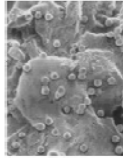
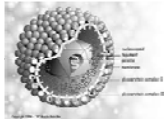


Viruses causing hepatitis outside the alphabet EBV, CMV, HHV6 and beyond



Bill Rawlinson

Virology Division, SEALS Microbiology

August 2012



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What did the Flintstones teach us?

What were the names of the main characters?

What were some of the prehistoric gadgets?



1. What is hepatitis
 - Aetiology
 - Clinical, virological
2. Hepatitis due to CMV
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OUTLINE



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OUTLINE



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Hepatitis

- Syndromic diagnosis
 - Hepatitis = 'inflammation of the liver' and not a single disease
- Aetiology viruses
 - drugs
 - secondary manifestation of systemic illness
 - connective tissue diseases
 - other agents
- There are 15 virus families infect and damage hepatocytes, most have 1-2 species only



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Hepatitis definitions

- **Acute:** Short term
- **Chronic:** Lingering or lasting > 6months, can be severe
- **Fulminant:** Develops quickly, high mortality rate
- **Cirrhosis:** Hepatic scarring any cause
- **Jaundice:** Yellowing of the skin, eyes due to raised levels of bilirubin in the blood due to liver damage



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Hepatitis epidemiology

- Acute viral hepatitis is common
- Annual incidence of viral hepatitis
 - developed countries is 0.25 per 1000 population
 - underestimate - correct figure 1-2 cases per 1000
 - higher in developing countries
- Mortality overall is 1% for hepatitis infection
- higher in older people, especially fulminant disease



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Hepatitis – acute viral

- Due to all forms of hepatitis virus
- Hepatitis A, EBV, CMV and HHV6 only cause acute hepatitis.
- Presentation with malaise, anorexia, nausea, vomiting, RUQ pain or asymptomatic
- Examination
 - jaundice
 - dark urine
 - pale stools



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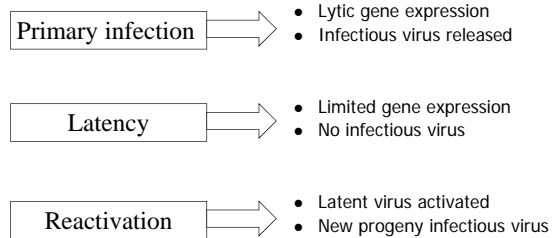
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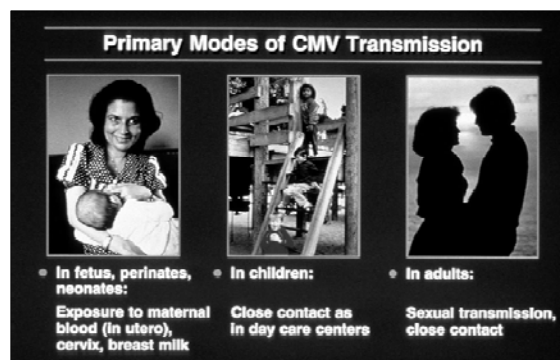
Herpesvirus Subfamilies

Sub-family	Host Range	Growth Cycle	Cytopathic Effect
HSV1, 2, VZV α	Variable Broad	Short	Cell lysis
CMV, HHV6, 7 β	Restricted	Long	Cytomegalia
GBV, HHV8 γ	Restricted	Medium	Cell lysis

Phases of herpesvirus infection

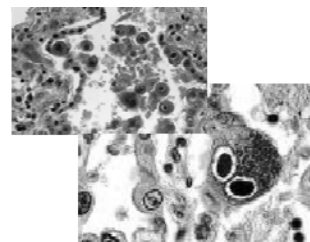


CMV Transmission



CMV Clinical Disease

- Immunocompetent individuals
 - Asymptomatic, mononucleosis
- Reactivation and reinfection



CMV Clinical Disease

- Immunocompromised individuals
- HIV AIDS patients
- Transplant patients
 - Reactivation of previous infection and primary infection by donor strain
- GIT disease, CNS encephalitis, retinitis, hepatitis, myocarditis, pancreatitis, organ rejection and pneumonitis

CMV hepatitis clinically

- Usually associated with mononucleosis (not always)
- Usually asymptomatic
- Granulomatous hepatitis
 - Also fever, vomiting
 - Large numbers of atypical lymphocytes (50%)
 - Scattered microscopic granulomas ?CMV



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[Snova 1984]



CMV hepatitis pathology

- Mononuclear portal and sinusoidal infiltrate,
- Increased hepatocellular mitotic activity
- Minimal hepatocellular necrosis
- Less commonly
 - granuloma formation
 - bile duct epithelial damage
- Typical CMV nuclear inclusions and CMV antigen identified 1/6
- **Large numbers CD8+ cells (persistence) or NK cells (clearance)**



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[Snova 1984]



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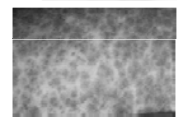


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EBV clinical presentation

- Usually subclinical childhood
- 90-95% adults seropositive
- 50% of <5 yrs seropositive
- Glandular fever
- Haematologic presentation
 - Haemolytic anaemia AIHA
 - Thrombocytopaenia
- Splenic rupture
- CNS <1%
 - Encephalitis
 - Guillain Barre
 - Bell's palsy
 - Transverse myelitis



EBV clinical presentation

- **Hepatitis presentation**
 - Usually biochemical hepatitis
 - Asymptomatic elevation of AST, ALT, GGT
 - Present in 85% of patients
 - Jaundice rare
- **Severe hepatitis**
 - Cirrhosis, hepatic failure rare
 - Severe unlikely
- **Other complications**
 - Cardiac rare myo/pericarditis
 - Respiratory rare unsubstantiated
 - Death rare
 - Tumours OHL, Burkitt's Hodgkin's, NPC



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EBV hepatitis pathology

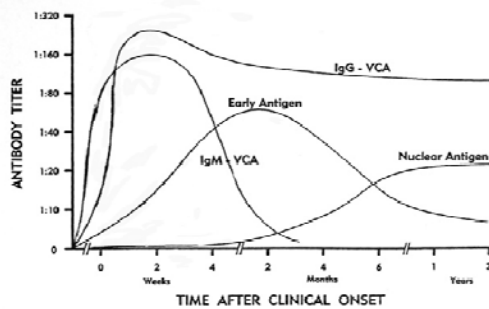
- **Liver**
 - Mild changes
 - Hepatocyte swelling, vacuolization minor
 - Lymphocytes and monocytes periportal
 - Biliary stasis rare
- **CNS**
 - Alterations in fatal cases
 - Neuronal degeneration, mononuclear infiltration minor, astrocyte proliferation
 - Generalised



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EBV Serology



EBV virology

- **Gamma-1 herpesvirus**
 - Infects epithelial cells, ? then B lymphocytes
 - Marked CTL response seen as atypical monos
 - Binds CD21(C3d complement receptor) via envelope gp350 + MHCII via gp42
 - Latency in B cells (1-50 per 106 cells)



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EBV virology

- **Gamma-1 herpesvirus**
 - EBV driven B lymphocyte proliferation/immortalisation
 - Episomal maintenance
 - Type A and B indistinguishable serologically
 - Different proteins expressed during latency LMP1, LMP2, EBNA x 6, EBEB x 2



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EBV virology

- **Shedding oropharynx**
 - Healthy adults 10-25%
 - Infectious mononucleosis syndrome 50-100%
 - HIV-1 infected 50%
 - Renal tx recipients 50-70%
- **Spread**
 - Intimate contact
 - Not recovered from fomites
 - Post pump syndrome (most CMV)



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Atypical lymphocytosis DDx

- EBV infectious mononucleosis
- CMV primary infection (heterophile neg)
- HHV primary infection (roseola infantum)
- HIV primary infection
- Toxoplasmosis primary infection
- Viral hepatitis A/B/C
- Rubella
- Mumps
- Drug reactions



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EBV Serology

- **Potential cross-reactivity with HAV**
 - HAV IgM co-detected with EBV IgM in 9/15 cases [Naveau 1985]
 - 4/9 were RA +ve
 - EBV IgM acute hepatitis, 0/5 HAV IgM +ve [Naveau 1985]
 - EBV reactivation during HAV [Ritter 1996]
- **Potential cross-reactivity with autoimmune**
 - EBV +ve post AIH in 7/13 [Vento 1995, Cabibi 2008]



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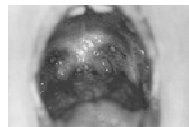


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Other viruses

- 15 families
- Herpesviruses
 - HHV6
 - VZV
- Adenovirus
- Flaviviruses
 - Dengue, Yellow fever (HCV)
 - Akhurma virus, Kyasanur Forest disease, Omsk Hemorrhagic fever
- Picorna
 - ECHOvirus (HAV)
- Arenaviruses
 - Guanarriot, Junin, Lassa fever, Lujo, Mchuip, Sabia



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Other viruses

- Bunyaviruses
 - Crimean-Congo haemorrhagic fever, Dobrava, Hantaan, Pumala, Rift Valley fever, Seoul, SFTS
 - VZV
- Coronaviruses
 - SARS
- Erythrovirus
 - Parvovirus B19
- Filoviruses
 - Ebola, Marburg
- Orthomyxoviruses
 - Influenza
- Reoviruses
 - Colorado tick fever, Reovirus



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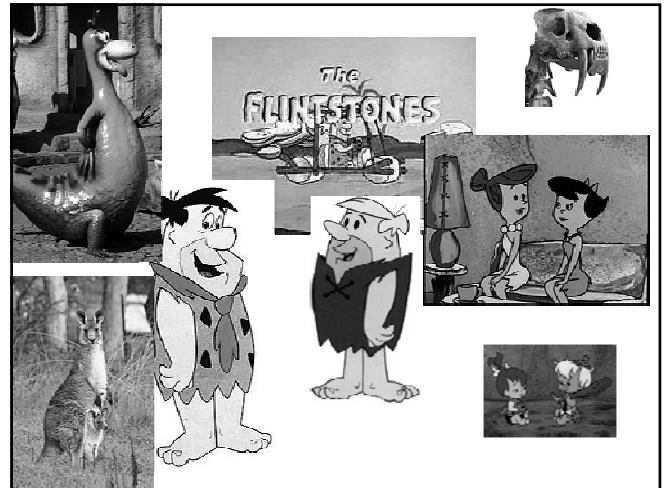


Viral hepatitis investigations

- General
 - liver tests (bilirubin, AST, ALT, GGT)
 - bleeding studies
 - exclusion of non viral causes
 - rule out mechanical obstruction (abdominal US,CT)
- Specific tests
 - HAV (IgM, IgG)
 - HBV (HBsAg, HCV Ab, HBe Ag, DNA PCR)
 - HCV (Ab, PCR)
 - HDV (HBsAg, HDV Ab)
 - HEV (western blot)
 - CMV (IgG IgM IgG avidity)
 - EBV (IgG IgM IgG avidity)
 - HHV6 (PCR)



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What did the Flintstones teach us?

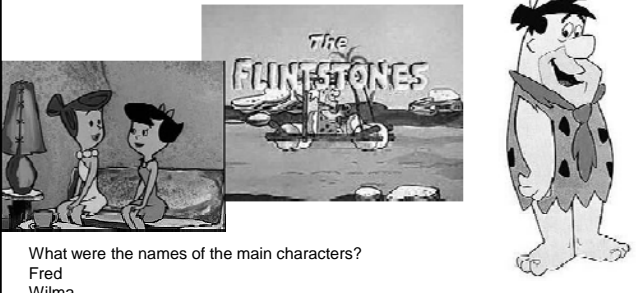


How to smoke Winston cigarettes in the closing credits



What did the Flintstones teach us?


What were the names of the main characters?



What were the names of the main characters?

Fred
Wilma
Pebbles Flinstone-Rubble (nee Flinstone)

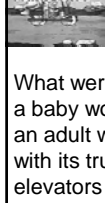
Barney Rubble
Betty Rubble
Bamm-Bamm Rubble

What did the Flintstones teach us?


What were the names of the main characters?

What were some of the prehistoric gadgets?




What were some of the prehistoric gadgets?

a baby woolly mammoth used as a vacuum cleaner
an adult woolly mammoth acting as a shower by spraying water with its trunk
elevators raised and lowered by ropes around brontosaurus' necks
"automatic" windows powered by monkeys on the outside
birds acting as "car horns," sounded by the driver pulling on their tails or squeezing their bodies
an "electric" razor made from a clam shell, vibrating from a honey-bee inside
a pelican as a washing machine, shown with a beakful of soapy water
a woodpecker whose beak is used to play a gramophone record



What was the town where they lived called?

What was the other name for the town where they lived?



What was the town where they lived called?

BEDROCK

What was the other name for the town where they lived?

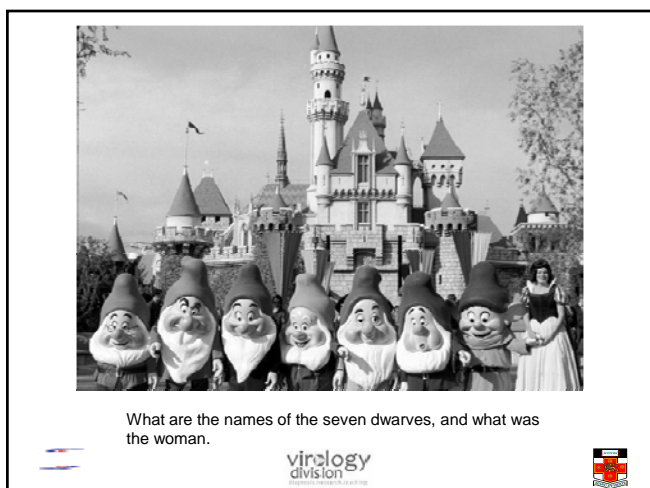
ROCKVILLE



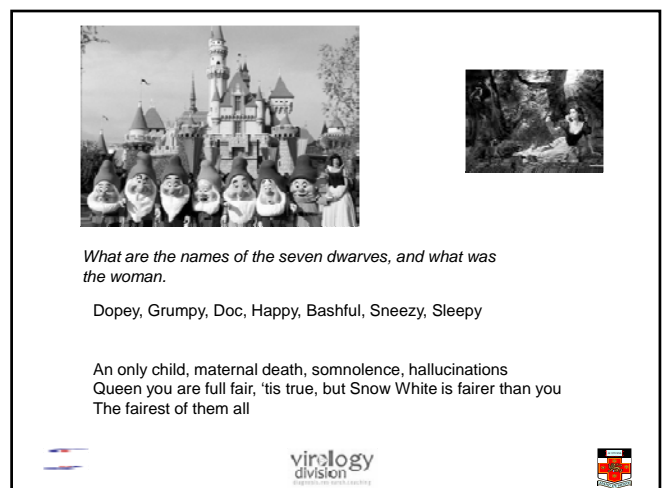
Blood Supply testing

- Mainly viral
- Ignores persistent non-threatening viruses
- Constantly changing
- Role of emerging viruses

HEPATITIS VIRUS	ACUTE HEPATITIS	CHRONIC HEPATITIS	FULMINANT HEPATITIS	CIRRHOSIS	HCC
A	+	0	+	-	-
B	+	5-10%	+	+	+
C	+	75%	+	+	+
D	+	<5% 50%	+	+	+
E	+	0	+	-	-
G	+	20%	-	-	-
TTV	+	60%	-	-	-



What are the names of the seven dwarves, and what was the woman.



What are the names of the seven dwarves, and what was the woman.

Dopey, Grumpy, Doc, Happy, Bashful, Sneezzy, Sleepy

An only child, maternal death, somnolence, hallucinations
Queen you are full fair, 'tis true, but Snow White is fairer than you
The fairest of them all