GENITAL TRACT

REVIEW OF NORMAL

I. **GONADAL DEVELOPMENT** - In both sexes, the gonads develop from bilateral genital ridges comprised of specialized mesenchyme that is covered by the coelomic (germinal) epithelium. Soon after the appearance of these genital ridges, germinal epithelium penetrates the underlying mesenchyme to produce the primary sex cords which are invaded by the germ cells migrating from the yolk sac along the root of the mesentery. In males, under the influence of the Y chromosome, the primary sex cords ultimately differentiate into the seminiferous tubules (consisting of Sertoli cells derived from germinal epithelium and spermatogonia derived from germ cells) and the rete testis. Leydig cells develop from the mesenchyme that separates the seminiferous tubules. In females, the primary sex cords evolve into the rudimentary rete ovarii while secondary sex cords develop from the cortex and ultimately form the primordial follicles. The granulosa cells surrounding the follicles are derived from the secondary sex cords. The stromal cells adjacent to the granulosa cells differentiate into the concentric perifollicular theca interna and externa.

II. **GENITAL TRACT DEVELOPMENT** - At about six weeks gestation, invaginations of the germinal epithelium covering the genital ridges form the paramesonephric (*müellerian*) ducts which lie adjacent to the previously existing mesonephric (*wolffian*) ducts. In males, under the influence of the developing testes, the paramesonephric duct degenerates as the mesonephric duct develops into the epididymis, vas deferens, and seminal vesicles. In the female, the paramesonephric duct develops to ultimately form the fallopian tubes and, by fusing together in the midline, the uterus, cervix, and upper vagina. The lower 2/3 of the vagina develops from the urogenital sinus which grows cephalad to fuse with the upper portion. During this process, the mesonephric duct degenerates.

III. **ENDOCRINE FUNCTION** - In both sexes, germ cell development and sex hormone production are under the influence of the pituitary gonadotropins, FSH and LH. FSH promotes testicular spermatogenesis and ovarian follicle development. It also induces the secretion of *inhibin* which acts to decrease FSH release. LH promotes androgen production. In the male, testosterone (the most potent androgen) is produced by the Leydig cells with lesser amounts of androstenedione and dehydroepiandrosterone (DHEA). In the female during the proliferative (pre-ovulatory) phase of the menstrual cycle, LH promotes the production of androstenedione and testosterone by the theca interna cells of the developing follicle. Also during the proliferative phase, the rising FSH levels stimulates the aromatization of testosterone to estradiol (the most potent estrogen) and androstenedione to estrone (a weak estrogen) by the granulosa cells of the follicle. Increasing estrogen levels have an inhibitory effect on FSH secretion but are responsible for the LH surge at midcycle which induces rupture of the follicle and ovulation. During the secretory (post-ovulatory) phase, LH promotes the production of progesterone (primarily 17-hydroxyprogesterone) by the luteinized theca cells and lesser amounts of androgens. [Progesterone has weak mineralocorticoid activity accounting for the edema and weight gain during secretory phase.] If the egg is fertilized, the

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syncytiotrophoblasts of the developing placenta produce beta HCG which maintains the progesterone production of the corpus luteum until the placenta can produce its own progesterone. The placenta will also produce estrogens in the form of estriol.

Androgens are also produced by the adrenal cortex and the ovarian hilar cells. The adrenals produce primarily androstenedione and DHEA (both of which are 17 ketosteroids and can be measured in urine). Most of the testosterone in females, however, is derived from ovarian conversion of androstenedione to testosterone. Androstenedione can also be aromatized to estrone in the peripheral adipose tissue and becomes an important source of estrogen in the post-menopausal female. Estrogen compounds are metabolized in the liver and excreted in bile.

Estrogens and androgens are both bound to sex hormone binding globulin (SHBG), a transport protein synthesized in the liver. SHBG has a greater affinity for testosterone so that with SHBG excess (such as seen with hyperestrinism conditions), there is more binding of testosterone which exaggerates the effects of the hyperestrinism. With SHBG deficiency (such as seen with obesity and hypothyroidism) there is more unbound testosterone and a tendency toward virilization (hirsutism, etc.)

DEVELOPMENTAL DISORDERS

I. **MUELLERIAN DUCT ANOMALIES** - Embryologic fusion anomalies may result in unusual conditions such as organ agenesis, abnormal septation, organ duplication, etc.

II. **GARTNER'S DUCT CYST** - These arise in women from remnants of the degenerted mesonephric/wolffian duct. They appear in the anterolateral vaginal wall submucosa and may measure 1 - 2 cm in size.

III. **IMPERFORATE HYMEN** - This may not be recognized until puberty when patients complain of failure to menstruate. Physical exam may reveal vagina, uterus, and fallopian tubes distended with retained blood (*hematocolpos*, *hematometria*, and *hematosalpinx*).

IV. **HYPOSPADIAS/EPISPADIAS** - In males, abnormal development of the urethral canal may result in the urethral opening lying along the ventral (*hypospadias*) or the dorsal (*epispadias*) surface of the penile shaft. This is often associated with other genitourinary malformations (cryptorchism, bladder exstrophy, etc). Either may produce partial urinary obstruction predisposing to urinary tract infection.

V. **PHIMOSIS** - This refers to the inability to retract the foreskin over the glans penis because of an abnormally small preputial opening. This may result from abnormal development or may be acquired by inflammation of the glans and foreskin (*balanoposthitis*) with resultant adhesions to the foreskin. Phimosis prevents adequate cleansing of the glans and predisposes to additional infection. *Paraphimosis* refers to the inability to replace the foreskin after retraction and is usually due to constriction and swelling of the glans.

VI. **CRYPTORCHIDISM** - This refers to the failure of the testis to descend into the scrotum from its embryologic position in the coelomic cavity and is usually unilateral. Although there is early arrest of germ cell production due to the higher ambient temperature, gross atrophy usually does not become apparent until puberty. These patients have an increased risk of subsequent testicular cancer in both the cryptorchid testis (regardless of surgical repositioning) and the contralateral "normal" testes.

SEXUALLY TRANSMITTED/INFECTIOUS DISEASES

I. VIRAL

A. **HERPES** (Herpes simplex II virus) - This virus causes painful red papules which develop into crops of vesicles which then ulcerate. The ulcers heal in 10-20 days but may recur over a lifetime. Histologically, there are intraepidermal vesicles formed by acantholysis due to balloon degeneration of infected epidermal cells. Characteristic features on cytologic scrapings of the lesions include large multinucleated giant cells and intranuclear eosinophilic inclusions. Clinically, the vesicles are paingul, dysuria is frequent, and systemic symptoms of fever and malaise may be present.

B. **CONDYLOMA ACUMINATA** (Human papilloma virus) - These appear as either flat or verrucous alterations of squamous epithelium (venereal warts). They are most frequently seen, but not limited to, the cutaneous surfaces of the perineal/perianal/penile areas but may also affect the vagina, cervix, and other mucosal surfaces. The verrucous condylomas show hyperkeratosis, parakeratosis, acanthosis and *koilocytosis* of the epidermis. Flat condylomas may result from infection by a different viral strain and do not have the verucoid appearance but do tend to have more cellular atypia of the epidermis. They may be associated with subsequent dysplasia/neoplasia.

C. **HEPATITIS B** [see Hepatobiliary Section]

D. **AIDS**

II. BACTERIAL

A. **GONORRHEA** (N. gonorrhoea) - In women, the initial site of infection is frequently Bartholin's glands, Skene's glands, or the endocervix. The organism tends to spread superficially along mucosal surfaces and incites a heavy purulent exudative response. Acute inflammation of Bartholin's gland may lead to occlusion of the duct and abscess formation (*Bartholin's gland abscess*) which, with resolution of the suppurative exudate, becomes a *Bartholin's duct cyst.* Whether the site of primary or secondary infection, the endocervix also exudes a purulent exudate. Traversing the endometrial cavity (usually during or immediately following menses) to the fallopian tube, gonorrhea is one of the leading causes of *purulent salpingitis.* If untreated, the fimbria agglutinate and pus accumulates to form a *pyosalpinx.* With time, the pus is reabsorbed and replaced by clear fluid to form a *hydrosalpinx.* In males, the organism infects periurethral glands and generally presents as dysuria and a milky urethral discharge. From the urethra, it can spread to prostate, seminal vesicles, etc.

B. **BACTERIAL VAGINOSIS** - This is caused principally by gardnerella vaginalis (hemophilus gardnerella) in addition to mixed aerobic and anaerobic bacteria. It is the cause of most cases of non-specific vaginitis and produces a thin, scanty, grey-white, malodorous discharge. The organism does not penetrate the mucosa and does not incite much of an inflammatory response so that wet mount shows *clue cells* (epithelial cells having a stippled-appearing cytoplasm due to bacterial coating of the cell) with a meager inflammatory background.

C. **CHANCROID** (H. ducreyi) - This causes genital ulcers ("soft chancre") and regional lymphadenitis. The latter, if untreated, may progress to form an inguinal abscess (*bubo*). Histologically, the most notable feature is lumenal occlusion and thrombosis of blood vessels beneath the ulcer due to rapid endothelial cell proliferation. The organism can only rarely be shown in tissue with special stains but smears of the lesion often demonstrate the short, gram-negative rods.

D. **GRANULOMA INGUINALE** (Calymmatobacterium granulomatis) - This occurs in perianal or genital skin as a solitary lesion or a small group of ulcers filled with granulation tissue. The ulcers spread by peripheral extension and can become quite large. The dermis contains a dense infiltrate of macrophages and plasma cells and occasional neutrophilic abscesses. The most conspicuous histologic finding is the presence of intracytoplasmic inclusion bodies (*Donovan bodies*) within macrophages. Their demonstration is requisite for the diagnosis which may be accomplished by special stains of tissue or smears of biopsy material.

III. **CHLAMYDIA** (C. trachomatis) - This is a common organism that infects the same tissues as gonococcus but, in general, produces few clinical symptoms.

A. **NON-SPECIFIC URETHRITIS, CERVICITIS, SALPINGITIS** - This is a common chlamydial infection most of which have few clinical symptoms and are often unrecognized. In females, chlamydia is probably responsible for a majority of the cases of salpingitis resulting in infertility. In males, it may produce a non-specific urethritis with mild dysuria and a mucoid discharge. The organism is hard to culture but may be identified by monoclonal antibodies.

B. **LYMPHOGRANULOMA VENEREUM** - This is an uncommon disease caused by a different serotype of C. trachomatis which produces papular and ulcerative skin lesions. Lymphatic involvement results in fibrosis, scaring, and strictures of the anus and rectum.

IV. **SYPHILIS** (T. pallidum) - The spirochete penetrates small abrasions in the skin or mucous membranes and after an incubation of 3 weeks causes a painless papule at the site of infection which soon ulcerates (*chancre*) but will eventually heal spontaneously. Weeks to months later, during the stage of secondary syphilis, systemic symptoms (headache, low-grade fever, lymphadenopathy, etc) develop and syphilitic warts (*condyloma lata*) and rashes appear. This, too, heals spontaneously to possibly be followed by the cardiovascular and neurologic effects of tertiary syphilis years later.

V. **CANDIDA** (C. albicans) - This is a common disorder in females, especially in diabetics and in conditions of high progesterone states (pregnancy, BCP, etc.). Vaginal infections are characterized by itching/burning and a white, curdy discharge. Diabetic vulvitis results from repeated candida infections and causes a thickened, red, pruritic vulva. With KOH prep, budding yeast and pseudohyphae can be seen.

VI. **TRICHOMONAS** (T. vaginalis) - In females who are symptomatic (itching, dysuria, dyspareunia), the vaginal mucosa has a bright red "strawberry" appearance with thick, frothy, yellow-green to grayish discharge adherent to the mucosal surface. Wet mount may identify the flagellated pear shaped protozoan. In males, it is generally asymptomatic.

VULVA/VAGINA

I. **INFLAMMATORY DISEASE** - In the prepubertal and post-menopausal periods, the vulva and vagina are prone to infection because of the warm, moist environment and the effects of hypoestrinism. Hypoestrinism tends to decrease skin vascularity and results in atrophy and decreased cornification of the epithelium, rendering the tissue more prone to trauma and infection. In elderly patients, this is called *senile atrophic vulvitis or vaginitis*. A *urethral caruncle* is a painful polypoid nodule of granulation tissue occurring at the urethral meatus 2^{O} to epithelial atrophy, but it regresses rapidly with topical estrogen treatment.

II. **VULVAR DYSTROPHY** - This disorder generally occurs in middle aged to elderly post-menopausal women as white plaque-like lesions of the skin (*leukoplakia*) which are often multiple. There are two histologic forms and, on occasion, both may be seen in the same lesion. It tends to develop in women with anal-compulsive, rigid personalities and the primary symptom is itching. Scratching produces minor lacerations and inflammation which causes more itching, etc. Difficult to manage clinically - must break the scratch-itch cycle.

A. **ATROPHIC DYSTROPHY** (*lichen sclerosis et atrophicus*) - This is characterized by atrophic labia, narrowed introitus, and smooth vulvar skin with small papules that coalesce into thin gray parchment-like areas that are susceptible to trauma and infection. Histologically, there is epithelial atrophy overlying a hypocellular, "collagenized" upper dermis and a band-like lymphocytic infiltrate. It does not progress to cancer.

B. **HYPERTROPHIC DYSTROPHY** (with or without atypia) - Clinically similar to atrophic dystrophy, microscopically there is hyperkeratosis and acanthosis with or without cellular atypia. Those lesions which do have atypia have a low (< 10%) malignant potential. This form may also be seen in prepubertal females but usually regresses at the time of puberty.

III. **VULVAR NEOPLASIA**

A. **GRANULAR CELL TUMOR** - This tumor is probably derived from Schwann cells and is composed of large cells with prominent granular cytoplasm. Most are small and almost all are benign, but they may induce a pseudoepitheliomatous hyperplasia of the overlying skin that may histlogically closely resemble squamous cell carcinoma. These tumors may also appear in other areas (vagina, breast, tongue).

B. **HIDRADENOMA PAPILLIFERUM** - This is a benign tumor derived from apocrine sweat glands which presents as a nodular mass usually on or between the labia. Histologically, there is a complicated papillary architecture which may be mistaken for adenocarcinoma although close observation will disclose a two cell layered epithelium (epithelial and myoepithelial).

C. **BOWEN'S DISEASE** (*squamous cell carcinoma-in-situ*) - This appears to be increasing in frequency and arising at a younger age (mean age ≈ 40). It may present as raised, red, velvety lesions often involving the labia but also has a tendency to be multicentric (especially with involvement of the periclitoral and perianal skin). Histologically, condylomatous features may be present. HPV can be identified in 80% of these lesions and HSV antigens in ≈ 50%. Only about 10% - 20% of patients will progress to invasive carcinoma of the vulva (usually elderly or immunosuppressed) but 25% are associated with CIS or invasive carcinoma of cervix and/or vagina.

D. **SQUAMOUS CELL CARCINOMA (SCC)** - Invasive SCC occurs primarily in post-menopausal women but has shown an increasing frequency in younger populations (associated with preexisting HPV infection). Clinically, SCC, in the early stages, looks like vulvar dystrophy with itching and local discomfort the predominant symptoms. However, with time, they will become firm and indurated

with possible central ulceration. They may be multicentric - both geographically and temporally. Although most squamous carcinomas are histologically well differentiated, at the time of diagnosis 65% have metastasized to regional lymph nodes (inguinal, femoral, pelvic) and will later metastasize to viscera. Lesions > 2 cm and with lymph node metastases have only a 25% 5-year survival (25%). Smaller lesions treated with vulvectomy and pelvic lymphadenectomy have 60-80% 5-year survival and, if there are no lymph node metastases, the 5-year survival approaches 90%. *Verrucous carcinoma* is a variant of squamous cell carcinoma in which the cells are extremely well differentiated although the gross appearance is that of a large fungating tumor. Typically this cancer will invade locally but will not metastasize.

E. **EXTRAMAMMARY PAGET'S DISEASE** - This presents as a red, crusted, well demarcated lesion usually on labia majora in women who give a history of chronic pruritus and irritation. Vacuolated tumor cells are present singly and in clusters within the epithelium and probably arise from adnexal epithelium. They are PAS and mucicarmine positive and are usually confined to the epidermis and skin appendages. Unlike Paget's disease of the breast, underlying adenocarcinoma is uncommon. Intraepithelial neoplasia may persist for years with lateral spread but without invasion. Once invasion occurs, however, the prognosis is poor.

IV. **VAGINAL NEOPLASIA** - The most frequently identified malignancy involving the vagina is metastatic. Primary malignancies are uncommon and include:

A. **SQUAMOUS CELL CARCINOMA (SCC)** (1% of genital cancer) - Most are well differentiated and arise in the posterior fornix. They can invade the cervix and perivaginal structures by direct extension. The upper 1/3 of vagina drains to iliac nodes while the lower 2/3 drain to femoral, inguinal, and pelvic nodes. SCC may come to clinical attention as the result of vaginal discharge or spotting and is primarily seen in older women. Prognosis depends on clinical stage but ranges from 20%-90% 5-year survivals.

B. **ADENOCARCINOMA** - Arising on the anterior wall (upper 1/3), *clear cell carcinomas* may occur (.001%) in young (15 - 27 yo) daughters of women treated with diethylstilbestrol (DES) during pregnancy. It is preceded by *vaginal adenosis* (which occurs in 30-50% of DES exposed patients and represents a persistence of fetal histology where there is a delayed transformation of glandular epithelium to squamous epithelium). Although often disappearing by the 4th decade, adenosis appears as red areas contrasted against the normal pink mucosal background imparting a "cobblestone" appearance. DES related tumors in general have a more favorable 5 year survival rate than regular vaginal carcinomas.

C. **SARCOMA BOTRYOIDES** - This is a rare form of rhabdomyosarcoma that occurs in young girls, has a polypoid grape-like appearance, invades locally, and metastasizes widely. Poor prognosis in general.

PENIS

I. PREMALIGNANT AND MALIGNANT CONDITIONS

A. **ERYTHROPLASIA OF QUEYRAT** - This is essentially the same disorder as Bowen's disease of the vulva and appears grossly as a raised, erythematous plaque usually on the glans. Microscopically, there is severe epithelial dysplasia/carcinoma-in-situ and chronic inflammation. Without treatment, a small number (5-10%) may progress to invasive squamous cell carcinoma.

B. **BOWENOID PAPULOSIS** -This also represents a squamous cell carcinoma-in-situ that clinically presents as multiple (rather that solitary) lesions of the penis and tends to occur in a younger age group. HPV-16 can be demonstrated in about 80%.

C. **SQUAMOUS CELL CARCINOMA** - This reaches a peak incidence in the fifth to seventh decade and occurs more frequently in uncircumcised males. Chronic inflammation of the glans and foreskin associated with poor hygiene and accumulation of smegma are predisposing conditions. Although some studies show an association with HPV, it is much less convincing than the relationship between HPV and SCC of the female genital tract. The tumors usually begin near the coronal sulcus as a painless, white, plaque-like lesion which eventually ulcerates (or less commonly grows in a fungating fashion). The tumors are usually well-differentiated and slow growing with only 20% showing metastases to superficial inguinal nodes at the time of diagnosis. Prognosis depends on the depth and extent of invasion and nodal involvement.

D. **VERRUCOUS CARCINOMA** - This is an uncommon condition (5% of penile cancers) representing a well differentiated papillary squamous cell carcinoma that spreads horizontally and does not appear to be associated with HPV. It is recurrent and locally invasive but does not metastasize until late in its course.

CERVIX

I. REVIEW OF NORMAL

A. **ANATOMY** - The junction between the squamous epithelium of the exocervix and the columnar mucin secreting epithelium of the endocervix (*transition zone*) migrates anatomically over time. At birth, columnar epithelium is present on the exocervix but progressively recedes due to replacement by squamous metaplasia. In perimenopausal and postmenopausal women, the junction may be high in the endocervical canal and may interfere with the accuracy of routine PAP screening. Although occasionally gradual, the transition between cell types at the squamo-columnar junction is usually abrupt and the mucus secreting endocervical "glands" are, in reality, clefts whose epithelium is an extension of the surface epithelium.

B. **HORMONAL RESPONSE** - Estrogen produces maturation of the superficial squamous cells while progesterone produces maturation of the intermediate squamous cells. Conditions of estrogen excess (tumors, drugs, etc) will show a preponderance of superficial cells on Pap smears; conditions of progesterone excess (pregnancy, etc) will show a preponderance of intermediate cells; and absence of these hormones will result in a preponderance of parabasal cells. The character of cervical mucus also changes with fluctuating hormone levels and can be used as a diagnostic tool. If cervical mucus is air-dried on a glass slide, a crystalline or "ferning" pattern indicates estrogen predominance while an amorphous appearance indicates progesterone predominance. This can be used to differentiate between the two major causes of amenorrhea - pregnancy (increased progesterone) and anovulation (increased estrogen).

II. INFLAMMATORY DISEASE

A. **ACUTE** - Although gonococcus is probably the most commonly identified agent causing acute cervicitis, Chlamydia may be the more common etiologic agent, but it is less symptomatic and more difficult to diagnose. Other organisms may also cause cervicitis particularly in post-abortion, post-partum, or post-trauma states. Unlike gonococcus, most other organisms tend to spread via

lymphatics (rather than over the mucosal surface) and therefore cause less purulent exudation and discharge but may nevertheless lead to bacteremia, peritonitis, bowel adhesions, etc.

B. **CHRONIC** - Nonspecific lymphocytic infiltrates are present to some extent in virtually all adult women. Grossly, chronic cervicitis appears as a reddened granular cervical mucosa. When severe, lymphoid follicles may develop (*follicular cervicitis*). Stenosis and obstruction of the endocervical "glands" may result in mucus retention and cystic dilatation (*Nabothian cysts*) which imparts a pebbly appearance to the endocervical canal but has little clinical significance.

III. POLYPS

A. **INFLAMMATORY** - Occurring in ≈ 5% of women, cervical polyps arise in the 4th to 5th decade and are usually solitary. They develop from the endocervical canal and produce soft sessile or pedunculated lesions of varying size composed of a loose fibromyxomatous stroma containing cystically dilated glands, thick-walled blood vessels, and varying degrees of inflammatory infiltrate. With trauma, the surface epithelium erodes and easily bleeds so that they come to clinical attention due to irregular spotting.

B. **HYPERPLASTIC** (*microglandular hyperplasia, "pill" polyp*) - These are usually seen in hyper-progesterone conditions (pregnancy, BCP) and consist of tightly packed hyperplastic endocervical glands. Clinically, they look similar to inflammatory polyps but potentially may be confused with adenocarcinoma by microscopic appearance.

IV. CARCINOMA

CARCINOMA - The vast majority of cervical malignancies are squamous cell carcinomas (90%). The frequency of cervical squamous dysplasia/neoplasia appears to be increasing, but the frequency of invasive carcinoma and mortality due to cervical squamous cell carcinoma has decreased. Although much less frequent, adenocarcinomas derived from endocervical epithelium tend to occur at a somewhat older age and present at a more advanced stage with a correspondingly poorer prognosis. Adenosquamous carcinoma combines elements of both, arises from the reserve cells of the endocervical epithelium, and also has a less favorable prognosis.

A. **ETIOLOGY** - A recent study suggests that women who have used oral contraceptives have a significantly greater risk of developing cervical carcinoma and that the risk increases in proportion to the duration of usage. The bottom line risk factors, however, appear to be 1) early onset of sexual activity, 2) increasing numbers of sexual partners, and 3) the promiscuity of those sexual partners. With the exception of cigarette smoking, all other identified risk factors are probably related to these three and suggests that a sexually transmissible agent may be involved. An association between viral infections and cervical carcinoma has been noted which suggests four possibilities: 1) viruses may simply have greater affinity for neoplastic cells; 2) viral infection predisposes to cancer under appropriate environmental conditions; 3) viral infection precedes and causes cancer; or 4) viruses and cancer may both be venereally transmitted but independent disease processes. Suspected agents include:

1. **HPV** - The cellular changes characteristic of cells infected with HPV (*koilocytosis*) are seen in dysplastic epithelium and HPV DNA has been found in both dysplastic and neoplastic epithelial cells. Strains 16, 18, and 31 are felt to represent high risk strains in terms of carcinogenic potential while strains 6 and 11 (those most typically associated with condyloma acuminata) are felt to be lower risk strains.
2. **HSV II** - Statistically, women with genital herpes have a higher incidence of dysplasia and carcinoma than the general population. Antibodies to HSV II antigens (specifically AG-4) are higher in women with cervical dysplasia/neoplasia, and the AG-4 antigen can be

demonstrated in neoplastic cells in 90% of cervical cancer biopsies compared to 10% of non-cancer cervical biopsies. HSV II DNA sequences have been found in the DNA structure of malignant cells and dysplasia has been induced in animals after inoculation with HSV II. Although the herpes virus is primarily a cytopathic virus, it may be that HSV II hastens the transforming properties of HPV.

B. **PATHOGENESIS** - Invasive carcinoma follows a long history of progressively worsening dysplastic changes. Dysplasia, therefore, must be considered a premalignant lesion. Dysplastic/neoplastic cells are characterized by increased N/C ratio, greater nuclear pleomorphism, increased mitoses, and loss of polarity. These changes first appear in the basal layer and, with increasing severity of dysplasia, progressively involve a greater percentage of the epithelial thickness disrupting the normal maturation sequence. ***Dysplasia/neoplasia (cervical intraepithelial neoplasia) virtually always begins at the squamo-columnar junction*** and can be graded as mild dysplasia (CIN I), moderate dysplasia (CIN II), severe dysplasia (CIN III), or carcinoma-in-situ (also CIN III). The newer Bethesda classification utilizes two categories (low grade and high grade intraepithelial neoplasia). Each grade may persist or progress to a more severe level. The more severe, the shorter the time interval to the development of CIS. Whether or not dysplasia can spontaneously regress has been subject of controversy, but at least it can be easily eradicated.

C. **EVALUATION** - Although dysplasia/neoplasia begins at the squamo-columnar junction, there are no consistent grossly recognizable changes. Diagnostic evaluation, therefore, involves:

1. **PAP SMEARS** - Smears are 95% reliable (5% false negatives) assuming proper specimen collection and competent evaluation.
2. **SCHILLER TEST** - The cervix is painted with a solution of iodine and potassium iodide. Normal cells will stain brown due to their glycogen content. Abnormal cells (neoplastic or inflammatory) lose cytoplasmic glycogen and therefore will not stain. Biopsy is directed at the non-staining areas.
3. **COLPOSCOPY** - The colposcope is a lighted instrument which magnifies cervical mucosa 20x. Areas of abnormality of the epidermis (thickened white plaques) or vasculature (punctuation, mosaicism) have been found to be associated with dysplasia/neoplasia, and the biopsy is directed to these abnormal areas.

D. **MORPHOLOGY** - Grossly, invasive carcinomas appear *infiltrative*, *ulcerative*, or *exophytic* (most common appearance), and there are three microscopic patterns of squamous cell carcinoma, *large cell nonkeratinizing* (most frequent), *large cell keratinizing*, and *small cell*.

E. **BEHAVIOR** - Growth by local extension may involve the bladder, ureter, rectum, and vagina. Metastases occur primarily via lymphatics to regional (paracervical, hypogastric, and external iliac) and periaortic lymph nodes, then to liver, lung, bone, etc. Hematogenous spread is unusual.

F. **PROGNOSIS** - This is generally related to the clinical stage of the tumor with an overall 5 year survival rate of approximately 60%. Chemotherapy is notoriously ineffective, and death frequently results from uremia due to ureteral obstruction.

G. **STAGING**

Stage 0	Carcinoma-in-situ
Stage Ia	Microinvasive and confined to cervix
Stage Ib	Invasive and confined to cervix
Stage IIa	Extends to upper vagina but not to parametrium
Stage IIb	Involves parametrium
Stage III	Extension to pelvic sidewall or involves lower vagina
Stage IV	Beyond the pelvis or involvement of rectal or bladder mucosa

UTERUS

I. **REVIEW OF NORMAL** - Uterine pathology can be divided into those conditions that primarily affect the endometrium (both endometrial glands and endometrial stroma) and those that affect myometrium. The endometrium is responsive to the cyclic variations in hormones throughout the menstrual cycle which is reflected in its histologic appearance. During the proliferative phase of the menstrual cycle (the first 14 days starting with the onset of menses), the endometrium responds primarily to the increasing serum estrogen levels by proliferation of both the glands and stroma to increase endometrial thickness and volume. The glands are lined by pseudostratified columnar epithelium and mitoses are apparent in both the glands and the stroma. Ovulation, produced by the LH surge in mid-cycle, initiates the secretory phase of the menstrual cyle which is characterized by progesterone induced glandular secretions and predecidual changes of the stroma in anticipation of the implantation of a fertilized ovum. If a fertilized ovum does not implant, the declining progesterone and estrogen levels results in necrosis and sloughing of the endometrium down to the basal layer, and the cycle begins anew.

II. **DYSFUNCTIONAL UTERINE BLEEDING** - This refers to abnormal uterine bleeding in the absence of an organic lesion of endometrium or uterus.

A. **ANOVULATORY CYCLE** - Failure of ovulation results in prolonged estrogenic stimulation without progesterone-induced secretory change. This may result in mild hyperplasia and generally occurs just after menarche and just before menopause. The etiology is unknown in the majority of cases, but endocrine dysfunction (thyroid, adrenal, pituitary), ovarian abnormalities (polycystic ovaries, functional neoplasms), or metabolic abnormalities (obesity, malnutrition, chronic disease) can result in failure to ovulate.

B. **OVULATORY CYCLE**

1. **INADEQUATE LUTEAL PHASE** - This results from low progesterone output by the corpus luteum and is clinically manifested by infertility (endometrium is not adequately primed for implantation) and either amenorrhea or increased bleeding.
2. **IRREGULAR SHEDDING** - This is possibly due to delayed involution of corpus luteum with prolonged progesterone stimulation. Secretory endometrium may be admixed with proliferative endometrium. Clinically manifested by profuse, regular menstrual bleeding lasting 1-2 weeks.

III. **INFLAMMATORY DISEASE**

A. **ACUTE ENDOMETRITIS** - Although the normal endometrium is generally resistant to acute infection, when it occurs it is most commonly seen in post-abortion or post-partum states when there has been retained fetal or placental parts. Microabscesses or neutrophilic destruction of endometrial glands will be present. An accumulation of pus may develop within the endometrial cavity (*pyometra*) especially if there is some obstruction of the endocervical canal.

B. **CHRONIC ENDOMETRITIS** - This may be seen in post-abortion/post-partum states or associated with IUDs, but in 15% of cases they are without definable underlying cause. Clinically, patients may present with pelvic pain, abnormal bleeding, and/or infertility. Histologically, it is characterized by presence of ***plasma cells*** in the endometrial stroma.

IV. **ADENOMYOSIS** - This refers to the presence of endometrial tissue (glands and stroma) buried within the myometrium and is felt to arise from abnormal downgrowth of basal endometrium into the myometrium. Rarely are these foci responsive to cyclic hormonal change but when extensive they may

cause myometrial hypertrophy and uterine enlargement. Clinically, adenomyosis may present as menorrhagia, menstrual cramps, or dyspareunia.

V. **ENDOMETRIOSIS** - Estimated to occur in 20% of adult females (usually 3rd and 4th decade) and a significant cause of infertility, endometriosis is characterized by the presence of benign, potentially functional endometrial tissue (glands and stroma) outside of the uterus. The most common site of involvement is the ovaries followed by uterine ligaments, rectovaginal septum, and pelvic peritoneum, but it may occur anywhere (lungs, umbilicus, soft tissue, etc).

A. **PATHOGENESIS** - Although the mechanism of dissemination of the endometrial tissue is unknown, theories include focal differentiation of the coelomic epithelium (remember this is the same epithelium that forms the muellerian duct) into endometrial tissue, regurgitation of endometrial tissue through the fallopian tubes during menses, and lymphatic or hematogenous dissemination.

B. **MORPHOLOGY** - Grossly, the lesions appear as red-blue to yellow-brown nodules on or beneath serosal surfaces. Bleeding induces fibrous adhesions with consequent problems of pelvic visceral distortion. Large *"chocolate" cysts* may develop in the ovaries. The histologic diagnosis rests on the identification of ectopic endometrial glands and stroma or hemosiderin associated with ectopic placement of either glands or stroma.

C. **CLINICAL PRESENTATION** - Endometriosis most often presents due to pain and/or infertility, but the presentation may depend on the site of involvement and the functional activity of the tissue. Most often, the tissue is functional and bleeds cyclically. Patients may complain of dysmenorrhea and pelvic pain from periuterine adhesions; pain on defecation due to rectal involvement; dysuria from bladder involvement, etc.

VI. **ENDOMETRIAL POLYPS** - These may be solitary or multiple, are often pedunculated and of varying size, and tend to occur postmenopausally. They may be composed of non-functional endometrium or, more commonly, hyperplastic endometrium with cystically dilated glands, a cellular stroma, and thick walled vessels. Many are asymptomatic but they may cause intermittent bleeding and a small proportion (<3%) may harbor adenocarcinoma.

VII. **ENDOMETRIAL HYPERPLASIA** - This represents an increased proliferation of both epithelial and stromal elements with a concomitant increase in endometrial volume. Hyperplasia is seen primarily in the post-menarchal or peri-menopausal age groups and is associated with prolonged or excessive estrogen stimulation. Therefore, estrogen secreting tumors, increased adrenocortical function, Stein-Leventhal syndrome, and exogenous estrogen administration may be associated with endometrial hyperplasia. Clinically, hyperplasia causes irregular or excessive bleeding (i.e. metrorrhagia or menorrhagia) but the majority of cases are self-limiting and spontaneously regress. If they do not, however, over a period of years there is a definite risk of progression to endometrial adenocarcinoma related to the degree of hyperplasia.

A. **CYSTIC (MILD) HYPERPLASIA** - Cystically dilated glands of varying sizes are lined by mitotically active columnar epithelium. There is increased stroma but scant stromal mitoses and a minimal risk of subsequent carcinoma.

B. **ADENOMATOUS (MODERATE) HYPERPLASIA** - An irregularly thickened grayish endometrium shows an increased number of irregularly shaped glands. There is a moderately increased risk for development of subsequent carcinoma.

C. **ADENOMATOUS HYPERPLASIA WITH ATYPIA (ATYPICAL HYPERPLASIA)** - There is increased mitoses and glandular crowding with cellular atypia ranging from mild to severe. This is associated with a high risk of subsequent cancer.

VIII. **ENDOMETRIAL GLANDULAR EPITHELIAL TUMORS** - These are now the most common female genital malignancies and appear to be increasing in frequency with 90% occurring after menopause.

Although there are exceptions, in general ***the development of adenocarcinoma is related to prolonged or excessive estrogen stimulation.*** Endometrial carcinomas have been experimentally induced in animals with high dose estrogens. In humans, risk factors include obesity, diabetes, hypertension, and infertility. In the peripheral adipose tissue of post-menopausal women, there is increased synthesis of estrogens from adrenal and ovarian androgens. Carcinoma may also be associated with functional ovarian tumors, pre-existing hyperplasia, and a history of breast cancer. The most common symptoms are irregular vaginal bleeding and leukorrhea.

A. **MORPHOLOGY** - Carcinomas may be focal and polypoid or widespread and diffuse. Eventually the endometrial cavity becomes filled with nodular and partially necrotic tumor. 60%-75% are *adenocarcinomas* varying from well-differentiated (Grade I) to poorly differentiated (Grade III). 20%-30% contain foci of squamous differentiation. Although these used to be subclassified as *adenoacanthoma* if the squamous component was benign and *adenosquamous carcinoma* if the squamous component was malignant, current evidence suggests that the prognosis is better predicted by the grade of the glandular component. A particularly aggressive tumor that should be distinguished from "ordinary" adenocarcinoma is the uterine papillary serous carcinoms (UPSC) which tends to spread widely over the peritoneal surfaces

B. **NATURAL HISTORY** - With time, tumor may extend into the myometrium and through the serosal surface to involve adjacent structures. Lymphatic spread is to regional and periaortic lymph nodes, and hematogenous spread is to lung, liver, bone, etc. The prognosis is dependent on depth of myometrial invasion, degree of cellular differentiation, and type of tumor. Tumors in older women tend to be less well-differentiated and more invasive than those in younger women.

C. **STAGING**

I - confined to corpus (80%)	95% 5 yr survival
II - involves corpus and cervix	30-50% 5 yr survival
III - outside uterus but within pelvis	< 20% 5 yr survival
IV - bladder or rectal mucosal involvement or outside pelvis	< 15% 5 yr survival

IX. **ENDOMETRIAL STROMAL TUMORS** - These tumors are characterized by the presence, within the myometrium, of endometrial stroma of varying cytologic atypia.

A. **BENIGN STROMAL NODULES** - These appear as expanding nodules of endometrial stroma buried within the myometrium.

B. **ENDOLYMPHATIC STROMAL MYOSIS** - This represents a low-grade sarcoma in which endometrial stromal tissue in the myometrium tends to invade lymphatics and blood vessels. 50% recur and 15% show distant metastases.

C. **ENDOMETRIAL STROMAL SARCOMA** - This usually arises high in the fundus, fills the endometrial cavity, and grows into the myometrium with extensive vascular invasion. The cellular cytology shows variable differentiation but mitoses are > 10/hpf. There is a 50% 5 yr survival.

X. **MALIGNANT MIXED MÜELLERIAN TUMORS** - These tend to occur in elderly postmenopausal patients and present with bleeding. Derived from müellerian mesoderm, the tumor consists of malignant glandular and stromal components. The stromal component may be homologous (stromal sarcoma, leiomyosarcoma) or heterologous (chondrosarcoma, rhabdomyosarcoma, etc). There is only a 25% 5 yr survival.

XI. MYOMETRIAL TUMORS

A. **LEIOMYOMA** - This is probably the most common neoplasm in women and affects up to 25% during their reproductive life. They tend to be more common in Blacks and are usually first noticed to arise in the 3rd to 4th decade, tending to decrease in size after menopause. Grossly these are well circumscribed, grey-white, rubbery spheroids which have a whorled cut surface. They may be pedunculated, submucosal, subserosal, or intramural and are often multiple and of varying size. Some may undergo cystic degeneration, hyalinization, or calcification. Histologically, they are composed of interlacing bundles of benign smooth muscle cells. Malignant transformation is distinctly unusual (< 0.1%). When symptoms occur, they are usually related to the size of the tumors (pressure on bladder or rectum, sensation of heaviness) to abnormal bleeding patterns (particularly submucosal tumors), or to pain from degeneration, infarction, and hemorrhage.

B. **LEIOMYOSARCOMA** - Malignant smooth muscle tumors are uncommon. They may present as fleshy masses invading into the uterine wall or as polypoid masses growing into the endometrial cavity. They are felt to arise de novo rather than from a preexisting leiomyoma. They vary in histologic appearance from low-grade (well-differentiated) to high-grade (poorly differentiated). Criteria of malignancy may simply rest on number of mitoses/HPF and cytologic atypia. In the uterus, smooth muscle tumors which have a mitotic rate of > 5 mitoses per 10 HPF should be considered malignant. The overall 5 yr survival is 40-50%.

FALLOPIAN TUBES

Transport of ova and sperm is an active process aided by the ciliated epithelium of the tubal mucosa. Anything that interferes with the tubal epithelium (inflammatory changes, etc.) or tubal mobility (peritubal adhesions, etc.) may also interfere with fertility.

I. INFLAMMATORY DISEASE

A. **SALPINGITIS** - Acute saplingitis is usually an extension of a pre-existing cervicitis or endometritis, and gonorrhea and chlamydia are the most frequent etiologic agents. Unless recognized and treated, the salpingitis may become chronic and result in infertility due to intratubal adhesions of the plica. Microscopically, this produces follicle-like spaces (*follicular salpingitis*) that interfere with tubal transport.

B. **TUBO-OVARIAN ABSCESS** - These usually result from microabscess formation in the cortex of the ovary which secondarily involves the fimbria of the tube in the inflammatory process.

II. **SALPINGITIS ISTHMICA NODOSA** - This refers to nodular lesions that develop at the isthmus of the tube. Histologically, the tube has a decreased lumenal size and increased thickness of the muscular wall which contains gland-like spaces lined by tubal epithelium. The etiology is not known, but the process may be similar to adenomyosis and may interfere with tubal transport of the fertilized egg to the endometrial cavity.

III. **CYSTS** - Embryologic remnants of the muellerian and wolffian ducts are present in the mesosalpinx and may become cystic (paratubal cysts, *hydatids of Morgagni*). Most are small, clinically asymptomatic, and do not interfere with fertility.

IV. **ECTOPIC PREGNANCY** - This occurs when the fertilized ovum implants in an area other than the endometrium and is increasing in frequency. Most ectopic pregnancies involve the fallopian tube (90%), but on rare occasions it may occur in the ovary or peritoneal cavity. Predisposing factors include those that

inhibit tubal transport of the ovum (chronic salpingitis, peritubal adhesions, large cysts, tumors, etc), but in about half of the cases, no underlying pathology can be identified. Since the tubal mucosa has a limited ability to undergo decidual change, the developing placental tissue is poorly anchored and hemorrhage occurs at the implantation site creating a *hematosalpinx*. Ectopic pregnancy is the most common cause of hematosalpinx. As the placenta grows, it burrows through the thin wall of the tube and may rupture the tube causing life-threatening intraperitoneal hemorrhage. This usually occurs 2-6 weeks after pregnancy ensues if the implantation is in the isthmic portion of the tube but may be as late as 12 weeks if the implantation is in the ampullary portion. Clinically, at the time of rupture, there is abrupt onset of severe abdominal pain, and the patient may go into shock. A negative pregnancy test is not sufficiently reliable to rule out an ectopic pregnancy, but finding blood in the pouch of Douglas on culdocentesis may be helpful in establishing the diagnosis.

V. **NEOPLASIA** - Malignant involvement of the tubes is most likely to represent metastatic disease. Primary neoplasms are rare but adenocarcinomas and benign *adenomatoid tumors* (mesotheliomas) can occur.

OVARY

I. **NON-NEOPLASTIC OVARIAN ENLARGEMENT** - The clinical finding of an adnexal mass on pelvic examination must be pursued. Non-neoplastic masses are generally caused by the development of cysts within the ovary. They may be asymptomatic or present with abdominal pain and/or abnormal menstrual cycles.

A. **"GERMINAL" INCLUSION CYSTS** - Common cysts (particularly in the premenopausal period), these may be multiple and of varying size (although usually < 1 cm), and result from downgrowth and entrapment of the surface epithelium into the ovarian cortex.

B. **PHYSIOLOGIC OR FUNCTIONAL CYSTS** - Several follicles develop during each menstrual cycle but only one ruptures. The remainder regress and become *atretic*. The theca cells of the ruptured follicle undergo hyperplasia and luteinization to produce a corpus luteum. Ultimately, the corpus luteum becomes hyalinized to form a corpus albicans. Physiologic cysts arise from exaggerations of these normal cyclic changes.

1. **FOLLICLE CYSTS** - These are extremely common and consist of one or more cysts developing from follicles that are undergoing atresia. They vary in size, are lined by granulosa cells or flattened atrophic cells and contain clear fluid. Usually they are of no clinical significance although rarely they may continue to secrete estrogens with resulting endometrial hyperplasia.
2. **CORPUS LUTEUM CYST** - This represents a cystic enlargement of a corpus luteum and usually shows central hemorrhage. It too is usually of no significance, but if it ruptures through the capsule, it may mimic an ectopic pregnancy. Persistent secretion of progesterone may cause menstrual irregularities.
3. **THECA LUTEIN CYSTS** - These may develop after improper atresia of unruptured follicles so that there is hyperplasia and persistence of luteinized theca cells stimulated by conditions in which there are high circulating levels of gonadotropins (pregnancy, hydatidiform moles, superfecundations, erythroblastosis fetalis, etc). Often this is a bilateral condition and, on occasion, these cysts may rupture to cause hemorrhage.

C. **POLYCYSTIC OVARIES** - One of the more common causes of infertility, the ovaries are bilaterally enlarged with multiple cysts underlying a thick white collagenous capsule. The cysts are lined by

granulosa-theca cells which may be luteinized (and androgen secreting). Corpora lutea are absent. Clinically, there are a variety of symptoms ranging from symptoms of hyperestrinism (abnormal bleeding, hypermenorrhea) to symptoms of virilization (amenorrhea, hirsutism). The *Stein-Leventhal syndrome* consists clinically of 2° amenorrhea, obesity, hirsutism, and infertility. The etiology is not known but probably involves a dysfunction of the hypothalamic-pituitary-ovarian axis so that abnormal secretion of gonadotropin releasing factor from the hypothalamus results in pituitary gonadotropin release and continuous ovarian stimulation. LH stimulates production of androstenedione and testosterone by the theca cells which is converted to estrogens (primarily estrone) in the peripheral adipose tissue. The increased estrogens inhibit FSH release by the pituitary and therefore follicles never develop normally. For unknown reasons, wedge resection of the ovary will restore normal cycling in a majority of patients.

D. **STROMAL HYPERPLASIA** - Occasionally, particularly in postmenopausal women, proliferation of ovarian stromal cells will result in nodular masses (primarily in the ovarian medulla) of both ovaries that clinically present as ovarian enlargement. Many of the stromal cells are luteinized (*hyperthecosis*) and produce androgens which may lead to virilization. Peripheral conversion of androgens to estrone, however, may lead to hyperestrogen symptoms such as endometrial hyperplasia and carcinoma.

II. **NEOPLASTIC OVARIAN ENLARGEMENT** - Most (80%) ovarian neoplasms are benign. Ovarian carcinoma, however, is the third most frequent female genital tract malignancy, and although ranking behind endometrial and cervical carcinomas in incidence, ovarian carcinoma results in greater mortality (50%) than those two combined. This is primarily due to late presentation. Unless endocrinologically active, they tend to be asymptomatic until the size of the tumor causes symptoms of abdominal pain and distension, GI or urinary tract compression or invasion, or abdominal bleeding. Ovarian neoplasms tend to be most prominent during reproductive years with the malignant forms tending to occur pre- or perimenopausally. The risk of ovarian neoplasia appears to be increased in women with a family history of ovarian tumors and women who have not borne children. Unlike breast or endometrial cancer, estrogen does not appear to play a role.

A. **TUMORS DERIVED FROM SURFACE (GERMINAL) EPITHELIUM** - These are the most common of the ovarian neoplasms. The paramesonephric (Muellerian) duct which ultimately provides the epithelial lining of the fallopian tube, uterus, and endocervix is embryologically derived from the same coelomic epithelium that covers the surface of the ovary. This epithelium therefore has the potential to differentiate into tubal epithelium (serous secreting, ciliated columnar), endometrial epithelium (non-ciliated columnar) or endocervical epithelium (mucus-secreting, nonciliated columnar), and ovarian neoplasms may mimic any of these cell types. As a group, the surface epithelial tumors are most frequently seen in adults with the malignant forms tending to occur in an older age bracket. They tend to grow relatively slowly causing low abdominal pain and distension. GI and urinary symptoms may intervene. Because of their location, the malignant forms are often not recognized until they have spread, many by diffuse peritoneal seeding which can cause massive ascites. Even benign tumors, however, can torse, infarct, and behave similar to an acute abdomen. CA 125 has been used as a serum marker for the presence of these tumors.

1. **SEROUS TUMORS** - These mimic the epithelium of the fallopian tube and overall are the most common of the ovarian tumors.

a. **Serous cystadenoma** (50% of serous tumors) - Typically this benign lesion is a unilocular cystic structure filled with clear fluid. The capsule is generally smooth and glistening, but there may be a few papillary projections on the internal or

external surface of the cyst wall. The cyst is lined by tall ciliated and nonciliated columnar epithelium without cellular atypia. As the size of the tumor increases, it may become multilocular and the epithelial lining may become flattened against the cyst wall. 20-30% are bilateral.

b. **Serous cystadenocarcinoma** (35% of serous tumors) - These make up about half of all malignant ovarian tumors. The cyst wall shows papillary projections on both sides and there are usually solid, nodular thickenings of the capsule. The histology shows piling up and stratification of the epithelium to more than three cells in thickness. Papillary structures, cellular cords, or solid cellular masses penetrate the tumor capsule and invade surrounding ovarian stroma. *65-70% are bilateral.* Although psammoma bodies are commonly seen in (and are characteristic of) serous tumors, they do not necessarily imply benignity or malignancy. Depending on the degree of cellular atypia, the tumors are graded I (well-differentiated) to III (poorly differentiated), however the clinical stage appears to be of greater prognostic significance than the histologic grade. 10 year survival is 10-20%.

c. **Serous borderline tumor** (15% of serous tumors) - These tumors show the cyst lining cells beginning to stratify (2-3 layers) with the potential to form complex papillary and glandular patterns. Although cellular atypia and mitoses are present, the atypia is not as severe nor are the mitoses as frequent as is seen in carcinoma. A cellular stroma separates the neoplastic glands and there is no evidence of capsular or ovarian stromal invasion. 10 year survival is ≈ 75%.

2. **MUCINOUS TUMORS** - These tumors mimic the epithlium of the endocervical canal and are most frequently seen in the 30-60 year age range.

a. **Mucinous cystadenoma** - This is about equal in incidence to the benign serous tumors. Grossly, they also appear similar to serous tumor but have a greater tendency to be unilateral, multiloculated, and large. They contain a mucinous, gelatinous fluid. Histologically, the cyst is lined by a non-ciliated mucous secreting epithelium. The mucin will stain variably with PAS, alcian blue, and mucicarmine. As the tumor enlarges, and pressure within the cyst increases, the epithelium may become flattened.

b. **Mucinous cystadenocarcinoma** - This is much less frequent than its serous counterpart, but basically the same gross and histologic criteria apply for diagnosis: piling up of the epithelium into more than 3 layers, complex papillary and glandular formations creating a cribriform pattern or solid cellular proliferations, and invasion of the ovarian stroma. The epithelial cells have decreased amounts of cytoplasmic mucin. If peritoneal seeding occurs, pseudomyxoma peritoneii may result. 10 year survival is ≈35% (60% if confined to ovary).

c. **Mucinous borderline tumor** - These show piling up and stratification (2-3 layers) of the epithelium with mild to moderate cellular atypia and occasional mitoses. The epithelium forms papillary structures with secondary cyst formation. A true cribriform pattern, however, is confined to the malignant lesions. 10 year survival ≈68% (96% if confined to ovary).

3. **ENDOMETRIOID TUMORS** - These tumors mimic endometrial glandular epithelium. Almost all of these are malignant at inception and overall comprise 20-30% of ovarian epithelial malignancies. 30-40% are bilateral. Histologically, these are more of a glandular neoplasm

than a papillary neoplasm and closely resemble endometrial carcinoma. Up to 30% of patients will have a coexistent endometrial cancer. This tumor, however, is felt to arise de novo rather than as a metastasis from the endometrium or a malignant transformation of a focus of endometriosis. Foci of squamous differentiation within the tumor is a helpful diagnostic sign. The overall 5 year survival is 40-50%. *Clear cell carcinoma* is a variant of endometrioid carcinoma and appears similar to clear cell carcinoma of the endometrium. If confined to the ovary there is a 5 year survival of 50%, but if not, survival is less than 10%. Other endometrial-like tumors (mixed mesodermal tumors, endometrial stromal sarcomas, etc) can also arise in the ovary but are rare.

4. **BRENNER TUMORS** - These are infrequent tumors having peak incidence in the 40-70 age range. They are usually unilateral, small, solid, and benign. Up to 25% may also be associated with another surface epithelial tumor of the ovary. Although the proportions vary, generally there is a fibrous stroma punctuated by nests of epithelial cells resembling the transitional epithelium that might be found lining the ureter or urinary bladder. They may alternatively resemble squamous epithelium (prekeratin can be demonstrated in the cell cytoplasm). Occasionally these cellular nests may have small cystic spaces in the center and resemble mucinous glandular structures. The stromal component may also contain lipid and appear luteinized and these have been reported in association with endometrial hyperplasia and adenocarcinoma. Borderline Brenner tumors resemble low-grade papillary transitional cell carcinomas with cellular mitoses but no stromal invasion. Malignant Brenner tumors resemble higher-grade transitional cell carcinomas.
5. **SEROUS SURFACE PAPILLOMA, CYSTADENOFIBROMA, ETC.** - These are primarily benign stromal proliferations with a surface epithelial component (usually serous in nature).

B. **TUMORS DERIVED FROM SEX CORD/STROMA** - These are derived from the specialized gonadal mesenchyme and, as such, have the potential of endocrinologic function.

1. **GRANULOSA-THECA CELL TUMORS** - Although pure granulosa cell and pure theca cell tumors occur, generally there is a mixture of the two to varying degrees. Although the greatest incidence is in the post-menopausal years, they can occur during the reproductive years but rarely appear before puberty. Usually unilateral, they vary in size and may be solid and/or cystic. If endocrinologically active, they secrete estrogens and will have a yellowish hue due to the presence of the lipid precursors to steroid hormones. There is a large histologic variability with different architectural patterns (microfollicular [*Call-Exner bodies*], macrofollicular, trabecular, solid, insular, etc.) but this has little prognostic value. Theca cells are sometimes difficult to tell from fibrous stroma. It may also be very difficult to differentiate benign from malignant, but they should be considered potentially malignant even though they generally follow a relatively benign course. Those with greater proportion of granulosa component are more frequently malignant while those with greater proportion of theca component are more frequently functional. The functional tumors may cause precocious puberty or, in adults, they may be associated with endometrial hyperplasia and breast carcinoma. Without treatment 15-25% of patients will develop endometrial carcinoma. If the androstenedione production by these cells is not converted to estrogens, these tumors may on occasion be virilizing. Clinically, there is a 5-25% recurrence rate with an 88% 5 year survival.
2. **FIBROMA** - Most (90%) are unilateral, solid, round, firm, white masses 5-10 cm in size. A thecal component may be present and estrogen secreting (*fibrothecoma*). For unknown reasons, when the tumor grows larger than 6 cm in size, 40% of patients will develop ascites and right-sided pleural effusion (*Meig's syndrome*).

3. **SERTOLI-LEYDIG CELL TUMOR** (arrhenoblastoma, androblastoma) - These may occur at any age but have a peak incidence during adolescence and young adulthood. They usually are unilateral, grey-white, solid masses with focal hemorrhage and necrosis. The tumors contain sertoli cells, Leydig cells, and a primitive gonadal stroma. The histology varies considerably but tends to recapitulate testicular development. Well differentiated, intermediate (most common), and sarcomatoid forms are present. With the less well differentiated tumors, the stroma becomes increasingly prominent and heterologous elements (usually mucinous intestinal epithelium but also cartilage, skeletal muscle, etc) may appear. On occasion these may have estrogenic activity, but the majority, if functionally active, elaborate androgenic hormones causing defeminization (amenorrhea, hair loss, breast atrophy) and virilization (hirsutism, male hair distribution, lowering of voice, clitoral hypertrophy, muscular build, etc.). Most follow a benign course and early surgical excision may reverse some of the endocrine effects.
4. **HILUS (HILAR) CELL TUMOR** - These consist of large lipid laden cells felt to arise from ovarian hilus cells, the counterpart of the testicular Leydig cells. Intracytoplasmic *Reinke crystalloids* confirm the diagnosis. Appearing in postmenopausal women, they are usually small, unilateral, virilizing, and benign. Increased urinary 17 ketosteroids are unresponsive to cortisone suppression.
5. **LIPID CELL TUMORS** - These cells may resemble Leydig cells and/or adrenal cortical cells. Although some feel that they may arise from adrenal rests, others feel that they simply represent Leydig cell tumors devoid of Reinke crystalloids. They are usually small, benign, and may be hormonally active (estrogen or androgen).
6. **SERTOLI CELL TUMORS** - These tumors are rare and tend to develop in young adults. The majority are functional with 45% secreting estrogens and 20% secreting androgens. The cells resemble the Sertoli cells that are present in the Sertoli-Leydig cell tumors.

C. **TUMORS DERIVED FROM GERM CELLS** - Although most of these tumors are benign, the malignant forms constitute the most common form of ovarian malignancy in children.

1. **TERATOMA** - These tumors all have a 46XX karyotype which implies parthenogenetic origin from a single postmeiotic haploid germ cell.

   a. **Mature cystic teratoma** (*dermoid cyst*) - These constitute 95% of germ cell tumors. They most often arise in young adults, are unilateral, and usually less than 10 cm. These tumors are prone to torsion and infarction and clinically, patients may present with abdominal pain, pelvic mass, irregular periods, etc. Grossly they appear as a unilocular or multilocular cyst lined by squamous epithelium and containing cheesy sebaceous debris, matted hair, cartilage, teeth, etc. Microscopic elements are derived from all germ layers and may consist of mucus glands, cartilage, respiratory or GI epithelium, skin and skin adnexa, brain, thyroid, etc. *Struma ovarii* refers to a teratoma consisting predominantly of thyroid tissue. 10% of patients are hyperthyroid and thyroid carcinomas may originate in this tissue.
   b. **Immature (malignant) teratoma** - These are rare tumors which tend to arise in a slightly younger age group (adolescents) than the mature teratomas. Almost always unilateral, these are predominantly solid tumors (with areas of necrosis and hemorrhage) which grow rapidly with local extension and metastases. Histology shows immature elements in addition to mature elements. Often there is immature neuroepithelium and unless the tumor is sampled carefully, it may be missed.

2. **DYSGERMINOMA** - This represents 2% of malignant ovarian tumors but over 50% of malignant germ cell tumors. The majority arise in adolescence and early adulthood, and are usually unilateral, solid, lobulated yellow-white to grey-pink fleshy masses. The size varies but they are usually relatively large when first discovered. The malignant cell is derived from primordial germ cells and recapitulate the undifferentiated embryologic gonad. This is the ovarian counterpart to testicular seminoma. Sheets and cords of medium sized cells with vesicular nuclei and clear or granular glycogen-rich cytoplasm are separated by scant fibrous stroma infiltrated by mature lymphocytes and occasional granulomas. Mitoses may be frequent. Although all are malignant, cellular atypia is variable and only 30% are aggressive. Like seminoma, these are radiosensitive and the 5 year survival runs 70-90%.
3. **ENDODERMAL SINUS (YOLK SAC) TUMOR** - These arise in young women and children and are derived from malignant germ cells showing extra-embryonic yolk sac differentiation with histologic recapitulation of the endodermal sinus. Grossly, it is usually a large unilateral, solid tumor with small cystic spaces and extensive necrosis and hemorrhage. The most common microscopic pattern is reticular with small tubules lined by single layered cuboidal to flattened epithelium arranged in a loose reticular stroma. Alternatively, papillary projections having a central blood vessel and lined by immature epithelium sometimes in hob-nail pattern may be present. Papillary structures may project into the tubules (*Schiller-Duval bodies*). Hyaline droplets are scattered throughout the neoplasm and the cells are rich in alpha fetoprotein and alpha 1-antitrypsin. Rapid aggressive growth and poor response to therapy originally characterized these tumors, however current survival rates are greater than 50% even with advanced disease.
4. **EMBRYONAL CARCINOMA** - This is a rare tumor similar to the more common embryonal carcinoma of the testis. They occur in children and adolescents, are unilateral, and are usually large when first discovered. They may result in precocious puberty and menstrual abnormalities. They secrete HCG from syncytiotrophoblastic giant cells and alpha fetoprotein from the embryonal cells.
5. **CHORIOCARCINOMA** - This is often seen in combination with other germ cell tumors. Pure choriocarcinomas, however, are almost always seen in younger patients and produce a hemorrhagic unilateral mass composed of malignant syncytiotrophoblasts and cytotrophoblasts. They produce high quantities of HCG. Unlike the placentally derived choriocarcinoma, these metastasize hematogenously and have an extremely high fatality rate.

D. **METASTATIC TUMORS** - These are relatively common (7%) with GI tract (*Krukenberg tumor*), breast, and other pelvic organs as the usual primary sites.

TESTIS

I. INFLAMMATORY DISORDERS

A. **INFECTIOUS ORCHITIS**

B. **GRANULOMATOUS ORCHITIS** - This is probably an autoimmune disease that usually presents as a painful mass in the testis. Histologically, there is granulomatous inflammation which must be differentiated from infectious granulomas.

II. NON-NEOPLASTIC ENLARGEMENT OF SCROTAL CONTENTS

A. **HYDROCELE** - This refers to an accumulation of serous fluid within the tunica vaginalis secondary to trauma, infection, systemic edema, etc.

B. **HEMATOCELE** - This refers to an accumulation of blood within the tunica vaginalis secondary to trauma or hemorrhagic diathesis.

C. **CHYLOCELE** - This refers to an accumulation of lymphatic fluid within the tunica vaginalis due to lymphatic obstruction by tumor, parasites, etc.

D. **SPERMATOCELE** - This refers to a cystic dilatation of epididymal ducts containing semen.

E. **TORSION** - This refers to a twisting of the spermatic cord (usually due to trauma) which may induce infarction, hemorrhage, and testicular enlargement.

III. NEOPLASTIC ENLARGEMENT OF SCROTAL CONTENTS

- Like their ovarian counterparts, testicular neoplasms can arise from the surface epithelium (tunica vaginalis), sex cord/stromal tissue, or germ cells. Unlike the ovaries, however, the vast majority of testicular neoplasms take origin from the germ cell. Testicular neoplasms are increasing in frequency, have a peak incidence in young adults (15-30 years), and generally cause ***painless*** enlargement of the testis. In the 15-34 year age group, testicular tumors are the most common neoplasm of males and account for 14% of all cancer deaths. Predisposing factors include cryptorchidism, genetic factors, and testicular dysgenesis.

A. **GERM CELL TUMORS** (95% of testicular neoplasms)

1. **SEMINOMA** - This is the most common testicular tumor and is the male counterpart of the ovarian dysgerminoma. It is most prevalent in the 4th-5th decade. They are bulky, firm, lobulated, tan-yellow tumors without necrosis or hemorrhage. They first spread to common iliac and para-aortic lymph nodes but are very radiosensitive and, in general, have an excellent prognosis. Three morphologic variants are recognized:

   a. **Classic seminoma** (85%) - This consists of uniform cells with round nuclei, clear cytoplasm, and distinct cytoplasmic borders. There is a variable amount of fibrous stroma with a prominent lymphocytic infiltrate, and occasional granuloma formation.

   b. **Anaplastic seminoma** (5-10%) - This shows greater cellular pleomorphism and increased numbers of mitoses. Although controversial, it may be associated with a more aggressive clinical course.

   c. **Spermatocytic seminoma** (4-6%) - This shows cellular pleomorphism and features of spermatocytic maturation. The lymphocytic component of the classic seminoma is absent. Typically affecting elderly males, these are slow growing tumors that do not metastasize and have an excellent prognosis.

2. **EMBRYONAL CARCINOMA** (15%) - This has a peak incidence in the third decade and is often a small infiltrative mass lesion consisting of large pleomorphic cells with a variable architectural pattern and often exhibiting necrosis and hemorrhage. Up to 90% may contain HCG and AFP. It does not respond well to radiation but if found early, prognosis is relatively good.

3. **TERATOMAS** (5%) - These are tumors which contain a mixture of tissue derived from the three embryologic germ cell layers. The *mature teratoma* tends to occur in younger individuals and contains benign differentiated tissue (neural, muscle, cartilage, thyroid

tissue and squamous, bronchial, and GI epithelium). The *immature teratomas* are composed of incompletely differentiated elements, and although the tissue elements may only appear immature rather than cytologically malignant, these tend to behave clinically in a malignant fashion. *Malignant teratomas* contain cytologically malignant tissue.

4. **ENDODERMAL SINUS (YOLK SAC) TUMOR** (1%) - Although not a common tumor, it is the most frequently seen testicular tumor in babies and young children and consists of undifferentiated cells with a variable architectural pattern (microcystic, glandular, alveolar, and papillary formations with characteristic *Schiller-Duval bodies* and intra- and extracytoplasmic hyaline inclusions. Like its ovarian counterpart, the tumor is rich in alpha fetoprotein and α-1-antitrypsin. If found early, and with current methods of treatment, the prognosis is generally good.
5. **CHORIOCARCINOMA** (1%) - This tumor is uncommon in its pure form. It is usually small, necrotic, and hemorrhagic consisting of both cytotrophoblasts and syncytiotrophoblasts. Like the ovarian choriocarcinomas, HCG is produced by the syncytiotrophoblasts and is a clinically useful marker. The tumor spreads quickly and widely via the bloodstream and the initial clinical complaints may be due to metastases. The tumor is highly aggressive, and the prognosis is generally poor.
6. **MIXED TUMORS** (40%) - These contain a mixture of two or more "pure" germ cell tumors, most commonly a mixture of teratoma and embryonal carcinoma (*teratocarcinoma*). Most will contain HCG or AFP. The prognosis is dependent on the more aggressive element.

B. **SEX CORD/STROMAL TUMORS** - In general, these are benign tumors but, as in the ovary, they may be endocrinologically active.

1. **LEYDIG CELL TUMOR** (2%) - This can occur at any age and may secrete androgens or estrogens creating feminization or precocious masculinization in boys. The only clinical effect in adult males would be gynecomastia in estrogen secreting tumors. They are bilateral in up to 10% of cases and microscopically may show *Reinke crystalloids*.
2. **SERTOLI CELL TUMORS** - These are rare tumors which may also secrete androgens or estrogens and may contain cells resembling ovarian granulosa cells. Most are benign.

C. **SURFACE EPITHELIAL TUMORS** - Unlike the ovary, these tumors are rare in the testis and consist primarily of the testicular mesothelioma (*adenomatoid tumors*).

D. **STAGING OF MALIGNANT TUMORS**

Stage I - Tumor confined to testis (with or without involvement of testicular adnexa or scrotum).
Stage II - Metastases to retroperitoneal lymph nodes below the diaphragm.
Stage III - Extranodal infradiaphragmatic metastases or any metastases above the diaphragm.

PROSTATE

I. **INFLAMMATORY DISEASE** - This may be asymptomatic or associated with low back pain or symptoms of urinary tract infection.

A. **ACUTE PROSTATITIS** - Focal or diffuse acute suppurative inflammation in the prostatic parenchyma leads to a swollen acutely tender gland. It most frequently is an extension from other genitourinary bacterial infections but may arise as complications of trauma (catheterization, transurethral resection, etc).

B. **CHRONIC PROSTATITIS** - This has a more insidious onset and is characterized by infiltrates of lymphocytes, plasma cells, and macrophages. When bacterial in origin, it is frequently a source of recurrent urinary tract infections. More commonly, however, no bacteria can be cultured.

C. **GRANULOMATOUS PROSTATITIS** - This is a non-specific granulomatous inflammatory reaction to prostatic secretions that are exposed to the stroma following acute or chronic prostatitis. Infectious etiologies (TB, etc), however, must be ruled out when granulomas are encountered.

II. **BENIGN PROSTATIC HYPERTROPHY (BPH)** - This is actually a misnomer since the lesion primarily represents a nodular hyperplasia of the gland. It is a common disorder which usually begins in the fifth decade and which increases in frequency with increasing age (95% of men over age 70). Only 5-10% of patients, however, will require surgical treatment. Although the etiology is unclear, there is an apparent relative imbalance between androgens and estrogens with the increasing estrogen levels seen with advancing age somehow sensitizing the prostatic tissue to the effects of testosterone since BPH will only occur in the presence of intact testes. The periurethral tissue is the most susceptible and leads to a spongy nodular enlargement of the median and lateral lobes which may cause symptoms related to partial urinary obstruction or retention of urine and predispose to urinary tract infections. ***There does not appear to be any causal relationship to the subsequent development of prostatic cancer.*** Microscopically, there is epithelial hyperplasia causing papillary budding and infolding of epithelium into the lumen of cystically dilated glands, inspissated prostatic secretions, focal squamous metaplasia, and fibromuscular hypertrophy.

III. **PROSTATIC CARCINOMA** - This is probably the most common malignancy in males, but ranks behind lung and colon cancer in terms of mortality. Unusual before the age of 50, it increases in frequency with advancing age so that prostatic cancer occurs in up to 70% of men by the age of 80. Many of these cancers, however, are small, biologically indolent, and identified incidentally on microscopic examination of the prostate for other reasons (Stage A carcinoma). Again, the etiology is unclear but it appears that genetic, environmental, and hormonal factors are involved. The tumor originates in the "peripheral" zone of the gland. It frequently involves the posterior lobe and may be palpated as a hard irregular nodularity on rectal examination (Stage B carcinoma). Microscopically almost all are adenocarcinomas and most of these are well-differentiated with few mitoses and little pleomorphism. "Back-to-back" glandular crowding without intervening stroma, a single layer epithelium, and capsular, vascular, or perineural "lymphatic" invasion are all indicators of malignancy. The Gleason grading system is the most widely used and assigns a tumor grade based on the degree of glandular differentiation and the growth pattern of the tumor in relation to the stroma. The major symptom is urinary obstruction, but this usually does not occur until late in the course of the disease so that the majority of patients present with extension of the tumor through the prostatic capsule (Stage C) or metastases (Stage D). Lymphatic spread is to regional lymph nodes and hematogenous spread is generally to bone (where the tumor produces ***osteoblastic*** lesions). Death is usually due to disseminated disease or obstructive nephropathy. *Prostate specific antigen (*PSA) is a protease that is excreted exclusively by prostate epithelial cells and can be measured in the serum. Although it can be elevated in men with either benign (BPH/prostatitis) or malignant disease of the prostate, it may be of value in screening for malignant disease in those patients at increased risk.

PLACENTAL DISORDERS

I. **REVIEW OF NORMAL** - Histologically, first trimester villi are large and hydropic. They are bordered by two layers of trophoblast: an outer *syncytiotrophoblast* and an inner *cytotrophoblast*. The vessels contain erythroblasts and nucleated red blood cells, but persistence of these beyond 10 weeks gestation is abnormal. In the latter part of the first trimester, *Hofbauer cells* become increasingly numerous; these cells function in nutrient transport and, probably, in host defense. Second trimester villi become about half the size of a first trimester terminal villus. The trophoblastic border progressively condenses. Its double-layered appearance becomes lost as the inner cells become less and less apparent. These inner Langhans cytotrophoblastic cells never completely disappear but, rather, are obscured by syncytiotrophoblast. Third trimester villi progressively halve their size again. Early in the third trimester the Hofbauer cells become less conspicuous as their villous boundary develops syncytial knots. Development of knotting becomes recognizable in the latter half of the third trimester. Irrespective of the histologic plane of sampling, no more than four or five vascular channels are ever present in a normal third trimester terminal villus. Grossly, although there is a variability in the size and weight of "normal" placentas, term placentas (trimmed of their membranes) in excess of 600 grams are abnormal. This may be due to diabetes, any kind of fetal immunohemolytic anemia, chronic intrauterine infection, fetal heart failure or maternal anemia; but most often, the cause is idiopathic.

II. **VASCULAR DISORDERS**

A. **TOXEMIA OF PREGNANCY**

1. **PRE-ECLAMPSIA** - This consists of a clinical triad of edema, hypertension, and proteinuria which usually develops during the third trimester of pregnancy and may clinically present as headaches, blurred vision, and abdominal cramps. Placental prostaglandins protect pregnant women against an increased vascular sensitivity to angiotensin. If this protection is lost, the increased sensitivity leads to vasoconstriction, hypertension, and vascular damage. Preeclamptic toxemia is evidenced by shrinkage of villi and by placental infarction.
2. **ECLAMPSIA** - This refers to the development of convulsions in addition to the findings of pre-eclampsia and is usually associated with DIC. Immunologic damage to uterine vessels causes placental ischemia leading to the release of thromboplastic substances which initiate DIC.

B. **INFARCTS** - Many placentas show an occasional infarct. There are times when infarcts are associated with severe fatal and neonatal compromise and other times when infarction of up to one-third of the placenta is free of complication. 40% of small-for-gestational age newborns have placentas with severe infarction and chronic ischemic change.

III. **INFLAMMATORY DISORDERS** - Acute inflammatory cells which infiltrate throughout the membranes and placental surface (*chorioamnionitis*) are a consequence of ascending infection, even if it be that the specific etiology is not proven by routine culture techniques. Causative organisms include chlamydia, mycoplasma and anaerobes, in additional to the more popularly recognized organisms such as group B beta-hemolytic streptococcus and E. coli. Spontaneous abortion between 20-28 weeks gestation is almost always associated with chorioamnionitis, and some initially normal neonates, who have severe chorioamnionitis, later succumb to sepsis. It has become clear in the past few years that congenital infections traditionally regarded as "transplacental" (e.g. cytomegalovirus, herpes simplex virus and rubella virus) may also have as their origin the ascent of an agent from an infected cervix. Group B hemolytic

Streptococcus is now the commonest cause of perinatal bacterial sepsis. The organism can be isolated from cervical cultures of anywhere from 5 to 30% of asymptomatic pregnant women, and also from their sexual partners. There are two neonatal clinical presentations: an acute septicemic form occurs in the first few hours or days of life, typically with features of pneumonia; a delayed meningitic manifestation presents anywhere from the 2nd to the 12th week of life. E. coli accounts for about 75% of gram negative perinatal infections while Staphylococci, listeria monocytogenes, and other organisms may, on occasion, cause pneumonia, meningitis and sepsis. The main causes of chronic congenital infections can be conveniently listed as Toxoplasmosis, Rubella virus, Cytomegalovirus, Herpes simplex virus and Syphilis. These diseases, conveniently called "TORCH(S)", have similar overt and/or inapparent clinicopathologic features: fetal growth retardation, hepatosplenomegaly, (hepatitis and extramedullary hematopoiesis), skin petechiae and/or purpuric lesions (EMH), encephalitis, cataracts, chorioretinitis, microcephaly, encephalomalacia, cerebral calcifications, disseminated intravascular coagulation, and cardiac and hearing defects.

IV. **GESTATIONAL TROPHOBLASTIC NEOPLASMS** - This group of tumors include a spectrum of neoplastic diseases of trophoblastic tissue which range from benign (hydatidiform mole) to overtly malignant (choriocarcinoma).

A. **COMPLETE HYDATIDIFORM MOLE** - This occurs in approximately 1:2000 pregnancies and tends to have a higher incidence in older women (40-50 yrs). It is felt to arise from loss or inactivation of maternal chromosomes in the fertilized egg. The embryo dies at an early stage, but the placenta continues with abnormal growth. Clinically these often present in the 4th to 5th month of pregnancy with the passage of vesicular tissue from the vagina, and there may be a history of uterine bleeding since early pregnancy. The uterus is usually larger than would be expected for the gestational age but no fetus is detectable. HCG levels are elevated and there may be bilateral ovarian enlargements due to theca-lutein cysts. Grossly, a delicate bulky tumor consisting of grape-like cystic structures fills the endometrial cavity. Microscopically, there is hydropic swelling of avascular villi with variable degrees of trophoblastic hyperplasia and anaplasia. The major complication is the potential for the development of choriocarcinoma.

B. **INCOMPLETE (PARTIAL) MOLE** - This refers to a mixture of normal and hydropic villi without appreciable trophoblastic proliferation. A fetus with a triploid phenotype is generally present. There is much less risk of subsequent development of choriocarcinoma as compared to a complete mole.

C. **INVASIVE MOLE** (*chorioadenoma destruens*) - Invasion into and/or through the myometrium by molar villi and trophoblastic tissue can result in uterine perforation. This is clinically characterized by bleeding associated with irregular uterine enlargement. The neoplasm may embolize to distant sites (i.e. lungs) but the embolic lesions will usually spontaneously regress when the uterine lesion is removed. The response to chemotherapy is usually good and can be monitored by HCG levels.

D. **CHORIOCARCINOMA** - This is a trophoblastic malignancy which may arise from either a preexisting normal pregnancy (20%) or an abnormal pregnancy (50% of which are hydatidiform moles). Clinically, it is characterized by irregular bleeding during otherwise apparently normal pregnancy or continued bleeding after miscarriage. The tumor is usually soft and friable with areas of hemorrhage and necrosis. It consists of neoplastic trophoblastic tissue containing both cytotrophoblasts and syncytiotrophoblasts without the presence of chorionic villi. The tumor spreads early and widely by lymphatic and hematogenous dissemination. Metastases are usually present at the time of diagnosis and most commonly involve lungs, vagina, brain, liver, and kidney. Metastatic lesions are occasionally found without evidence of a primary uterine lesion. As long as viable syncytiotrophoblasts are present, there are markedly elevated levels of HCG which can be used to monitor the course of the disease. Chemotherapy with methotrexate and actinomycin has been very effective with cures being possible. Unfortunately, choriocarcinomas arising outside of the gestational setting do not show the same response or prognosis.