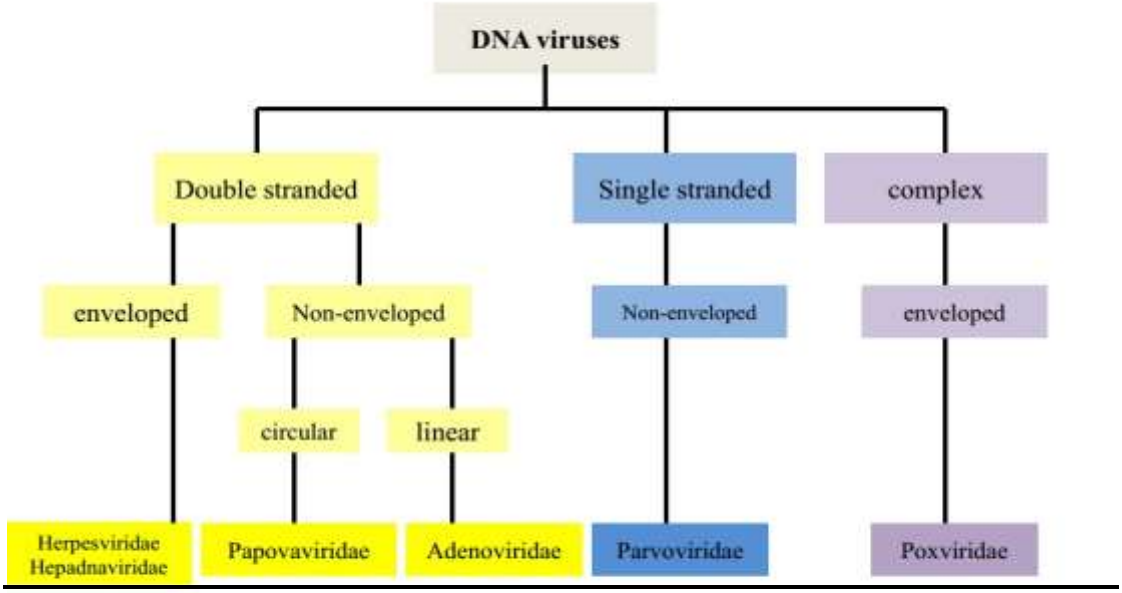
- In this sheet we will: 1) finish DNA viruses 2) begin with Hepatitis viruses
  - The info. between these brackets { } the doctor didn't mention them , they are only to make it clear while studying .

- In the previous lecture we talked about Herpesviridae family (DNA viruses) in details, and now we will continue what we had begin but without details (only a general overview).

- We have 6 families of DNA viruses and 13 families of RNA viruses
- Q:what are the DNA viruses' families that we know ?
  1) Herpesviridae 2) Hepadnaviridae 3) Papovaviridae 4) Adenoviridae
  5) Parvoviridae 6) Poxviridae



2) Adenovirus

slide #2

- Icosahedral, non-enveloped (naked)
- Double-stranded DNA
- Proteins : important antigens on the surface (hexon , penton , base , fiber) are associated with the major outer capsid proteins **[for attachment also they are toxic ,so we can see the cytopathic effects in cell cultures infected with adenovirus due to these proteins]**
- Replicates in the nucleus since it is a DNA virus.

- **<u>Virus classification</u>**: **Family**: Adenoviridae ; **Genus**: Mastadenovirus
  Species: Human adenovirus (H Ad)
- There are more than 100 serotypes , but those which cause illness in humans are about 54-55 serotypes
- classified into 7 subgenera: A to G

slide #3

outstanding characteristic

- virion has unique "spike" or fiber associated with each penton base of the capsid that aids in attachment to the host cell via the coxsackie-adenovirus receptor on the surface of the host cell, which leads to virus entry , causing toxicity to the cells **.**

- Adenovirus has tropism {to target specific type of cells/species} for cells of epithelial origin **[in the body we have many sites of epithelial cells, so it causes a wide array of diseases in the body] such as:**
  1) RTI
  2) Gastroenteritis
  3) cystitis التهاب المثانة
  4) keratoconjunctivitis
  5) meningitis

- Replicative cycle is sharply divided into EARLY & LATE events. **O**nce the late begins no longer the early are produced **[as we said in replication there might be an overlap between the events or it might be sharply demarcated]**
  - remember : in Herpesviridae it was demarcated ,when the intermediate early stage ends the early stage begins ((sheet 31 – page 6))

- **Infected by :**
  1) **oral route**: in Gastroenteritis
  2) **droplets (aerosol)**: in the Upper respiratory tract infection
  3) **fomites** (inanimate objects contaminated by the virus)

- The virus enters the epithelial cell and replicate there , then it spreads to the blood causing viremia , after that it goes to other organs (kidney, bladder, liver, lymph nodes)
  - In the lymph nodes specially the mesenteric lymph nodes, it replicates there [associated with abdominal pain] .
  - so if you see an URT infection associated with abdominal pain or conjunctivitis , it could be an Adenovirus infection .

- May remain in the lymphoid structures (tonsils and adenoids) after an acute infection, remain shedding asymptomatically for 6-18 months.
  -**nomenclature of the virus**: because of finding the virus in the adenoids of an asymptomatic patient.

- As a DNA virus it can integrate its DNA into the host cell genome.
  - Integration of part/whole viral DNA into the cellular genome and the expression of some viral proteins are usually associated with transformation, BUT Adenoviruses don't cause transformation in human cells.
  P.S. If we infect animal cells with Adenovirus transformation will occur.

- Produce smudgy intranuclear inclusion bodies [since it replicates in the nucleus.]
  - not necessarily that viruses that replicate in the nucleus will produce nuclear inclusion bodies only.
  - e.g. CMV (cytomegalovirus) replicates in the nucleus and produce both nuclear and cytoplasmic inclusion bodies . ((sheet 31 – page 4))

slide #4

- Clinical Syndromes associated with Adenovirus infection:

1. Pharyngitis
2. Pharyngoconjunctival fever
3. Acute respiratory disease (3, 4, 7, 14, 21)
4. Pneumonia
5. Follicular conjunctivitis
6. Hemorrhagic cystitis (11)
7. Acute infantile gastroenteritis (40, 41)
8. Meningitis

*the no. next to each one of them are the serotypes.

*you should know these numbers written above ONLY.

slide #5

Laboratory Diagnosis

- (1st) medical history → (2nd) physical examination → (3rd) diagnostic tests or routine lab test (for adenoviruses)
  - diagnostic tests may include:
  1) blood work
  2) culture of respiratory secretions
  3) stool culture
  4) chest x-ray
- If you couldn't reach the diagnosis → Antigen detection, PCR, serology could be useful.

slide #6

Prevention & Management

- There is **NO** specific antiviral drug, but patient specially immunocompromised might benefit from **cidofovir .** ((sheet 28))

- Q : do we have a vaccine for Adenovirus??
  Ans : yes, but we don't use it routinely.
  e.g.
  1) for newly military recruits because they have high risk to be infected by Adenovirus. (not in Jordan)
  2) for immunocompromised patients

- Good hygiene is very imp. to break the cycle of Adenovirus infection .

3) Parvovirus B19

slide #7

- Called **Erythema infectiosum**
- Naked, icosahedral, ssDNA
- Three capsid proteins VP(1-3)
- Cultured in bone marrow cells, fetal liver cells.
- The receptor is P antigen on erythrocytes.

- Infects immature nucleated erythrocyte. {replicate inside the nucleus}
- Infected patient presents with high fever, headache, malaise, arthralgia .
- Associated with Anemia and aplastic crisis [by infecting immature erythrocyte]
  - P.S. aplastic crisis : severe decline in production or maturation of the RBCs → aplastic anemia

slide #8

Manifestations

- Fever, malaise, headache and myalgia

- Indurated characteristic rash on the face (slapped-cheek) in children which spreads in 1-2 days to arms and legs [typical/classical presentation] ((check slide#9))
  - might present in other ways , and most of the time it is difficult to differentiate Parvovirus infection with other infections which cause : Exantheme (rash on the skin) .
  P.S. Enantheme: rash inside specially the buccal mucosa.

- It infects the lymph nodes and leads to enlargement in the spleen & liver.

- It is associated with thrombocytopenia, nephritis and encephalitis.

Transmission

- Main route of transmission is through the aerosol or droplets {respiratory route}
- Mainly spread in spring months.
- Viremia last 7-12 days.

Diagnosis & treatment

- **Diagnosis**: PCR and serology
- **Treatment**:
  - there is no specific treatment
  - Immunocompromised patients might benefit from immunoglobulins.

4) Poxvirus

- Some **characteristics** that we had taken before:
1) complex capsid 2) one of the biggest viruses 3) replicates in the cytoplasm {although it is a DNA virus ((sheet 12 – page 3))}

slide #10

- We have different **species** :
  1) Variola (smallpox)
  2) Vaccinia
  3) Molluscum contagiosum
  4) Orf {a disease caused by parapox virus}
  5) Cowpox
  6) Pseudocowpox

  *the doctor didn't read the other notes in the slide, but we have to know that it is an enveloped dsDNA virus .

slide #11

- Q: How many cases are infected with smallpox do we have nowadays in Jordan?
  Ans : It was eradicated in 1977 from the whole world .
  P.S. in 1950s WHO worked on eradication of poxvirus , and the last case was seen in 1977 .
- The incubation period = 2 weeks (can be as short as 4 days)
- Associated with abrupt onset, fever, chills, myalgia and 3 to 4 days later rash appears.
- **Rash (skin lesions) can be**:
  1) macule : change in the color of the skin , small lesion (5-10 mm) , most the time it is erythematous {red in color}
  2) papule : solid raised skin lesion [like the mosquito bite]
  3) vesicle : raised skin lesion containing clear fluid .
  4) pustule : raised skin lesion containing cloudy fluid .
  5) crust : the final phase of recovery with this fluid solidify or become crust-like , which will fall off and then the lesion heals.
- What is unique in smallpox that all lesions start and finish together .
  P.S. in chickenpox you can see the lesions in all stages of development
- Heal in 2-3 weeks
- These lesions are prone to bacterial superinfection

Vaccine & Diagnosis

- **Vaccine** :
  - resembles exactly the actual infection in terms of developing of post stages .
  - localized to the area of injection
  - associated with increase in the immune system for development of antibodies
- Immunity to smallpox is not lifelong (they worked hard to eradicate it using vaccine at short intervals).

slide #12

- **Diagnosis** :
  - take vesicular scraping, culture, electron microscopy, PCR

- **Return back to vaccine** :
  Edward Jenner is a cow milker, we have a cowpox virus in the cow . And by milking the cow and become in contact with it , he should be infected by the virus . But they found that he is Immune against smallpox. (This is from where they start looking for the vaccine)

- **Vaccinia virus** :
  - is a harmless virus
  - used as a vector for smallpox vaccine

slide #13

- **Molluscum contagiosm** :
  - another pox virus species
  - Spread by direct contact [with the virus or the lesions] , towels, sex .
  - incubation period 2-8 weeks
  - the lesion itself disappears in 2-12 month
  - characteristics of the lesion : 1) painless nodule
    2) pearl-like lesion (shiny surface)
    3) cheesy material in the center
  - no symptomatic illness [imp.] , only the skin lesion
  - Diagnosis : eosinophilic inclusion bodies in cytoplasm of epithelial cells (**molluscum bodies**).
  - No specific treatment
  - no vaccine
  - disappear in 2 -12 months otherwise by curettage(كشط)
    for 2 reasons → cosmetically
    for 2 reasons → it is contagious to others

  P.S. curette : is something like a fork

slide #14

- The picture on the top :
  - Molluscum contagiosm lesion
  - shiny lesion which has a cheesy-like material
- The picture on the left :
  - orf postule
  - seen mainly in the sheep & goat
- The picture on the right :
  - milkers nodules & cowpox
  - seen mainly in the cows

5) Human papillomavirus (HPV)

slide #15

- Called the papovavirus
- In the papovaviridiae family we have 2 viruses :
  1) papillomavirus 2) polyomavirus (2 of them)
- There are over 100 different serotypes of the HPV virus :
  - most types are totally harmless and asymptomatic
  - certain serotypes (6,11) are associated with genital warts (الثالول)
  [warts : cauliflower-like lesions on the genitalia]
  - others are considered as "high risk" serotypes (16,18,31) and are associated with cervical cancer or neoplasia
- Most common transmission is by skin-to-skin contact with the penis, scrotum, vagina, vulva, or anus of an infected person. [genital area]
- No antiviral treatment
- Prophylaxis : 1) Pap smear (cervical smear)
  2) Vaccines (2 types) : - cervarix vaccine
  - cardasil vaccine
  * the difference between these 2 vaccines that one of them has serotypes 6,11,16,18 (high & low risk) and the other has 16,18 (high risk) only .
  * nowadays they are given as a prophylaxis for cervical cancer

The end of DNA viruses

HEPATITIS VIRUSES (new slides)

slide #2

- We have 6 hepatitis viruses A,B,C,D,E,G
  - we don't have a lot of information about Hepatitis G virus (HGV) ,so we will talk about it briefly .

  1) HAV → Picornaviridae family
  2) HBV → Hepadnaviridae family
     [the only DNA virus in this group , partially dsDNA]
  3) HCV → Flaviviridae family
  4) HDV → [it is an incomplete RNA virus , we called it satellites , it develops a co- or super- infection with HBV ((sheet 6 - page 4))]
  5) HEV → Caliciviridae family
  6) HGV → Flaviviridae family

slide #3

Transmission

- HAV , HEV → fecal-oral route
  - the virus replicate → excreted or shedded in the feces → contaminate water sources → plants contaminated → infection spread
- HBV, HCV , HDV → parenteral & sexual route
  - HBV was called "serum hepatitis"
  - HCV was called "NA:NB hepatitis"

  *nowadays each one has a name .

slide #4

Comparison

	A	B	C	D	E
Type	SS RNA	DS DNA	RNA	SS RNA	RNA
Source of virus	Feces	Blood Blood derived Body fluids	Blood Blood derived Body fluids	Blood Blood derived Body fluids	Feces
onset	Usually sudden	Usually slow	variable	Insidious	
Incubation Period	15-45	1-6 months mean 60-90	1-5 months mean 50	30-45	21-60
Transmission	FO,P	S, P	S, P	S, P	FO
Age	Children, young adults	All ages	All ages	All ages	Young adults
Chronic Infection	No	Yes	Yes	Yes	No
Carrier state	No	10	85	50-70	No
Prevention	Pre Post Exposure Immunization	Pre Post Exposure Immunization Blood donor Screening	Blood donor screening	Pre Post Exposure Immunization	Ensure Safe Drinking water
Vaccine	Y	Y	N	Y	N

FO: fecal-oral // P: perenteral // S: sexual

- **onset : HAV** → patient may present with diarrhea , vomiting , jaundice .
- **onset : HDV** → insidious : slow but very harmful .
- **Incubation periods** : you don't have to memorize all of them .
  what you should know that : HBV & HCV have the longest incubational period
  [in average of 2-3 months for HBV , 2 months for HCV]
- **Transmission** in : HAV → feco-oral , parenteral (blood product)
  HEV → feco-oral **only**
- **Age** : HAV → children → mild symptoms / adults → more severe symptoms
- **Chronic inf.** : in HAV , HEV → Acute lytic infection

- **Carrier state** : means that the virus remain in the body and can't be cleared [replicate in the body at a very slow rate → causing harm specially to the liver (hence the name)]
  - HBV → 10% of infected case will be a carrier for the virus
  - HCV → acute illness most of the time passes unnoticed and the patient diagnosed during the chronic stage (a **carrier**), which will be harm to the liver in the form of **cirrhosis** & **hepato-cellular carcinoma** and eventually death .
- **Prevention & vaccine** : HAV → immunoglobulins , vaccine , {but no Antiviral drug, since it causes acute infection }
  HEV → no immunoglobulins , no vaccine , no Antiviral drug , should ensure water , vegetables safety
  HBV → vaccine , immunoglobulins , screening for blood product
  HCV → no vaccine , screening for blood product
  HDV → if you can prevent Hepatitis B infection, you can prevent Hepatitis D. [but there is no space effect vaccine for HDV]

  *the doctor said : "pre and post exposure immunization also we are talking about those for HBV not HDV "

1) Hepatitis A virus

slide #5

- Naked +ve sense, single stranded RNA virus with icosahedral symmetry
- Related to enteroviruses [previously it was known as Enterovirus 72]
  - nowadays it is Hepatovirus which belongs to picornaviridae .
- One stable serotype
- Difficult but can be grown in cell culture
- There are 4 serotypes

slide #6

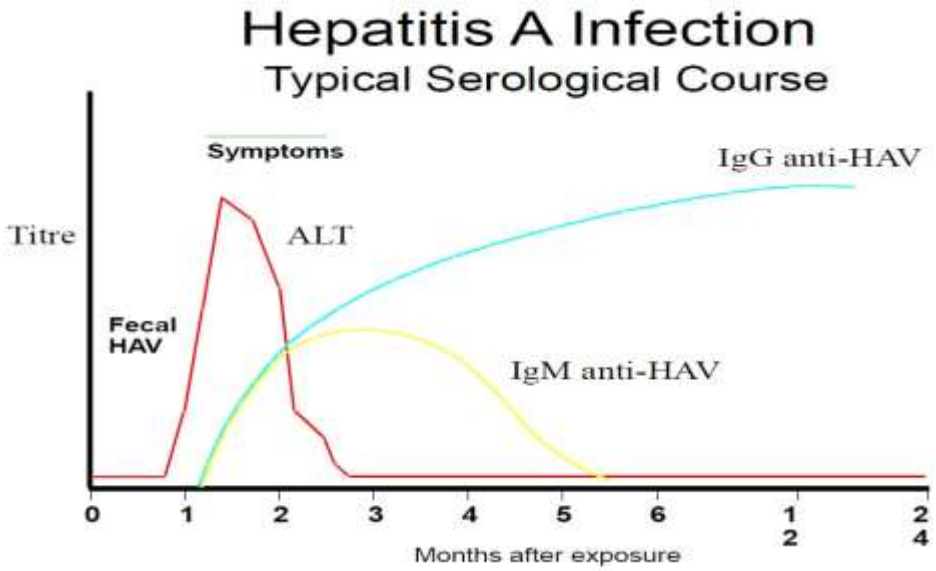
Pathogenesis

- Cause subacute disease in children & young adults. [we said that in children may pass unnoticed to mild symptoms (diarrhea , vomiting , jaundice) , but in adults symptoms are more severe]
- HAV invade into human body by fecal-oral route, multiplies in the intestinal epithelium & reaches the liver by hematogenous spread.
  [multiplies in the GI → goes to the blood → goes to the hepatocytes]

- After one week, the HAV reach liver cells replicate within, then enter intestine with bile and appear in feces.

slide #7

Serological Markers



- Incubation period→symptoms begin to appear
  - associated with increase in the:
  1) liver enzymes , e.g. ALT 2) IgM , IgG against HAV

slide #8

- We have two phases in Hepatitis [related to all hepatitis viruses]:

Prodromal [Preicteric] phase	Icteric phase
• before jaundice develops • symptoms: 1) fatigue 2) joint- and abdominal pain 3) malaise 4) vomiting 5) lack of appetite 6) hepatomegaly	• developing of jaundice - of skin, sclera, mucous membranes • associated with increase in bilirubin level . - bilirubinuria characterized by : 1)black urine 2)pale stool

slide #9

Treatment and prevention

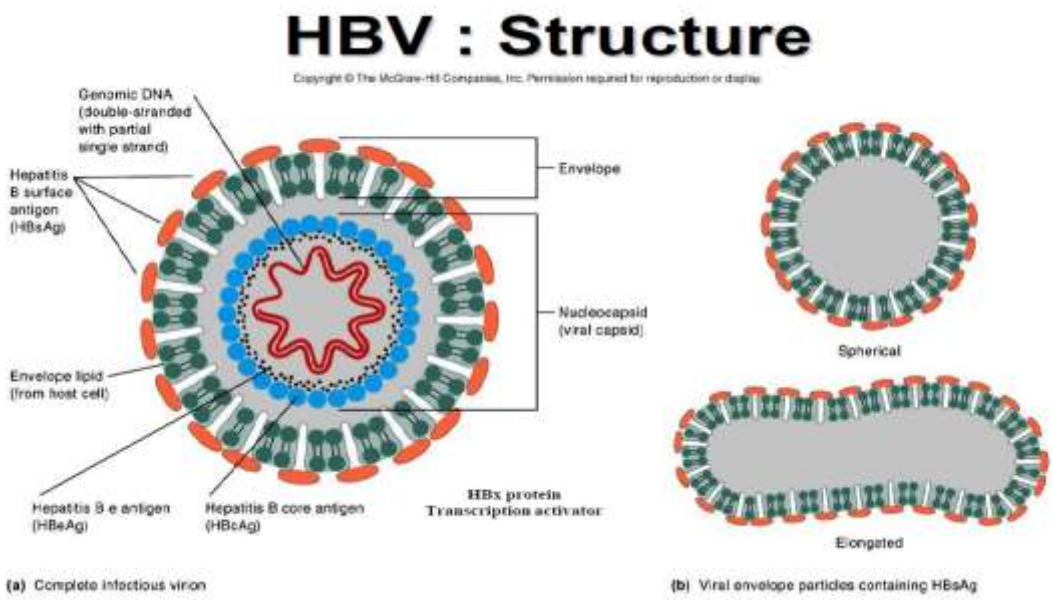
- No specific treatment for HAV ((this sheet - page 11))
- Supportive : adequate nutrition and rest
- We can give immunoglobulins which the patient might benefit from .
- Also we have a vaccine called **Formalin :**
  - kills HAV
  - 100% protective
  - 2 doses , 6-12 months apart

2) Hepatitis B virus

slide #11

- a member of the hepadnavirus group
- Enveloped, partially double-stranded DNA viruses
  - its genome size considered as the smallest in DNA viruses
- Replication involves a reverse transcriptase ((sheet 12 - page 11))
- endemic in the human population and hyperendemic in many parts of the world.
- 8 genotypes , type D in middle east
- 4 serotypes
- It has not yet been possible to propagate the virus in cell culture [the virus can't be grown in cell culture]

slide #12



- This structure in the picture (on the left) is called the "Dane particle" of hepatitis B virus.
- Also you can see (on the right) the viral envelope particles [surface antigens] without the nucleocapsid .
  - they are not infectious
  - that what Hepatitis D benefit from ,so it located in this structure and become a virus .
- Once the virus replicates, it either produces one of the above two structures (mature virus with nucleocapsid or surface antigens without nucleocapsid)
  - proportion of elongation or spherical filaments produced [which don't have a nucleocapsid] are more than the progeny [mature] virus produced.
- Surface antigens , 3 types : [important when we talk about serological markers]

Hepatitis B surface antigin (HBsAg)	Hepatitis B e antigen (HBeAg)	Hepatitis B core antigen (HBcAg)
•detected once the patient infected with HBV •if we detect **anti-HBsAg** this means that the patient had previous exposure (or a vaccine).	•detected once the patient infected with HBV •if we detect it , this means active replication of the virus at this stage. - if we detect **Anti-HBeAg** this means that the virus is no longer in replication.	•during the acute phase **anti-HBcAg (IgM)** is detected .

slide #13

HBV structure

- Virion also referred to as Dane particle {partial dsDNA} , enveloped virus
- Core antigens located in the center (nucleocapsid)
  - e antigen (HBeAg) an indicator of transmissibility (minor component of the core , antigenically distinct from HBcAg)
- (22nm) spheres and filaments other forms, no DNA in these forms, so they are not infectious. ((check the 2nd point in the previous page))