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Oncogenic viruses

Infectious Diseases/Microbiology Sequence Course

David J. Miller, M.D., Ph.D.

Spring 2010

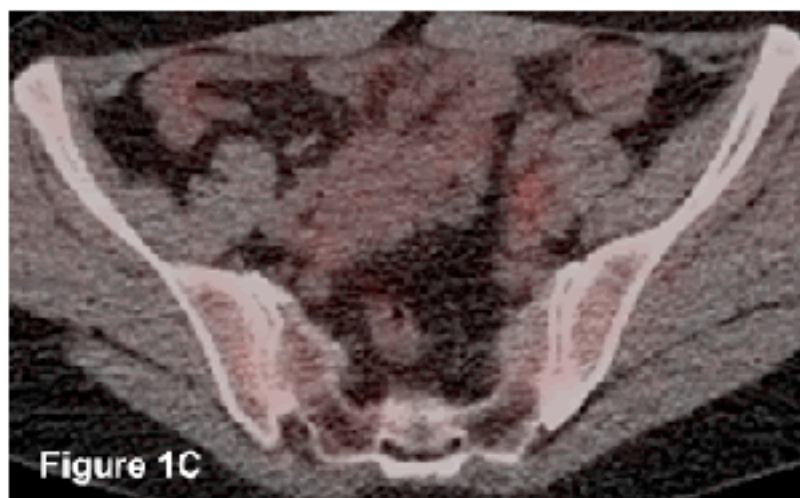
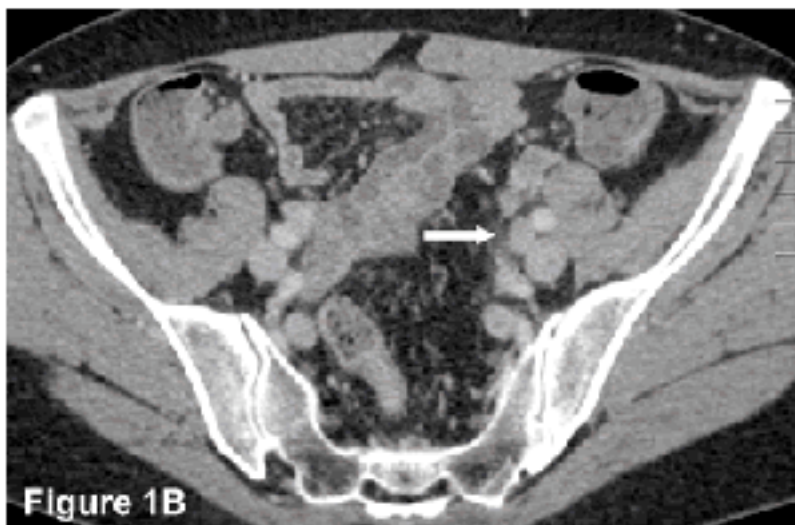
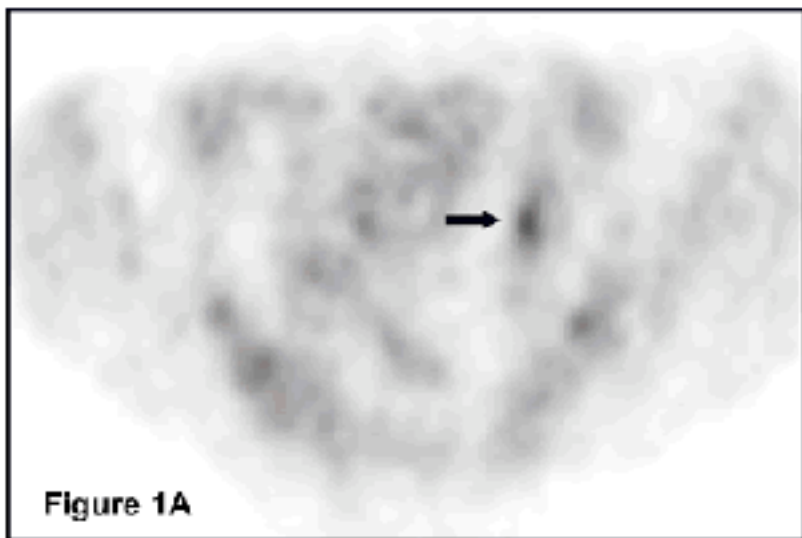


Objectives

- **Know the mechanisms of human papillomavirus (HPV) transmission and oncogenesis**
- **Appreciate the role of unique HPV types in the pathogenesis of distinct wart syndromes**
- **Understand the importance of HPV in the etiology of cervical and anal cancers**
- **Appreciate the importance of other viruses, in particular Kaposi's sarcoma herpes virus (KSHV)**

Reading assignment: Schaechter's 4th edition, chapters 38, 40, 42, and 43

54 year old female goes to her primary care physician because of weight loss and intermittent vaginal bleeding for the past six months. She went through menopause five years ago and thought that she was done with this particular “problem”. When she was younger her health care was marginal at best, and she rarely obtained the recommended screening tests. A chest, abdomen, and pelvis CT scan showed a large mass adjacent to her uterus, numerous enlarged pelvic and abdominal lymph nodes, and several pulmonary nodules.

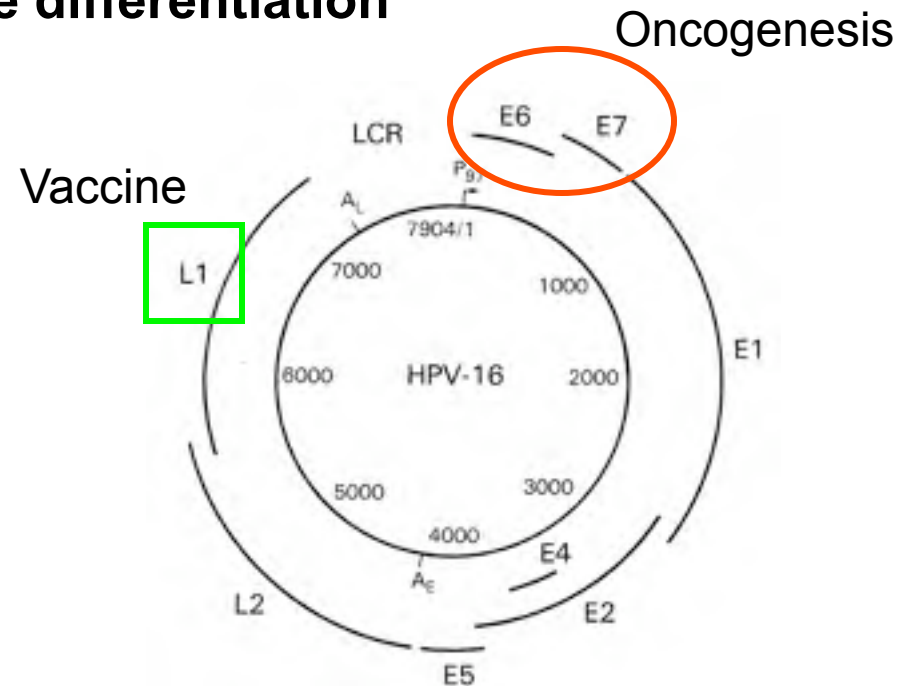
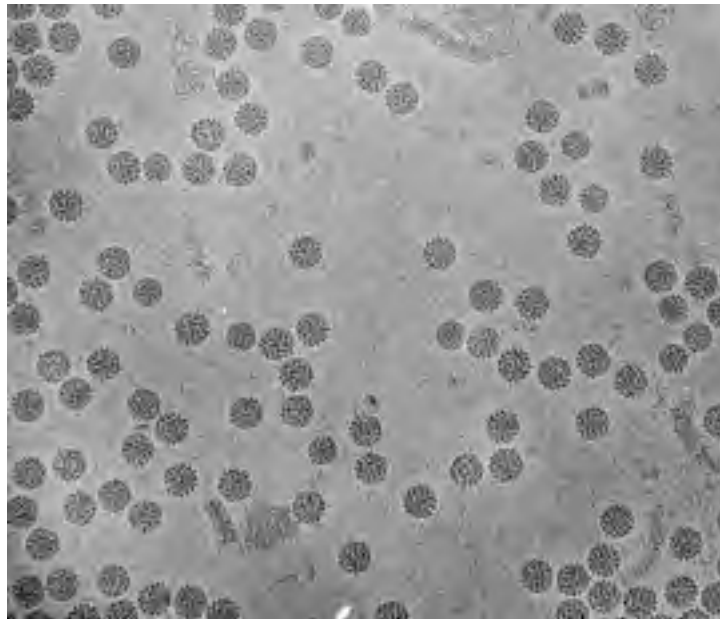


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Diagnosis?

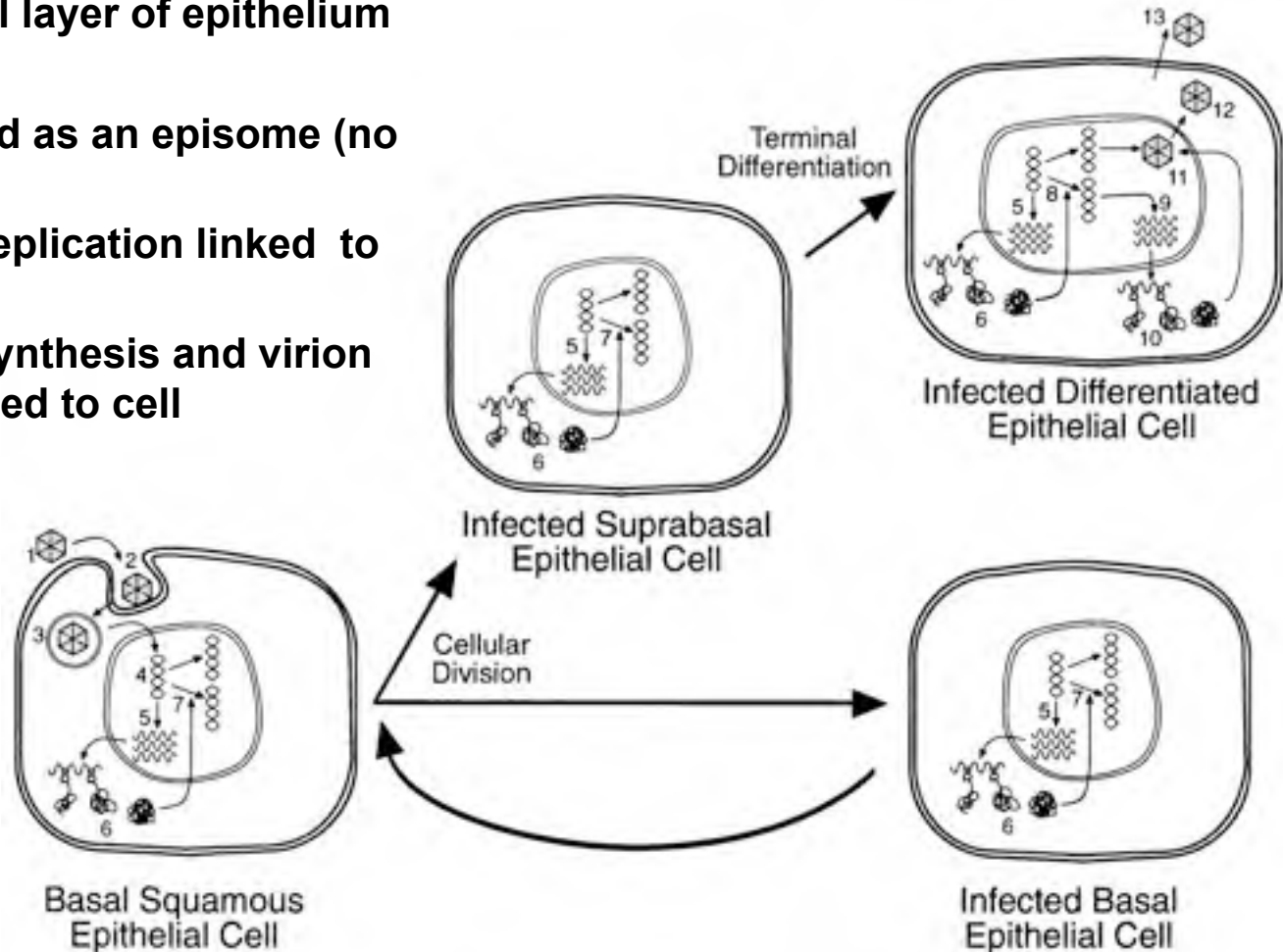
Human papillomavirus (HPV)

- Family: *Papillomaviridae*
- Non-enveloped
- Circular, compact double-stranded DNA virus
- > 100 *genotypes* exist
- Life cycle linked to keratinocyte differentiation

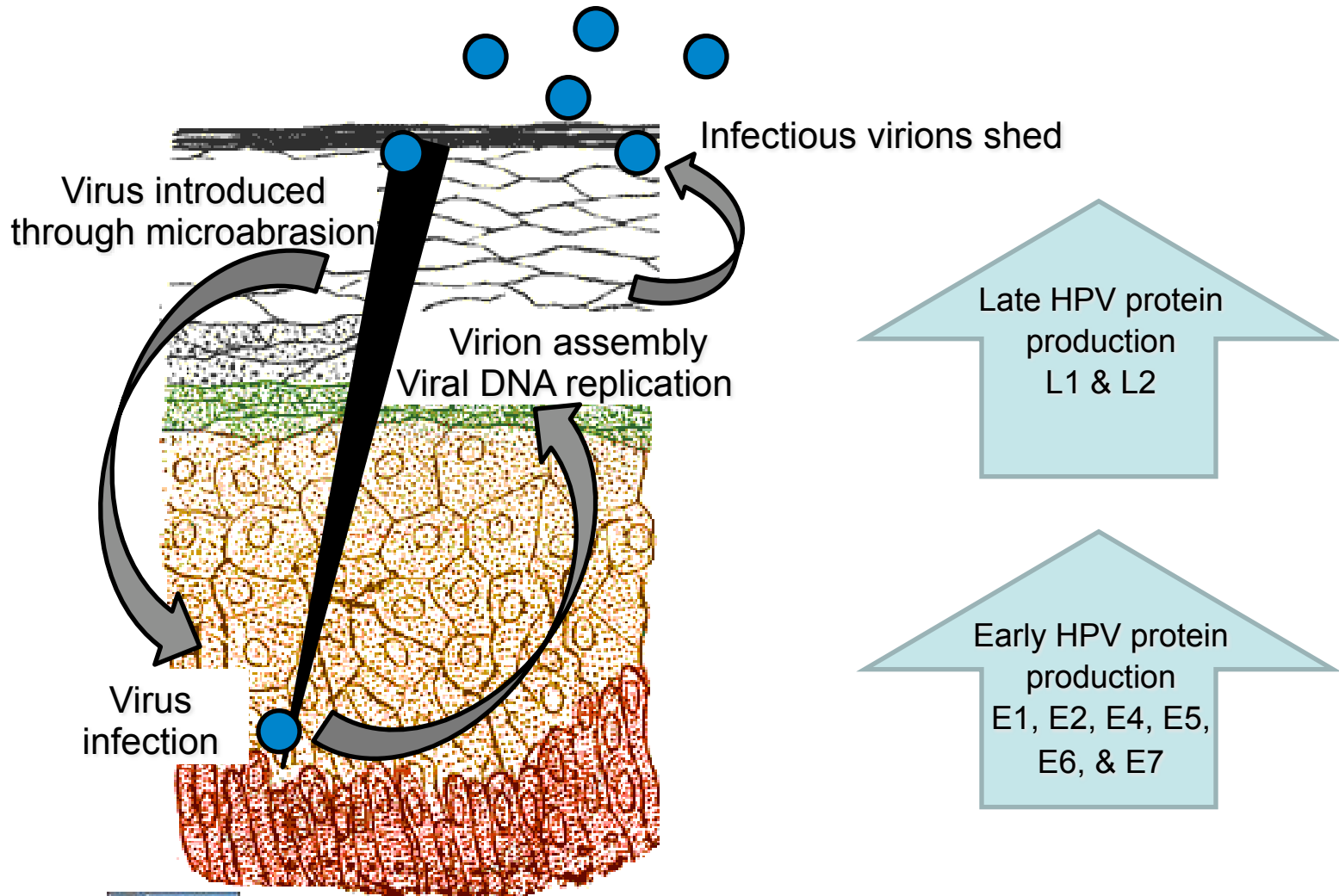


HPV replication

- Infect basal cell layer of epithelium
- No cell lysis
- DNA maintained as an episome (no integration)
- Viral genome replication linked to cell replication
- Virus protein synthesis and virion production linked to cell differentiation



HPV Infection and Productive Life Cycle



Serephine, [wikimedia commons](https://commons.wikimedia.org/wiki/File:HPV_infection.png), Adapted from Gray's Anatomy

HPV Epidemiology

- **Enormous disease burden in U.S.**
- **20-30 million currently infected**
- **5-6 million new infections per year**
 - Most common STD
 - 20-50% of college women become HPV⁺
 - 80% lifetime cumulative incidence in the U.S.
- **11,000 case of cervical cancer per year**
 - 4,000 cases of anal cancer per year
- **4,000 deaths per year from cervical cancer**

HPV Genotypes

Lesion	HPV genotype
Cutaneous warts	1, 2, 3, 4, 10
Anogenital warts Low malignancy risk	6, 11 (responsible for 90% of genital warts) 40, 42, 43, 44, 54, 61, 70, 72, 81
Anogenital warts High malignancy risk	16, 18 (responsible for 70% of cervical cancers) 26, 31, 33, 35, 39, 45, 51, many others

HPV Clinical Manifestations

- **Transmission**
 - Direct skin-skin and skin-fomite contact (stable virus)
- **Symptoms**
 - Frequently asymptomatic
 - Cutaneous changes occur slowly
 - Flat, slightly elevated, or pedunculated appearance
 - Frequently multiple “condyloma accuminatum”
- **Complications**
 - Malignancy
 - Increased risk with immunosuppression
 - Respiratory papillomatosis (infants)
 - Epidermodysplasia verruciformis



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HPV Treatment and Prevention

- **Treatment**

- Ablative therapy most often used
 - Cytotherapy, surgical excision, keratolytic chemicals
- Questionable viral “cure”

- **Prevention**

- Subunit vaccine
- L1 “virus-like particles” (VLPs) produced in yeast
- Highly effective in preventing HPV acquisition (almost 100%)
- Two FDA-approved versions
 - Gardasil (Merck), approved June 2006, quadrivalent (HPV 6, 11, 16, and 18)
 - Cervarix (GlaxoSmithKline), approved October 2009, bivalent (HPV 16 and 18)

HPV vaccine mimics the infectious virion

Infectious HPV

- Capsid protein L1
- L2 protein
- Viral DNA

Non-Infectious HPV Vaccine (VLP)

- Capsid protein L1
- Lacks L2 protein
- Lacks viral DNA

HPV Vaccine Recommendations


- **Target group (currently)**
 - Females 9 to 26 years old
 - Recommended age 11-12 years old (can be used as young as 9 yo)
 - “Catch up” vaccination for 13-26 year old females
 - No screening (HPV DNA or antibody) needed
 - Immunosuppressed and lactating females *NOT* disqualified
 - Booster requirements not yet known
- **Contraindications**
 - Hypersensitivity to yeast
 - Pregnancy (relative)
- **Future targets (studies ongoing)**
 - Females >26 years old
 - Males

Polyomaviruses and cancer

- **Family: *Polyomaviridae* (formerly grouped with papillomaviruses)**
- **Non-enveloped, closed circular double-stranded DNA genomes**
- **Link to carcinogenesis speculative**
 - Species-specific
 - Readily transform cells in culture (“non-permissive” cells)
- **Examples**
 - BK virus (BKV)
 - Hemorrhagic cystitis and polyomavirus nephropathy
 - JC virus (JCV)
 - Progressive multifocal leukoencephalopathy (PML)
 - Simian virus 40 (SV40)
 - Questionable link to human disease (poliovirus vaccine?)
 - Merkel cell virus (MCV)

28 year old homosexual male with HIV infection goes to his primary care physician because of ugly appearing raised “welts” on his back. They appeared about a year ago and are slowly getting bigger. They aren’t painful, but the patient is embarrassed to take his shirt off in public because his back looks so nasty. He also noticed a smaller reddish bump in his mouth that started bleeding the other day when he ate a hard bagel. He has never had his CD4 count or HIV viral load checked, and he has been reluctant to see an Infectious Diseases specialist about starting antiretroviral therapy. He has had several episodes of severe thrush in the past, he has been hospitalized twice for pneumocystis pneumonia, and has lost about 40 lbs over the past 6 months.



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Diagnosis?

Kaposi's sarcoma-associated herpes virus (KSHV)

- **Gammaherpes virus (related to EBV)**
 - Synonym: HHV-8 (human herpes virus-8)
- **Associated with malignancies**
 - Kaposi's sarcoma (virtually 100% are positive for KSHV)
 - Primary effusion lymphoma
 - Multicentric Castleman's disease (angiofollicular lymph node hyperplasia)
- **Probable sexual transmission**
 - Much more common (10-fold) in HIV infected patients with sexually-acquired infections than others (e.g. IVDU, blood transfusion)
- **Epidemiology**
 - Endemic disease in Africa, eastern Europe, and Mediterranean
 - Sporadic (?epidemic) disease in immunocompromised hosts
 - “canary in the coal mine” for HIV epidemic recognition

KS Clinical Manifestations

- **Symptoms**

- Red, purple, brown, or black papular nodules
- Skin, mouth, lung, and GI tract
- Varied growth rate (indolent to aggressive)

- **Pathology**

- Malignancy of lymphatic endothelium that forms vascular channels

- **Treatment**

- Incurable
- Minimize underlying immunosuppression



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KSHV oncogenesis

- **Actual mechanism still unclear**
 - KSHV infection alone likely not sufficient
- **KSHV encodes multiple cellular oncogene homologs**
 - IL-8 receptor (vGPCR, or viral G-protein coupled receptor)
 - cytokines (IL-6, MIP)
 - *bcl-2*
 - Cyclin D
- **Extensive immune system evasion**
 - LANA-1
- **Other factors**
 - HIV tat protein, saliva

Other oncogenic viruses

- **Epstein-Barr virus (EBV)**
 - lymphoma, nasopharyngeal carcinoma
- **Hepatitis B virus (HBV)**
 - hepatocellular carcinoma
- **Hepatitis C virus (HCV)**
 - hepatocellular carcinoma
- **Human T-cell lymphotropic viruses I and II (HTLV-1 and II)**
 - leukemia

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