Chapter 24
Introduction to Viruses That Infect Humans: The DNA Viruses
24.1 Viruses in Human Infections and Diseases

• DNA or RNA molecules are surrounded by a protein coat; obligate parasites that enter a cell, instruct its genetic and molecular machinery to produce and release new viruses

• All DNA viruses are double-stranded except for parvoviruses, which have ssDNA

• All RNA viruses are single-stranded except for dsRNA reoviruses
Medical Considerations in Viral Diseases

• Viruses are limited to a particular host or cell type
• Most DNA viruses are budded off the nucleus
• Most RNA viruses multiply in and are released from the cytoplasm
• Viral infections range from asymptomatic to mild to life-threatening
• Many viruses are strictly human in origin, others are zoonoses transmitted by vectors
• Course of viral disease: invasion at portal of entry and primary infection; some viruses replicate locally, others enter the circulation and infect other tissues
• Common manifestations: rashes, fever, muscle aches, respiratory involvement, swollen lymph nodes
• Body defenses: combined action of interferon, antibodies, and cytotoxic T cells; frequently results in lifelong immunity
• Many viral infections have rapid course; lytic cycle
• Some viruses establish long-term **persistent** infections that last many years or a lifetime
• 2 types of persistent infections:
  – **Chronic infections** – virus is detectable in tissue samples, multiplying at a slow rate; symptoms mild or absent
  – **Latent infections** – after a lytic cycle, virus enters a dormant phase; generally not detectable, no symptoms; can reactivate and result in recurrent infections
Figure 24.1 Possible effects of viral infections on host cells

1. Penetration of viral nucleic acid
2. Release of virus
3. Recurrence
4. Chronic infection
5. Virus induces transformation to malignancy

Viral multiplication and lytic infection
• Some persistent viruses are oncogenic
• Several viruses can cross the placenta causing developmental disturbances and permanent defects – teratogenic
• Diagnosis of viral diseases – symptoms, isolation in cell or animal culture, serological tests for antibodies; some tests for antigens
24.2 Survey of DNA Viruses

- Animal viruses are categorized according to nucleic acid, capsid, and presence or absence of envelope
- 7 DNA families, 14 RNA families
- DNA viruses causing human disease:
  - Enveloped DNA viruses
  - Nonenveloped DNA viruses
  - Nonenveloped ssDNA viruses
TABLE 24.1

DNA Virus Groups That Infect Humans

DNA Viruses

- Enveloped
  - Double-stranded genome
    - Poxviruses
    - Herpesviruses
    - Hepadnaviruses

- Nonenveloped
  - Double-stranded genome
    - Adenoviruses
    - Polyomaviruses
      - Papillomaviruses
  - Single-stranded genome
    - Parvoviruses
24.3 Enveloped DNA Viruses
Poxviruses: Classification and Structure

- Produce eruptive skin pustules called pocks or pox, that leave scars
- Largest and most complex animal viruses
- Have the largest genome of all viruses
- dsDNA
- Multiply in cytoplasm in factory areas
- Specificity for cytoplasm of epidermal cells and subcutaneous connective tissues
Figure 24.2 Poxviruses are larger and more complex than other viruses
Smallpox

- First disease to be eliminated by vaccination
- Exposure through inhalation or skin contact
- Infection associated with fever, malaise, prostration, and a rash
  - Variola major – highly virulent, caused toxemia, shock, and intravascular coagulation
  - Variola minor – less virulent
- Routine vaccination ended in U.S. in 1972
- Vaccine reintroduced in 2002 for military and medical personnel
Figure 24.3 Smallpox infections
Molluscum Contagiosum

- In endemic areas, it is primarily an infection of children
- Transmitted by direct contact and fomites
- In U.S., most commonly an STD
- Lesions are small, smooth macules in genital area and thighs
- AIDS patients suffer an atypical form which attacks the skin of the face and forms tumor-like growths
- Treatment: freezing, electric cautery, chemical agents
Other Poxviruses

• Many mammalian groups host some poxvirus – cowpox, rabbitpox, mousepox, elephantpox
• Humans are susceptible to monkeypox and cowpox
• Monkeypox in humans – skin pocks, fever, swollen lymph nodes
• Cowpox in humans – rare, usually confined to hands; other cutaneous sites can be involved
The Herpesviruses: Common, Persistent Human Viruses

- All members show latency and cause recurrent infection; viral DNA forms episome
- Clinical complications of latency and recurrent infections become more severe with advancing age, cancer chemotherapy, or other conditions that compromise the immune defenses
- Common and serious opportunists among AIDS patients
- Large enveloped icosahedral dsDNA
- Replicates within nucleus
Figure 24.5 Herpesviruses
Herpesviruses

- Large family; 8 infect humans
  - HSV-1 – herpes simplex 1
  - HSV-2 – herpes simplex 2
  - VZV – varicella zoster virus
  - CMV – cytomegalovirus
  - EBV – Epstein-Barr virus
  - HHV-6 – herpevirus 6 – roseola
  - HHV-7 – herpevirus 7
  - HHV-8 – herpevirus 8
Herpes Simplex Viruses

• Humans susceptible to 2 varieties
  • HSV-1 – usually lesions on the oropharynx, cold sores, fever blisters
    – Occurs in early childhood
  • HSV-2 – lesions on the genitalia, possibly oral
    – Occurs in ages 14-29
    – Can be spread without visible lesions
| Comparing Epidemiology and Pathology of Herpes Simplex, Types 1 and 2 |
|-------------------------------------------------|---------------------------------|
| **HSV-1**                                      | **HSV-2**                       |
| **Usual Etiologic Agent Of**                   |                                 |
| Herpes labialis*                               | Herpes genitalis*               |
| Ocular herpes                                  |                                 |
| Gingivostomatitis                              |                                 |
| Pharyngitis                                    |                                 |
| **Transmission**                               |                                 |
| Close contact, usually of face                 | Sexual or intimate contact       |
| **Latency**                                    |                                 |
| Occurs in trigeminal ganglion                  | Occurs primarily in sacral ganglia |
| **Skin Lesions**                               |                                 |
| On face, mouth                                 | On internal, external genitalia, thighs, buttocks |
| **Complications**                              |                                 |
| Whitlows                                        | Among personnel working on oral cavity |
| Causes up to 30% of cases**                    | Among obstetric, gynecological personnel |
| Neonatal encephalitis                          | Causes most cases through contact with birth canal |

*The other herpes simplex type can be involved in this infection, though not as commonly.
**Due to mothers infected genitally by HSV-1 or contamination of the neonate by oral lesions.
Epidemiology

- Transmission by direct exposure to secretions containing the virus; active lesions most significant source; genital herpes can be transmitted in the absence of lesions
- HSV multiplies in sensory neurons, moves to ganglia
  - HSV-1 enters 5th cranial nerve
  - HSV-2 enters lumbosacral spinal nerve trunk ganglia
- Recurrent infection is triggered by various stimuli – fever, UV radiation, stress, mechanical injury
- Newly formed viruses migrate to body surface, producing a local skin or membrane lesion
Figure 24.6 Site of latency and routes of recurrence in herpes simplex, Type I
Type 1 Herpes Simplex in Children and Adults

• Herpes labialis – fever blisters, cold sores; most common recurrent HSV-1 infection; vesicles occur on mucocutaneous junction of lips or adjacent skin; itching and tingling prior to vesicle formation; lesion crusts over in 2-3 days and heals

• Herpetic gingivostomatitis – infection of oropharynx in young children; fever, sore throat, swollen lymph nodes

• Herpetic keratitis – ocular herpes – inflammation of eye; gritty feeling in the eye, conjunctivitis, sharp pain, and sensitivity to light
Type 2 Herpes Infections

- Genital herpes – herpes genitalia – starts with malaise, anorexia, fever, and bilateral swelling and tenderness in the groin; clusters of sensitive vesicles on the genitalia, perineum, and buttocks; urethritis, painful urination, cervicitis, itching; vesicles ulcerate

- Recurrent bouts usually less severe, triggered by menstruation, stress, and concurrent bacterial infection
Herpes of the Newborn

- HSV-1 and HSV-2
- Potentially fatal in the neonate and fetus
- Infant contaminated by mother before or during birth; hand transmission by mother to infant
- Infection of mouth, skin, eyes, CNS
- Preventative screening of pregnant women; delivery by C-section if outbreak at the time of birth
Figure 24.8 Genital and neonatal herpes
**Miscellaneous Herpes Infections**

- Herpetic whitlow - HSV-1 or HSV-2 can penetrate a break in the skin and cause a localized infection; usually on one finger; extremely painful and itchy

- HSV-1 encephalitis – rare complication but most common sporadic form of viral encephalitis in the U.S.

- Those with underlying immunodeficiency are prone to severe, disseminated herpes
Figure 24.10 Herpetic whitlows
Diagnosis, Treatment, and Control of Herpes Simplex

- Vesicles and exudate are typical diagnostic symptoms, scrapings from base of lesions showing giant cells, culture and specific tests for diagnosing severe or disseminated HSV; direct fluorescent antibody tests

- Treatment: acyclovir, famciclovir, valacyclovir; topical medications
Figure 24.11 Diagnosis of herpesvirus infection from stained specimen
Varicella-Zoster Virus (VZV)

- Causes chickenpox and shingles
- Humans only natural host
- Transmitted by respiratory droplets and contact
- Primary infection – chickenpox – characteristic vesicles
- Virus enters neurons and remains latent
- Later, reactivation of the virus results in shingles with vesicles localized to distinctive areas, dermatomes
- More common in older patients
- Treatment: treat symptoms in uncomplicated infections; acyclovir, famciclovir, interferon for systemic disease
- Live attenuated vaccine for chickenpox and shingles
Figure 24.12 Relationship between varicella and zoster
The Cytomegalovirus Group

• Cytomegaloviruses – CMV
• Produce giant cells with nuclear and cytoplasmic inclusions
• Transmitted in saliva, respiratory mucus, breast milk, urine, semen, cervical secretions
• Commonly latent in various tissues
• Most infections are asymptomatic
• 3 groups develop a more virulent form of disease: fetuses, newborns, immunodeficient adults
Figure 24.13
Identifying cytomegaloviruses
Cytomegalovirus

- Newborns may exhibit enlarged liver and spleen, jaundice, capillary bleeding, microcephaly, and ocular inflammation; may be fatal
  - Babies who survive develop neurological sequelae, hearing, visual disturbances and mental retardation
- Perinatal CMV infection – mostly asymptomatic, or pneumonitis, and a mononucleosis-like syndrome
- AIDS patients – CMV mononucleosis, disseminated CMV, retinitis
- Transplant patients – pneumonitis, hepatitis, myocarditis, meningoencephalitis
- Treatment reserved for immunocompromised – ganciclovir, foscarnet
Epstein-Barr Virus (EBV)

- Ubiquitous virus; infects lymphoid tissue and salivary glands
- Transmission – direct, oral contact and contamination with saliva
- In industrialized countries, college-age population is vulnerable to infectious mononucleosis (mono or kissing disease)
- By mid-life, 90-95% of all people are infected
- Infectious mononucleosis – sore throat, high fever, cervical lymphadenopathy; develop after 30-50 day incubation
- Dormancy in B cells; reactivated; may be asymptomatic
Figure 24.14 and Figure 24.15
Epstein-Barr Virus
Tumors and Other Complications Associated with EBV

- Burkitt lymphoma – B cell malignancy; usually develops in jaw and grossly swells the cheek; central African children 4-8 years old; may be associated with chronic coinfections with malaria, etc.
- Nasopharyngeal carcinoma – malignancy of epithelial cells; occurs in older Chinese and African men
- Anyone with an immune deficiency is highly susceptible to EBV
Diagnosis, Treatment, and Prevention

• Differential blood count shows lymphocytosis, neutropenia, and large atypical lymphocytes; serological assays to detect antibodies and antigen

• Treatment directed at relief of symptoms of fever and sore throat

• Disseminated disease may be treated with IV gamma globulin, interferon, acyclovir, and monoclonal antibodies
Figure 24.16 Histology of lymphocytes infected with EBV
Other Herpesviruses and the Cancer Connection

- **Human herpes virus 6 (HHV-6)-human B-lymphotrophic virus**
- **Transmitted by close contact with saliva and other secretions; very common**
- **Causes roseola, an acute febrile disease in babies 2-12 months; begins with fever, followed by a faint maculopapular rash; usually self-limited**
- **Adults may get mono-like symptoms, lymphadenopathy and hepatitis**
- **Over 70% of MS patients show signs of infection**
- **Significant relationship between HHV-6 and Hodgkin’s lymphoma, oral carcinoma, certain T-cell leukemias**
Figure 24.17 Roseola infantum in 12-month-old baby
• HHV-7 is closely related to HHV-6 and causes similar diseases
• Kaposi’s sarcoma-associated virus or HHV-8 is linked with common tumor of AIDS patients; also may be involved in multiple myeloma
The Viral Agents of Hepatitis

• Hepatitis – an inflammatory disease of liver cells that may result from several viruses

• Interferes with liver’s excretion of bile pigments, bilirubin accumulates in blood and tissues causing jaundice, a yellow tinge in skin and eyes

• 3 principal viruses involved in hepatitis:
  – Hepatitis B, hepatitis A (RNA virus), hepatitis C (RNA virus)
## TABLE 24.3 Principal Morphological and Pathologic Features of the Major Hepatitis Viruses

<table>
<thead>
<tr>
<th>Property/Diseases</th>
<th>HAV*</th>
<th>HBV</th>
<th>HCV*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biology</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nucleic acid</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Cell culture</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Envelope</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Older Synonyms</strong></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Infectious hepatitis, yellow jaundice</td>
<td>Serum hepatitis</td>
<td>Non-A/non-B hepatitis</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reservoir</td>
<td>Endemic and epidemic</td>
<td>Endemic</td>
<td>Endemic</td>
</tr>
<tr>
<td>Active infections</td>
<td>Chronic carrier</td>
<td>Chronic carrier</td>
<td>Chronic carrier</td>
</tr>
<tr>
<td>Transmission</td>
<td>Oral-fecal; water- or food-borne</td>
<td>Contact with blood or serum; sexual and intimate contact</td>
<td>Contact with blood, serum; intimate contact</td>
</tr>
<tr>
<td><strong>Incubation Period</strong></td>
<td>2–7 weeks</td>
<td>1–6 months</td>
<td>2–8 weeks</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Fever, G1 tract disorder</td>
<td>Fever, rash, arthritis</td>
<td>Similar to HBV</td>
</tr>
<tr>
<td><strong>Jaundice</strong></td>
<td>1 in 10</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Onset/Duration</strong></td>
<td>Acute, short</td>
<td>Gradual, chronic</td>
<td>Acute to chronic</td>
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<tr>
<td><strong>Complications</strong></td>
<td>Uncommon</td>
<td>Chronic active hepatitis, cirrhosis, hepatic cancer</td>
<td>Chronic inflammation, cirrhosis, cancer</td>
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<tr>
<td><strong>Availability of Vaccine</strong></td>
<td>+</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td><strong>Diagnostic Tests to Differentiate</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Details of these viruses are covered in chapter 25.*
Figure 24.18 Comparative incidence of viral hepatitis 1970-2005
Hepadnaviruses

- Enveloped DNA viruses
- Never been grown in tissue culture
- Unusual genome containing both double- and single-stranded DNA
- Tropism for liver
Hepatitis B Virus and Disease

- Multiplies exclusively in the liver, which continuously seeds blood with viruses – chronic
- $10^7$ virions/mL blood
- Minute amounts of blood, blood products can transmit infection; sexually transmitted
- High incidence among homosexuals and drug addicts
- Can become a chronic infection
- Increases risk of liver cancer – hepatocellular carcinoma
Figure 24.20 The clinical features of hepatitis B

- Fever
- Low white cell count
- Rash
- Pain, tenderness
- Jaundice
- Enlarged liver
- Arthritis
Pathogenesis of Hepatitis B Virus

• Virus enters through break in skin or mucous membrane or by injection into bloodstream
• Reaches liver cells, multiplies, and releases viruses into blood; average 7 week incubation
• Most exhibit few overt symptoms and eventually develop HBV immunity
• Some experience malaise, fever, chills, anorexia, abdominal discomfort, and diarrhea
• Fever, jaundice, rash, and arthritis in more severe disease cases
• Small number of patients develop chronic liver disease – Necrosis and cirrhosis
Diagnosis and Management of Hepatitis B

• Diagnosis based on examination of risk factors, serological tests to detect viral antibodies or antigen; radioimmunoassay and ELISA tests for surface antigens

• Screening of blood for transfusion, semen for sperm banks, organs for transplant, and routine prenatal testing of all pregnant women

• Mild cases managed by treatment of symptoms and supportive care; chronic infections treated with interferon
• Passive immunization with HBIG for persons exposed, or possibly exposed, including neonates born to infected mothers

• Primary prevention is vaccination for high risk individuals and encouraged for all newborns and infants
  – Vaccines derived from surface antigen from cloned yeast – 3 doses with boosters
  – Vaccine derived from purified sterile antigen extracted from carrier blood; mainly for people who have yeast allergies
24.4 Nonenveloped DNA Viruses
The Adenoviruses

- Nonenveloped, dsDNA
- 30 types associated with human disease
- Infect lymphoid tissue, respiratory and intestinal epithelia and conjunctiva
- Oncogenic in animals, not in humans
- Spread by respiratory and ocular secretions
- Causes colds, pharyngitis, conjunctivitis, keratoconjunctivitis, acute hemorrhagic cystitis
- Severe cases treated with interferon
- Inactivated polyvalent vaccine
Figure 24.21 Distinctive adenovirus structures
Papilloma and Polyoma Viruses

- Small, nonenveloped dsDNA
- Circular DNA
- Cause persistent infections and tumors
Human Papillomavirus

- Papilloma – squamous epithelial growth, wart, or verruca
- Caused by 100 different strains of HPV
- Common seed warts – painless, elevated, rough growth; on fingers, etc.
- Plantar warts – deep, painful; on soles of feet
- Genital warts – most common STD in U.S.; morphology ranges from tiny, flat, inconspicuous bumps to extensive, branching, cauliflower-like masses
- Transmissible through direct contact or contaminated fomites; incubation – 2 weeks to more than a year
Figure 24.22 Human papillomas
• Nine HPV types increase risk for developing reproductive cancer; 2 account for 70% of metastatic tumors
• Early detection through inspection of genitals, women Pap smear to screen for abnormal cervical cells
• Most common warts regress over time; they can be removed by direct chemical application of podophyllin and physical removal by cauterization, freezing, or laser surgery
• Warts can recur
• Two effective HPV vaccines
Figure 24.23 Pap smear of cervix in patient with HPV infection
Polyomaviruses

- Induce tumors in experimental animals
- JC and BK viruses most important human polyomaviruses
- Common throughout the world
- Majority of infections are asymptomatic or mild
- Not much is known
- Progressive multifocal leukoencephalopathy (PML) is an uncommon fatal infection by JC
- BK infection in renal transplants causes complications in urinary function
24.5 Parvoviruses

- Nonenveloped, ssDNA
- Small diameter and genome size
- Causes distemper in cats, enteric disease in dogs, fatal cardiac infection in puppies
- B19 cause of erythema infectiosum (fifth disease); rash of childhood
  - Children may have fever and rash on cheeks
  - Severe fatal anemia can result if pregnant woman transmits virus to fetus
- Adeno-associated virus (AAV) is a defective virus; it cannot replicate in host cell without adenovirus
Figure 24.24 Typical “slapped face” rash of human parvovirus (B19)