in the salivary glands

Clinical phases of rabies:

- **Prodromal** phase – fever, nausea, vomiting, headache, fatigue
- **Furious** phase – agitation, disorientation, seizures, twitching, hydrophobia
- **Dumb** phase – paralyzed, disoriented, stuporous- progress to coma phase, resulting in death

Rabies

- Often diagnosed at autopsy – intracellular inclusions (**Negri bodies**) in nervous tissue
- Preventive therapy initiated if signs of rabies appear

Treatment passive and active postexposure immunization

- Infuse the wound with human rabies immune globulin (HRIG) and globulin;
- vaccination with human diploid cell vaccine (HDCV), an inactivated vaccine given in 6 doses with 2 boosters
- Control – vaccination of domestic animals, elimination of strays, and strict quarantine practices
- Live oral vaccine incorporated into bait for wild animals

Flaviviruses

- Hepatitis C virus – separate lecture

Flaviviruses

- Transmission: viremic verterbrate hosts
- blood-feeding arthropod (female mosquito, persistently infected)
- infect another host and cause damage (death) of target cells

Disease development:

- viremia - mild systemic disease might be due to interferon production after infection (fever, chills, headaches, backaches, etc., influenza-like symptoms)
- encephalitis, hepatitis, and hemorrhage disease

Togaviruses - Rubella virus

- There is only one serotype
- respiratory infection, classic childhood exanthems (German measles)
- severe congenital defects

Pathogenesis and immunity

- upper respiratory tract infection - local lymph nodes (lymphoadenopathy)- viremia - tissues - rash

Togaviruses - Rubella virus

Congenital Rubella Syndrome - Clinical Findings

- Cataracts and other ocular defects
- Heart defects (Patent ductus arteriosus)
- Deafness
- Intrauterine growth retardation
- Failure to thrive
- Mortality within the first year
- Microcephaly
- Mental retardation

- Before vaccination, congenital infection causes 1 % neonatal abnormality.
- Vaccination reduces congenital infection to <1 to 0.1 per 100,000 pregnancies)

Lab. Diagnosis

- difficult to isolate virus
- RT-PCR.
- Serology

Filoviruses

- Filamentous RNA viruses Africa, Philippines

Two genera

- **Ebolavirus**
- **Marburgvirus** (Africa only)
- Cause hemorrhagic fevers - fatality rates (up to 90%)
- Infection appears to be by close contact with infected person
- Highly contagious
- First outbreak: 1967 (Marburg, Germany; Yugoslavia)

Filoviruses

- Major clinical feature - inflammatory response resembling septic shock
- Nonhuman primate models - initial replication in monocytes, macrophages, dendritic cells
- systemic cytokine and chemokine inflammatory response
- Multisystem organ failure
- Disseminated intravascular coagulation
- no standard treatment for Ebola
- supportive therapy -balancing the patient’s fluids, electrolytes, maintaining their oxygen status and blood pressure, and treating them for any complicating infections

Coronaviruses – characteristics, structure

- solar corona–like appearance (the surface projections)

- viral nucleocapsid is a long, flexible helix
- composed of the positive-strand RNA and molecules of the phosphorylated nucleocapsid protein N
- viral envelope - lipid bilayer derived from the intracellular membranes of the host cell,
- viral glycoproteins (Spike [S], E, hemagglutinin-esterase [HE]), matrix protein.

Coronaviruses - Pathogenesis and Clinical Syndromes

- Animal coronaviruses - including SARS-CoV and MERS-CoV,
- replicate at 37° C and
- systemic , cytolytic infections - respiratory tracts of human

SARS-CoV and **MERS-CoV** – zoonoses

- can replicate - in epithelial cells, lymphocytes, leukocytes.
- significant lung, kidney, liver, gastrointestinal tissue damage
- **SARS-CoV** - atypical pneumonia -high fever (>38° C), chills, rigors, headache, malaise, myalgia, cough, or breathing difficulty, leading to acute respiratory distress syndrome. 20% of patients - diarrhea.
- **MERS-CoV** - acute respiratory distress syndrome, 50% mortality - Arabian peninsula.

Coronaviruses

- cause diseases in mammals and birds
- Mild illnesses in humans include some cases of the common cold
- more lethal varieties can cause SARS, MERS and COVID-19
- **Severe acute respiratory syndrome coronavirus (SARS-CoV)** and **Middle East respiratory syndrome coronavirus (MERS-CoV)** - transmitted from bats by civet cats and dromedary camels

Coronaviruses – SASRS CoV 2

- Covid 19 - contagious disease
- cause - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Nonenveloped doubla-stranded RNA viruses

Reoviruses

- **reo**: respiratory enteric orphan
- viruses caused respiratory and enteric infections

four genera – infections of humans and animals:

Orthoreovirus **Rotavirus** Orbivirus Coltivirus

Reoviruses - Rotavirus

- Latin- rota - "wheel"
- stable to: heat at 50°C to a 3.0–9.0 range of pH to lipid solvents, such as ether and chloroform
- inactivated by 95% ethanol, phenol, chlorine
- infect cells in the small intestine - multiply in the cytoplasm of enterocytes – impair transport mechanism
- diarrhea illness in infants & children - watery diarrhea, fever, abdominal pain, vomiting, dehydration (can be fatal)
- Virus in stool – lab.diagnosis

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