This PowerPoint is going to cover a large amount of information. The material, along with my notes, will be available online through the Student Pathology Association (http://pathology.unm.edu/medical-students/student-pathology-association.html).

For this material, I used a combination of resources:
1. First Aid for the USMLE Step 1 (2015; 2016)
3. First Aid Q&A for the USMLE Step 1 (3rd Edition)
5. Gray’s Anatomy for Students (3rd Edition)
11. UpToDate
Between 1966 and 1969, seven out of eight girls whose mothers had taken a certain agent during pregnancy were diagnosed with clear cell adenocarcinoma of the vagina. As a result, the researcher who identified the cause for the rise of this condition performed a case-controlled study. Which of the following teratogens is the most likely agent that pregnant mothers took to cause this condition in their daughters?

A. Alcohol  
B. Diethylstilbestrol (DES)  
C. Lithium  
D. Nicotine  
E. Folic Acid
Diethylstilbestrol (DES) → synthetic nonsteroidal estrogen
- once commonly used in pregnant women to prevent breast engorgement, among many other uses.
- Prenatal exposure increases risk of multiple conditions
  - vaginal clear cell adenocarcinoma
  - reproductive tract malformations

Fetal alcohol syndrome from maternal alcoholism
- mental and growth retardation
- morphogenetic disturbances

Lithium
- heart and great vessel abnormalities in utero

Nicotine
- premature delivery
- conotruncal defects
- urinary tract abnormalities
Teratogens (p. 560)
The black bars show the periods during development when severe structural malformations can occur.
The white bars to the right of the black ones show periods when damage can consist of minor structural malformations, growth restrictions, or functional deficiency.
Teratogens – First Aid Style

• Medications
• Substance Abuse
• “Other”
I was trying to figure out some clever way to split these meds into body systems, or by trimester, or by effect. However, I actually think the simplest means of learning these effects is just to look at the First Aid chart (p 560 in FA2015) and sort of memorize it. Once you get all your pharmacology down, however, maybe take a stab at thinking a bit more about WHY each of these drugs cause certain defects (i.e., warfarin can cause fetal hemorrhage due to its role in inhibiting vitamin K-dependent clotting factors.)
The only mnemonic I could come up with was LIMP FAT CAT VW AD for teratogenic medications...sorry.
A 20-year-old woman comes into the emergency department at 35 weeks’ gestation because she has started to have abdominal pain (cramping, 8/10) and vaginal bleeding. Her symptoms began a couple hours ago. Her pain is staying constant, and the cramping “comes and goes” but is severe when it is present. She has used five pads in the past 3 hours. She has sustained no trauma during her pregnancy, nor has she noticed any vaginal leaking of clear fluid. However, she does state she has used cocaine “a few times” over the past month, and she last used yesterday.

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<tr>
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<td>- HR = 100/min</td>
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What is the most likely diagnosis?

A. Abruptio placenta
B. Concealed abruption
C. Labor
D. Placenta accreta
E. Placenta previa
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- BP = 155/95 mmHg
- Temp = 37°C
- HR = 100/min

Exam:
- Bimanual exam → tenderness over fundus; nondilated cervix

Ultrasound:
- Normally implanted placenta with no abnormalities
- Fetal HR = 170-180/min
Because Harry Potter. That’s why.
Teratogens – Substance Abuse

1. Alcohol
   • Neurodevelopmental defects
   • Fetal alcohol syndrome

2. Cocaine
   • Abnormal fetal growth and fetal addiction
   • Placental abruption

3. Smoking (nicotine, CO)
   • Low birth weight (leading cause in developed countries)
   • Preterm labor
   • Placental problems
   • Intrauterine growth restriction (IUGR)
   • ADHD

Another part of the First Aid chart
A 28-year-old woman in her third trimester of pregnancy with a complaint of dizziness for several days is admitted to the hospital. Physical examination reveals that she has diabetes mellitus. Which of the following cardiac malformations is most likely to affect the fetus when the mother has this disease?

A. Tetralogy of Fallot  
B. Transposition of the great arteries  
C. Atrial septal and VSDs  
D. Truncus arteriosus  
E. Coarctation of the aorta
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Be sure to know your heart abnormalities. The “Heart morphogenesis” section of First Aid (p 268 in FA2015) is gold. Also related to this slide, at least as far as cardiac anomalies are concerned, is “Congenital cardiac defect associations” (p 290 of FA2015).
Teratogens – “Other”

1. Iodine (lack or excess)
   • Congenital goiter or hypothyroidism (cretinism)
2. Maternal diabetes
   • Caudal regression syndrome (anal atresia to sirenomelia)
   • Congenital heart defects → transposition of the great arteries
   • Neural tube defects
3. Vitamin A (excess)
   • Extremely high risk for spontaneous abortions and birth defects (cardiac, cleft palate)
4. X-rays
   • Microcephaly
   • Intellectual disability
During weeks 3 to 8, the embryo is most susceptible to teratogens because major organs develop during this time. Which of the following exposures during this period would most likely result in congenital deafness, low birth rate, inflammation of the retina, and jaundice?

A. Toxoplasmosis
B. Heroin
C. Mercury poisoning
D. Alcohol
E. Tetracycline
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This is actually assuming you are still in touch with Dr. Hickey’s lectures from last block. Make sure you study all teratogens, including maternal illnesses!
A 10-year-old child is unable to achieve many of the cognitive milestones appropriate for his age group and has impaired overall socioadaptive behavior. His mental age is determined to be 6 years. What is the most common cause of this disorder?

A. Head injury  
B. High maternal age at conception  
C. Hypoxia during birth  
D. Maternal alcohol consumption during pregnancy  
E. Perinatal infection
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Fetal Alcohol Syndrome (561)
Fetal Alcohol Syndrome

1. Leading cause of intellectual disability in the U.S.
2. Increased incidence of congenital abnormalities
   - Pre- and postnatal developmental retardation
   - Microcephaly
   - Facial abnormalities (e.g., smooth philtrum, hypertelorism)
   - Limb dislocation
   - Heart defects
3. In most severe form:
   - Heart-lung fistulas
   - Holoprosencephaly
4. Mechanism of problems: failure of cell migration
Fetal Alcohol Syndrome

- “Railroad track” ear → upper curve of ear is underdeveloped, folded over, and parallel to the curve beneath it
Fetal Alcohol Syndrome

- Clinodactyly (curvature in the plane of the palm) of the fifth finger
- “Hockey stick” configuration of the upper palmar crease
  - Widely curves and terminates between index and middle fingers
Fetal Alcohol Syndrome

- Short palpebral fissure length
- Smooth philtrum
- Thin upper lip
A new mother brings in her neonate for a well-child exam. You are aware that the baby was exposed to excess alcohol in utero (mom drank 4-6 beers a day throughout her pregnancy.) Assuming this child has evidence of fetal alcohol syndrome, what would you expect to find on physical exam and/or imaging?

A. Spina bifida
B. Heart block
C. Upslanting palpebral fissures
D. Hypoplasia of the distal phalanges
E. Smooth philtrum
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A. Spina bifida  
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D. Hypoplasia of the distal phalanges  
E. Smooth philtrum
A 1-year-old child was admitted to the pediatric clinic due to severe dyspnea. An electrocardiogram (ECG) reveals cardiac arrhythmia and right ventricular hypertrophy. An angiogram reveals a PDA. From which of the following embryologic arterial structures does the PDA take origin?

A. Left sixth aortic arch  
B. Right sixth aortic arch  
C. Left fifth aortic arch  
D. Right fifth aortic arch  
E. Left fourth aortic arch
The left sixth aortic arch is responsible for the development both of the pulmonary arteries and the ductus arteriosus. Without regression of the ductus arteriosus, a patent connection remains between aorta and the pulmonary trunk. The ductus arteriosus often reaches functional closure within 24 hours after birth, whereas anatomic closure and subsequent formation of the ligamentum arteriosum often occur by the twelfth postnatal week.
Aortic Arch Derivatives
(p. 564)
# Aortic Arch Derivatives

<table>
<thead>
<tr>
<th>Arch</th>
<th>Derivative(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• Maxillary artery</td>
</tr>
</tbody>
</table>
| 2    | • Stapedial artery  
• Hyoid artery |
| 3    | • Common carotid artery  
• Proximal part of internal carotid artery |
| 4    | • Left → Aortic arch  
• Right → Proximal part of right subclavian artery |
| 6    | • Proximal part of pulmonary arteries  
• Left → Ductus arteriosus |
Aortic Arch 5 Be Like...
Pages 189 & 190 in Langman’s have a great overview of the derivatives.

Remember:
1 → maxillary artery
2 → stapedial artery; hyoid artery
3 → common carotid artery; proximal portion of internal carotid artery
4 → (L) aortic arch; (R) proximal portion of right subclavian artery
6 → Proximal part of pulmonary arteries; (L) ductus arteriosus
A 30-year-old man is diagnosed with a blockage of arterial flow in the proximal part of the thoracic aorta. Brachial arterial pressure is markedly increased, femoral artery pressure is decreased, and the femoral pulses are delayed. The patient shows no external signs of inflammation. Which of the following structures failed to develop normally?

A. Second aortic arch  
B. Third aortic arch  
C. Fourth aortic arch  
D. Fifth aortic arch  
E. Ductus venosus
The fourth aortic arch develops into the aortic arch on the left side and the brachiocephalic and subclavian arteries on the right side of the embryo. Improper development of the arch of the aorta will cause an increased pressure in the subclavian artery and, subsequently, the brachial artery. Similarly, decreased flow through the aorta will lead to a decreased pressure in the femoral artery. The second aortic arch, specifically the dorsal aspect, develops into aspects of the small stapedial artery. The proximal part of the third aortic arch gives rise to the common carotid arteries, which supply the head. The fifth aortic arch is said not to usually develop in human embryos. The proximal part of the sixth aortic arch develops into the left pulmonary artery.
A 25-year-old man is admitted to the hospital with severe headache, cold feet and legs, and pain in his legs when he runs a short distance. During physical examination, femoral pulses are much weaker than radial pulses. Three-dimensional CT scan angiography reveals a coarctation of the aorta proximal to the left subclavian artery. The condition that creates these symptoms is a result of a failure of normal development of which structure?

A. Fourth pharyngeal arch  
B. Third pharyngeal arch  
C. Left dorsal aorta  
D. Left fifth pharyngeal arch  
E. Sixth pharyngeal arch
During embryonic development the left dorsal aorta gives rise to the thoracic aorta. The aortic arch is formed by the aortic sac and the fourth pharyngeal artery. The third pharyngeal artery will give rise to the common carotid artery. The fifth pharyngeal arch artery will disappear bilaterally, and the sixth will form the ductus arteriosus on the left and part of the pulmonary trunk. In this case the region of the arch of the aorta between the subclavian artery and the left common carotid artery is formed by the fourth aortic arch.

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A. Fourth pharyngeal arch  
B. Third pharyngeal arch  
C. Left dorsal aorta  
D. Left fifth pharyngeal arch  
E. Sixth pharyngeal arch
Branchial Apparatus
(p. 564)
Pharyngeal

Branchial Apparatus
Dr. Hartley: “Fish. Branchial is fish. Because, you know, they have no pharynx.”
Pharyngeal Apparatus

Wear a CAP for the outside:
C $\rightarrow$ Clefts = ectoderm
A $\rightarrow$ Arches = mesoderm
P $\rightarrow$ Pouches = endoderm
A 3-year-old boy is brought to the outpatient clinic with swelling of the side of his neck. Physical examination reveals a congenital mass of tissue anterior to the superior third of the sternocleidomastoid muscle. The swelling is asymptomatic, non-painful, and soft fluctuant. Which of the following is the most likely diagnosis?

A. Branchial cleft cyst  
B. Ruptured sternocleidomastoid muscle  
C. Lymph node inflammation  
D. Torticollis  
E. External carotid artery aneurysm
Pharyngeal (branchial) cleft cysts are the most common congenital cause of a neck mass. They are epithelial cysts that arise anterior to the superior third of the sternocleidomastoid muscle from a failure of obliteration of the second branchial cleft in embryonic development. The second arch grows caudally and, ultimately, covers the third and fourth arches. The buried clefts become ectoderm-lined cavities that normally involute. Occasionally this process is arrested and the entrapped remnant forms an epithelium-lined cyst, in some cases with a sinus tract to the overlying skin. Many branchial cleft cysts are asymptomatic; others may become tender, enlarged, or inflamed, or they may develop abscesses that rupture, resulting in a purulent draining sinus to the skin or pharynx. Surgery is indicated in these cases.
Pharyngeal Apparatus → Clefts

- Originally, there are 4 clefts
- Cleft 1 → Becomes external auditory meatus
Pharyngeal Clefts 2-4: That one friend...

Temporary cervical sinuses are formed by clefts 2-4, then are obliterated by proliferation of 2nd arch mesenchyme.
Pharyngeal Clefts 2-4: Persistent Sinus
A 3-year-old boy is admitted to the hospital because of a soft anterior midline cervical mass. When he is asked to protrude his tongue, the mass in the neck is observed to move upward. Which of the following is the most likely diagnosis?

A. A thyroglossal duct cyst  
B. Defect in sixth pharyngeal arch  
C. A branchial cyst  
D. Cystic fistula of the third pharyngeal arch  
E. Defect in first pharyngeal arch
Thyroglossal duct cysts occur due to retention of a remnant of the thyroglossal duct along the path followed by the descending thyroid gland during development. The path begins at the foramen cecum of the tongue and descends in the midline to the final position of the thyroid. The sixth pharyngeal arch provides origin to muscles and cartilage of the neck and would produce a midline mass connected to the tongue. A branchial cyst or fistula would not be present in the midline. The first pharyngeal arch gives rise to muscles of mastication and the malleus and incus. The third pharyngeal arch provides origin to the stylopharyngeus muscle and hyoid bone.
# Pharyngeal Arch Cartilaginous Structures

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      | 3. Incus  
      | 4. Sphenomandibular ligament |
| 2    | 1. Stapes  
      | 2. Styloid process  
      | 3. Lesser horn of hyoid  
      | 4. Stylohyoid ligament |
| 3    | 1. Greater horn of hyoid |
| 4-6  | 1. Thyroid  
      | 2. Cricoid  
      | 3. Arytenoids  
      | 4. Corniculate  
      | 5. Cuneiform |
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Gray’s for Students
The two arytenoid cartilages are pyramid-shaped cartilages with three surfaces, a base of arytenoid cartilage and an apex of arytenoid cartilage.
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<tr>
<th>Arch</th>
<th>Muscle</th>
<th>Muscle</th>
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<tbody>
<tr>
<td>3</td>
<td>1. Stylopharyngeus</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; Arch: Most pharyngeal constrictors&lt;br&gt;1. Cricothyroid&lt;br&gt;2. Levator veli palatini</td>
<td>6&lt;sup&gt;th&lt;/sup&gt; Arch: All intrinsic muscles of larynx except cricothyroid</td>
</tr>
</tbody>
</table>
A 2-day-old female infant was born with a cleft palate. The major portion of the palate develops from which of the following embryonic structures?

A. Lateral palatine process
B. Median palatine process
C. Intermaxillary segment
D. Median nasal prominences
E. Frontonasal eminence
The largest part of the palate is formed by the secondary palate, which is embryologically derived from the lateral palatine processes. The median palatine process gives rise to the smaller primary palate, located anteriorly. The intermaxillary segment gives rise to the middle upper lip, premaxillary part of the maxilla, and the primary palate. The median nasal prominences merge with each other and the maxillary prominences to give rise to the intermaxillary segment. The frontonasal eminence gives rise to parts of the forehead, nose, and eyes.
Cleft Lip and Cleft Palate
(p. 566)
Cleft Lip and Cleft Palate

• **Lip** $\rightarrow$ failure of fusion of **maxillary and medial nasal processes** (formation of primary palate)

• **Palate** $\rightarrow$ (formation of secondary palate) failure of fusion of
  • Two lateral palatine processes
  • Or
  • Lateral palatine shelves with nasal septum and/or median palatine shelf

• Can occur together, but don’t have to
Genital Embryology
(p. 567)
Genital Embryology

- Female: **PARAMESONEPHRIC duct** develops

- Male: **MESONEPHRIC duct** develops
Genetic Embryology

Paramesonephric Duct
- AKA Müllerian duct
- Forms female internal structures $\rightarrow$ FU U (?)
  - Fallopian tubes
  - Uterus
  - Upper portion of the vagina
- Male remnant = appendix testis

Mesonephric Duct
- AKA Wolffian duct
- Forms male internal structures (NOT prostate) $\rightarrow$ SEED
  - Seminal vesicles
  - Epididymis
  - Ejaculatory duct
  - Ductus deferens
- Female remnant = Gartner duct

$\rightarrow$ Müllerian Agenesis (one form is called Mayer-Rokitansky-Küster-Hauser Syndrome): can present as primary amenorrhea (variable lack of uterus, vagina) in females with fully developed secondary characteristics (due to functional ovaries)
SRY Gene (p. 567)

IT'S JUST A TESTICLE.

THE GODS SAW FIT TO GRACE ME WITH A SPARE.
SRY gene

SRY gene on Y chromosome → Testis-determining factor → Testes

1. Sertoli cell
   - Müllerian inhibitory factor
   - Degeneration of paramesonephric (Müllerian) duct (female internal genitalia)

2. Leydig cell
   - Testosterone
   - Male internal genitalia (except prostate)
   - Wolffian duct
   - DHT
   - Genital tubercle, urogenital sinus
   - Male external genitalia, prostate

SRY is the master of testes development

FA2015

1. No Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia
2. 5α-reductase deficiency → inability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when testosterone levels cause masculinization)
Male/Female Genital Homologs (p. 568)
Congenital Penile Abnormalities (p. 569)
Hypospadias
“Hypo is below”

- Abnormal VENTRAL opening
- Failure of urethral fold fusion
- More common
  - a/w:
    - Inguinal hernia
    - Cryptorchidism

Epispadias
“Hit your eye when you pee”

- Abnormal DORSAL opening
- Faulty genital tubercle position
- a/w:
  - Exstrophy of the bladder
“Bladder extrophy is classically characterized by an open, inside out bladder (the inner surface exposed) and exposed dorsal urethra on the surface of the lower abdominal wall.”
REPRODUCTIVE ANATOMY

• Male Reproductive Anatomy
  • Urethral Injury
• Autonomic Innervation of the Male Sexual Response
  • Seminiferous Tubules
Male Reproductive Anatomy (p. 571)
Anatomy – Pelvic Cavity and Peritoneum

Note the bladder lying outside the peritoneum
The “bridge over troubled water” – Note how the ductus deferens crosses the ureter

Gray’s for Students
Pathway of sperm during ejaculation
Pathway of sperm during ejaculation

1. Seminiferous tubules
2. Epididymus
3. Vas deferens
4. Ejaculatory ducts
5. (Nothing)
6. Urethra
7. Penis
Urethral Injury
Urethral Injury → look for blood at urethral meatus

**Posterior Urethra**
(essentially from bladder to external urethral sphincter)

- Membranous urethra → pelvic fracture
- Urine can leak into retropubic space
Urethral Injury → look for blood at urethral meatus

**Anterior Urethra**
(external urethral sphincter to external urethral meatus)

- Bulbar and penile urethra → perineal straddle injury
- Urine can leak into deep fascia of Buck
- If fascia is torn, urine into superficial perineal space
Autonomic Innervation of the Male Sexual Response
Autonomic Innervation of the Male Sexual Response

1. Point $\rightarrow$ erection
2. Squeeze $\rightarrow$ emission
3. Shoot $\rightarrow$ ejaculation
Point → Erection [Parasympathetic: Pelvic Nerve]

**Proerectile**
- NO
  - \( \uparrow \)cGMP
  - Smooth muscle relaxation
  - Vasodilation

**Antierectile**
- Norepinephrine
  - \( \uparrow \)Ca\(^{2+} \)\(_{in} \)
  - Smooth muscle contraction
  - Vasoconstriction
Squeeze $\rightarrow$ Emission [Sympathetic nervous system: hypogastric nerve]

Movement of ejaculate into proximal urethra, the result of peristaltic contractions of ampullary portion of the vas deferens, seminal vesicles, prostatic smooth muscles

Shoot $\rightarrow$ Ejaculation [Visceral and Somatic nerves: pudendal nerve]

Erectile Dysfunction Note: PDE-5 Inhibitors (eg, sildenafil) decrease cGMP breakdown
Seminiferous Tubules
(p. 572)

- Spermatogonia (germ cells)
- Sertoli cells (non-germ cells)
- Leydig cells (endocrine cells)
<table>
<thead>
<tr>
<th>Function</th>
<th>Location/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secrete testosterone in the presence of LH</td>
<td>Testosterone production unaffected by temperature</td>
</tr>
<tr>
<td>Interstitium</td>
<td></td>
</tr>
<tr>
<td>Homolog of female theca interna cells</td>
<td></td>
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Seminiferous Tubules → Sertoli Cells (non-germ cells)

- Secrete inhibin B → inhibits FSH
- Secrete androgen-binding protein → maintain local levels of testosterone
- Blood-testis barrier = tight junctions between adjacent Sertoli cells → isolate gametes from autoimmune attack
- Support and nourish developing spermatozoa
- Regulate spermatogenesis
- Produce MIF

<table>
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<tr>
<td>↑temperature → ↓ sperm production and ↓ inhibin</td>
<td>[increased temperature seen in varicocele, cryptorchidism]</td>
</tr>
<tr>
<td>Line seminiferous tubules</td>
<td></td>
</tr>
<tr>
<td>Convert testosterone and androstenedione to estrogens via aromatase</td>
<td></td>
</tr>
<tr>
<td>Sertoli cells Support Sperm Synthesis</td>
<td></td>
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<td>Homolog of female granulosa cells</td>
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REPRODUCTIVE PHYSIOLOGY

- Tanner Stages of Sexual Development
- Spermatogenesis
- Androgens
Tanner Stages of Sexual Development
<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Boys – External Genitalia</th>
<th>Girls – Breast Development</th>
<th>Boys and Girls – Pubic Hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prepubertal</td>
<td>Prepubertal</td>
<td>Prepubertal</td>
</tr>
</tbody>
</table>
| II          | Scrotal/Testicular
enlargement          | Breast buds form (thelarche) | Sparse growth of long, slightly pigmented hair along the base of the penis or along labia |
| III         | Enlargement of penis (length only at first) | Further enlargement of breast and areola; no contour separation | Darker, curly hair that spreads sparsely over junction of pubis |
| IV          | Increased size of penis with growth in breadth and glans development; testes and scrotum larger; scrotal skin darker | Areola and papilla form a secondary mound above level of the breast | Adult pubic hair without spread to medial surface of the thighs |
| V           | Penis and testes grow to adult size | Projection of papilla related to recession of areola | Adult in type and quantity; course hair across pubis and medial thigh |

Chart made from a mix of First Aid and UpToDate
Spermatogenesis
Junqueira explains the process a bit better than FA, I think, if you’re like me and have issues keeping your “ploidies” and whatnot straight. The book is available online through AccessMedicine.
Androgens
## Androgens

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Testes</strong></td>
<td>Differentiation of penis</td>
<td>Epididymis</td>
<td>Adrenal Gland</td>
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<tr>
<td></td>
<td>Differentiation of scrotum</td>
<td>Vasa deferent</td>
<td></td>
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<tr>
<td></td>
<td>Differentiation of prostate</td>
<td>Seminal vesicles</td>
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<tr>
<td></td>
<td>Prostate growth</td>
<td>Growth Spurt</td>
<td></td>
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<tr>
<td></td>
<td>Balding</td>
<td>Deepening of voice</td>
<td></td>
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<tr>
<td></td>
<td>Sebaceous gland activity</td>
<td>Closing of epiphyseal plates</td>
<td></td>
</tr>
</tbody>
</table>

### Notes

1. Testosterone converted to DHT by 5α-reductase $\rightarrow$ inhibited by finasteride
2. Aromatase $\rightarrow$ KEY enzyme in conversion of androgens to estrogen
3. If a dude takes too much exogenous testosterone $\rightarrow$ inhibition of HPG axis $\rightarrow$ decreased intratesticular testosterone $\rightarrow$ decreased testicular size $\rightarrow$ azoospermia
REPRODUCTIVE PATHOLOGY

- Penile Pathology
- Cryptorchidism
- Varicocele
- Extragonadal Germ Cell Tumors
- Scrotal Masses
- Testicular Germ Cell Tumors
- Testicular Non-Germ Cell Tumors
- Benign Prostatic Hyperplasia
- Prostatitis
- Prostatic Adenocarcinoma
Penile Pathology
Penile Pathology
Peyronie Disease [in ICD 10 now “Induration penis plastica”]

* What:
  - abnormal curvature of the penis due to fibrous plaque
* Location: Tunica albuginea
* Presentation:
  - Pain
  - Anxiety
  - Erectile dysfunction
* Tx:
  - Surgical repair once curvature stabilizes

*Note: NOT the same as penile fracture [rupture of corpora cavernosa due to forced bending]
Penile Pathology
Ischemic Priapism

• What:
  ➔ Painful sustained erection lasting longer than 4 hours

• Associated with:
  ➔ Sickle cell disease [sickled red cells stuck in vascular channels]
  ➔ Medications [i.e., sildenafil, trazodone]

• Presentation:
  ➔ Pain
  ➔ Erection

• Tx:
  ➔ corporal aspiration
  ➔ intracavernosal phenylephrine
  ➔ surgical decompression
Penile Pathology
Squamous Cell Carcinoma

• What:
  → Malignancy of cutaneous squamous epithelium

• Associated with:
  → High-Risk HPV (66% of cases)
  → Lack of circumcision
Cryptorchidism
Cryptorchidism

• What:
  → Undescended testis [can be one or both; bilateral shown in image]
• Associated with:
  → Premature birth
• Presentation:
  → Unilateral or bilateral absence of testis in scrotum
• Tx:
  → Orchiopexy [surgical manipulation of testis into scrotum]
• Complications:
  → Impaired spermatogenesis [sperm like lower temperatures, so don’t do well inside abdomen]
  → Increased risk of seminomas [a type of germ cell tumor]
  → ↓ inhibin B, ↑ FSH, ↑ LH
  → Testosterone normal in unilateral, decreased in bilateral [Leydig cells are unaffected by temperature]
Varicocele
Varicocele

• What:
  → Dilated veins in pampiniform plexus [due to increased venous pressure]

• Associated with:
  → Left renal cell carcinoma

• Presentation:
  → Scrotal enlargement
  → “Bag of worms” on palpation
  → does NOT transilluminate

• Tx:
  → Varicocelectomy
  → Embolization

• Notes:
  → Most often in the left due to gonadal vein drainage into the renal vein [right drains straight to IVC]
  → Can cause infertility due to increased temperature
Scrotal Masses
Scrotal Masses
[benign; present as mass in testicle; may be transilluminating]

Congenital Hydrocele
- Incomplete obliteration of processus vaginalis
- Scrotal swelling in infants
- Transilluminating

Acquired Hydrocele
- Scrotal fluid due to blockage of lymphatic drainage
- Usually secondary to infection, trauma, or tumor
- Blood filled = hematocoele

Spermatocele
- Cyst that presents as a paratesticular fluctuant nodule
- Due to dilated epididymal duct or rete testis
I think watching Pathoma is really helpful for these tumors. This is just an overview to help you classify them.
Prostate Pathology → Benign Prostatic Hyperplasia

- Common in men over 50
- NOT premalignant
- Hyperplasia of lateral and middle lobes of prostate
- Increased urinary frequency, nocturia, difficulty starting/stopping stream
- SLIGHT increase in PSA possible
Prostate Pathology → Prostatic Adenocarcinoma

- Most common cancer in men
- Risks: age, African-American descent, diet high in saturated fat
- Usually clinically silent
- Usually from POSTERIOR LOBE
- Increased PSA + biopsy needed to confirm diagnosis
REPRODUCTIVE PHARMACOLOGY
[Cards from “PharmCards”]

• Control of Reproductive Hormones
• Leuprolide
• Extrogens
• Selective Estrogen Receptor Modulators
• Hormone Replacement Therapy
• Anastrozole/Exemestane
• Progestins

• Mifepristone (RU–486)
• Oral Contraception
• Terbutaline, Ritodrine
• Danazol
• Testosterone, Methyltestosterone
• Antiandrogens
• Tamsulosin
• Sildenafil, Vardenafil, Tadalafil
• Minoxidil
Control of Reproductive Hormones
| Mechanism | Synthetic gonadotropin releasing hormone (GnRH):  
Given intermittently → stimulates release of FSH and LH. 
Given continuously → paradoxical effect: inhibits release of FSH and LH.  
GnRH is a decapeptide produced in the hypothalamus that binds to receptors on pituitary gonadotrophs.  
Intermittent, pulsatile release of GnRH results in release of FSH and LH. In contrast, continuous stimulation of gonadotrophs with GnRH or GnRH analogs results in stimulation of FSH and LH release initially, but subsequent inhibition.  
Clinical | Stimulation (given intermittently via a portable, programmable infusion pump):  
Infertility caused by hypothalamic hypogonadotropic hypogonadism (men and women).  
Suppression (given in depot form to induce hypogonadism):  
Prostate cancer: androgen synthesis; first-line androgen deprivation therapy.  
Endometriosis, polycystic ovarian disease, uterine fibroids.  
Central precocious puberty.  
Side Effects | Even when given continuously for gonadotroph suppression, there is an initial, transient stimulation phase, which can cause ovarian cysts in women and can cause \( \uparrow \) tumor activity with \( \uparrow \) bone pain in men with prostate cancer.  
Contraindic. | Pregnancy.  
Notes | NAFARELIN (Synarel), GOSERELIN (Zoladex), HISTRELIN (Vantas, Supprelin LA), and TRIPTORELIN (Trelstar) are also synthetic GnRH analogs.  
ABARELIX (Plenaxis) and CETRORELIX (Cetrodine) are GnRH antagonists. |
| Mechanism | Bind to estrogen receptors (ERα and ERβ) and are transported into nucleus. The receptor–hormone complex binds to specific sequences of nucleotides (called estrogen response elements) in promoters of certain genes, thereby regulating gene transcription. Estrogen receptors are found in the female reproductive tract, breast, pituitary, and hypothalamus. Exogenous estrogens inhibit endogenous FSH secretion and thereby suppress ovulation. |
| Clinical | **Oral contraceptives** (with a progestin): inhibits ovulation. Dysmenorrhea; polycystic ovarian disease (PCOD). Primary hypogonadism. Used for postmenopausal **hormone replacement therapy** to ↓ signs and symptoms caused by loss of ovarian function (vasomotor symptoms or “hot flashes,” genital atrophy, and so on) and to ↓ bone loss and fractures, but fallen out of favor because of cardiovascular side effects (see below). |
| Side Effects | **Postmenopausal uterine bleeding.** Hypertension, migraines, cholestasis, hepatic adenomas. Endometrial hyperplasia, ↑ risk of **endometrial cancer** (if given w/o progestin), ↑ risk of **breast cancer** (if given w/ progestin). ↑ **thromboembolic events**, both arterial (MI, stroke) and venous (DVT, PE). |
| Notes | Commercial estrogens include **ESTRADIOL**, **ESTRONE** (Premarin), and **ETHINYL ESTRADIOL** (Estinyl, Femviron). Oral contraceptives are available in a plethora of estrogen + progestin combinations. **Diethylstilbestrol** (DES), a semisynthetic estrogen previously used during the first trimester of pregnancy, was associated with an ↑ incidence of vaginal and cervical clear cell adenocarcinomas in female offspring. |
### CLOMIPHENE

**Fulvestrant**

<table>
<thead>
<tr>
<th>Hypothalamus and anterior pituitary</th>
<th>Breast</th>
<th>Ovaries</th>
<th>Uterus</th>
<th>Bone</th>
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<tr>
<td><strong>ER Agonism</strong></td>
<td>Feedback inhib. → ↓ GnRH/FSH/LH → Supress ovulation</td>
<td>Predisposes to cancer</td>
<td>Enlargement and cysts</td>
<td>Predisposes to cancer</td>
<td>Formation and ↓ osteoporosis</td>
</tr>
<tr>
<td><strong>ER Antagonism</strong></td>
<td>Disrupt feedback inhibition → ↑ GnRH/FSH/LH → Induce ovulation</td>
<td>Prevents and treats cancer</td>
<td>Atrophy</td>
<td>Atrophy</td>
<td>Osteoporosis</td>
</tr>
</tbody>
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**DRUG EFFECTS**

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Clomiphene</th>
<th>Tamoxifen</th>
<th>Raloxifene</th>
<th>Aromatase inhibitor (e.g., anastrozole)</th>
</tr>
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<tr>
<td>+++</td>
<td>7/+</td>
<td>?</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>++</td>
<td>7/+</td>
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+ = ER agonist; 7 = ER partial agonist; → = ER antagonist; Ø = no clinical effects in humans; ⟨⟩ = effect uncertain.
CLOMIPHENE (Clomid, Milophene, Serophene)  

**SERM**

**Mechanism**

A selective estrogen receptor modulator (SERM), this drug exhibits tissue-specific pro-estrogenic and anti-estrogenic effects.

- Binds to estrogen receptors (ERs) and competitively blocks binding of endogenous estrogens. The clomiphene-ER complex alters estrogen-responsive gene expression. Each SERM has a selective tissue-specific profile (see table on reverse).
- Clomiphene acts as an antagonist in the hypothalamus and as a weak agonist in the ovaries.
  - In premenopausal women: blockade at estrogen receptor in anterior pituitary and hypothalamus → disrupt feedback inhibition to GnRH, FSH/LH secretion → ↑ secretion of GnRH, FSH/LH → ↑ gametogenesis and steroidogenesis in ovaries.
  - In postmenopausal women: little to no effect.
  - In men, augmented gametogenesis and steroidogenesis have been observed.

**Clinical**

- Treatment of female infertility (anovulation).
- Treatment of male infertility (oligozoospermia): success variable.

**Side Effects**

- Multiple births.
- Excessive enlargement of ovaries and ovarian cysts (caused by ↑ FSH and LH and a direct effect of clomiphene).
- Hyperstimulation syndrome: although multiple ovulation is common, in some patients, this is accompanied by an intense hypersensitivity (anaphylactoid) response.

**Notes**

FULVESTRANT (Faslodex) is a related pure antiestrogen that may be indicated in the treatment of ER-positive breast cancer resistant to tamoxifen.
<table>
<thead>
<tr>
<th>DROG EFFECTS</th>
<th>Estrogen</th>
<th>S. Clomiphene</th>
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<td>=</td>
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TAMOXIFEN
Toremifene
Raloxifene

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</table>

ENDO
TAMOXIFEN (Nolvadex)

Mechanism: A selective estrogen receptor modulator (SERM), this drug exhibits tissue-specific pro-estrogenic and anti-estrogenic effects.

Binds to estrogen receptors (ERs) and competitively blocks binding of endogenous estrogens. The tamoxifen-ER complex alters estrogen-responsive gene expression. Each SERM has a selective tissue-specific profile (see table on reverse).

Tamoxifen acts as an antagonist within the breast (inhibiting cellular proliferation) and as an agonist within the bone (exerting an antiresorptive effect) and the uterus (inducing cellular proliferation).

Clinical: Endocrine treatment of both early and metastatic ER-positive breast cancer in both pre- and post-menopausal women.

May be useful in chemoprevention of breast cancer in women at high risk.

Reduces the severity of osteoporosis (but not used for that indication because of the availability of agents with superior side effect profiles).

Side Effects: Hot flashes, menstrual irregularities, vaginal bleeding and discharge, nausea, vomiting.

↑ risk of endometrial cancer.

Venous thromboembolic events (DVT, PE).

Notes: TOREMIFENE (Fareston) is a SERM with tissue specificities similar to tamoxifen; used to treat breast cancer.

RALOXIFENE (Evista) is a SERM that is an antagonist in the breast and uterus and an agonist in bone. It is used to treat postmenopausal osteoporosis. It is not associated with ↑ risk of endometrial cancer but is associated with DVT and PE. Compared with tamoxifen, raloxifene appears as effective in preventing invasive breast cancer (although less effective in preventing carcinoma in situ) and is less likely to cause endometrial cancer or DVT/PE.
See table on tamoxifen card.
ANASTROZOLE (Arimidex)  

| Mechanism | Competitive inhibitor of aromatase, the final enzyme complex in the synthesis of estradiol and estrone from the androgens androstenedione and testosterone, respectively. |
| Clinical | Endocrine treatment of both early and metastatic estrogen receptor-positive breast cancer in postmenopausal women (in premenopausal women, normal ovarian function leads to a counterproductive feedback loop: ↓ estrogens → compensatory ↑ gonadotropins → ↑ ovarian androgen synthesis and aromatase expression → ↑ estrogen). In clinical trials, efficacy superior to that of SERMs. |
| Side Effects | Arthralgias, myalgias. ↓ bone mineral density with ↑ risk of osteoporosis (mediated by blocking beneficial estrogen effects on the bone). Unlike tamoxifen, no excess of endometrial cancer or thromboembolic events. |
| Notes | LETROZOLE (Femara) and EXEMESTANE (Aromasin) are other aromatase inhibitors, with the latter being an irreversible inhibitor. Utility of aromatase inhibitors for chemoprevention of breast cancer is under study. AMINOGLUTETHIMIDE (Cytacon) was the first clinically used aromatase inhibitor. It also blocks cholesterol → pregnenolone, the first step in adrenal steroid synthesis. Used to treat prostate cancer, breast cancer, Cushing’s syndrome, and adrenal tumors, but has fallen out of favor because of its non-selectivity. |
PROGESTINS
Norethindrone
Norgestimate
Levonorgestrel
Medroxyprogesterone
Hydroxyprogesterone
Megestrol
Danazol
Mifepristone
## Progestins

**Mechanism**

Regulate transcription: bind to progestin receptor → activation of steroid response elements → ↑ transcription of certain genes.

Progestrone, the major naturally occurring progestin in humans, causes development of secretory tissue in the breast, maturation of uterine endometrium, and can inhibit GnRH, FSH, and LH secretion.

**Clinical**

Contraception: prevent ovulation by inhibiting midcycle LH and FSH surges. Also create suboptimal endometrial environment for egg implantation, make the cervical mucus “hostile” to sperm, and disrupt uterine and tubal motility.

Given with estrogens as part of postmenopausal hormone replacement therapy to ↓ endometrial hyperplasia and the risk of endometrial cancer (although HRT in general has fallen out of favor—see estrogen).

Dysfunctional uterine bleeding (DUB, usually due to continuous estrogen production without progesterone).

Endometriosis: progestins can prevent proliferation of ectopic endometrial tissue.

Withdrawal bleeding: a test used to evaluate amenorrhea. Menstruation after cessation of progestin therapy suggests that the uterus has been primed by endogenous estrogens.

**Side Effects**

Hypertension. May ↓ HDL.

**Notes**

NORETHINDRONE, NORGESTREL, and LEVONORGESTREL are components of oral contraceptives.

MEDROXYPROGESTERONE (Provera) and HYDROXYPROGESTERONE are used to treat DUB and endometriosis. MEGESTROL (Megace) is used to treat weight loss due to disease (e.g., AIDS).

DANAZOL (Danocrine) is a weak progesterational and androgenic agent. Used to treat endometriosis and fibrocystic disease of the breast.

MIFEPRISTONE (RU486, Mifeprex) is a progestin receptor antagonist and used as an abortifacient.
**ALBUTEROL (Proventil, Ventolin)**

**β-agonist**

**Mechanism**
Activated the β₂-adrenoceptor, causing stimulation of adenylyl cyclase, ↑ cAMP, myosin light-chain kinase phosphorylation and inactivation, and consequent relaxation of smooth muscle and bronchodilation.

β-agonists may also ↓ airway inflammation by ↓ release of leukotrienes and histamine.

**Clinical**
Acute treatment of bronchospasm such as in asthma, bronchitis, and COPD.
Long-acting β₂-agonists (see below) can be used for long-term control of asthma.

**Side Effects**
Skeletal muscle tremor, restlessness, apprehension. Sinus tachycardia and other arrhythmias.

**Contraindications**
Caution in patients with cardiovascular disease and hyperthyroidism. Avoid concurrent use of MAO inhibitors & TCAs.

**Metabolism**
PO, nebulized, inhaled. Not a substrate for COMT, hence long acting.

**Notes**
- **LEVALBUTEROL** (Xopenex), **METAPROTERENOL** (Alupent), and **PIRIBUTEROL** (Maxair) are similar. **TERBUTALINE** (Brethine) can be used IV for the treatment of status asthmaticus. Also used to suppress premature labor.
- **SALMETEROL** (Serevent), **FORMOTEROL** (Foradil), and **ARFORMOTEROL** (Bravune) have longer durations of action (due to high lipid solubility and hence easier entry and buildup in smooth muscle cells) and are used as long-term control medications for asthma and/or COPD. Although long-acting β-agonists (LABAs) ↓ frequency of asthma episodes, those episodes that do occur may be more severe and even fatal, underscoring that inhaled corticosteroids (see bexomethasone) are preferred long-term control medications.

**RITODRINE** (Upzar) is used in pregnancy to relax uterine smooth muscle and suppress premature labor (second-line agent).
Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) and androstenedione are adrenal steroids that are androgen precursors. DHEA and DHEAS have been marketed as dietary supplements to improve strength, well-being, cognition, and libido (with little data to support any of these claims) and have been abused by professional athletes as an alternative to anabolic steroids. Androstenedione was a dietary supplement used, most notably, by Major League Baseball players as a performance enhancing drug; it has since been banned.
<table>
<thead>
<tr>
<th><strong>TESTOSTERONE</strong></th>
<th><strong>androgen</strong></th>
</tr>
</thead>
</table>
| **Mechanism**    | Binds to cytosolic receptor and taken into nucleus, where it activates transcription of testosterone-responsive genes.  
In skin, prostate, seminal vesicles, and epididymis, testosterone is converted by 5a-reductase to the more potent dihydrotestosterone.  
Physiologic effects: overall body growth (↑ protein synthesis and ↓ protein breakdown), penile and scrotal growth, development of secondary sex characteristics.  
↑ RBC production: secondary to both ↑ erythropoietin production by kidney and direct stimulation of Epo-sensitive elements in bone marrow. (Also, ↑ erythrocyte 2,3-DPG levels, hence ↑ availability of oxygen.) |
| **Clinical**     | Replacement therapy in hypogonadism.  
Anabolic agent (frequently abused). |
| **Side Effects** | Men: acne, gynecomastia, testicular atrophy caused by suppression of gonadotropins, azoospermia, prostatic hypertrophy, aggression.  
Women: masculinization.  
Cholestatic jaundice, ↑ transaminases, hepatocellular carcinoma. |
| **Notes**        | METHYLTESTOSTERONE (Android) and FLUOXYMESTERONE (Halotestin) are similar agents.  
OXANDROLONE (Oxandrin) and NANDROLONE (Deca-Durabolin) are anabolic steroids that are structurally similar to testosterone and act as androgen receptor agonists. They can facilitate weight gain and, prior to the development of recombinant erythropoietin, were used to treat anemia of chronic kidney disease. |
| Mechanism | 5α-reductase inhibitor that blocks conversion of testosterone to the more potent dihydrotestosterone (DHT). DHT is the principal androgen that acts on the prostate. |
| Clinical | Benign prostatic hyperplasia (BPH): ↓ prostate size and hence obstructive symptoms of BPH such as difficulty in initiating voiding, ↓ caliber and force of urinary stream, a sensation of incomplete emptying, and the need for frequent urination. May take 6–12 months to have a noticeable effect. Androgenetic alopecia (male pattern baldness). |
| Side Effects | Loss of libido, erectile dysfunction. |
| Contraindic. | The drug is teratogenic and can be absorbed through the skin. Therefore, women who may be pregnant should not take or handle crushed or broken tablets. |
| Notes | DUTASTERIDE (Avodart) is a related inhibitor of 5α-reductase used for male androgenetic alopecia and BPH. α-blockers are also used to treat BPH (see prazosin). The utility of 5α-reductase inhibitors in the prevention of prostate cancer remains controversial. ↓ overall incidence of prostate cancer, but ↑ risk that tumors that do develop are high grade; no effect on mortality. |
## FLUTAMIDE (Eulexin)

### Mechanism
An anti-androgen that acts as a competitive antagonist at the androgen receptor. Prostate growth depends on androgens, so androgen deprivation↓progression of prostate cancer.

### Clinical
Androgen deprivation therapy in prostate cancer, both for locally advanced disease (in conjunction with radiation therapy or surgery →↑survival) and for metastatic disease (alleviate bone pain; modest survival benefit).

### Side Effects
Gynecomastia. Hepatitis.

### Notes
- **BICALUTAMIDE** (Casodex) and **NILUTAMIDE** (Nilandron) are similar androgen receptor blockers.
- **CYPROTERONE** (Androcur) is an antiandrogen with progestogenic effects that is used in women to↓hirsutism and in men to↓sexual drive.
- The four ways to achieve androgen deprivation are:
  1. Inhibition of pituitary gonadotropin release: GnRH analogs (see leuprolide).
  2. Inhibition of androgen synthesis: aminoglutethimide, ketoconazole, finasteride.
  3. Inhibition of androgen binding: androgen receptor blockers (flutamide and others).
  4. Surgical extirpation of the glands: castration and adrenalectomy.
**MICONAZOLE (Monistat)**

**Mechanism**
An imidazole antifungal, this drug prevents conversion of lanosterol into ergosterol by inhibiting 14α-demethylase, a P450-dependent microsomal enzyme. Without sufficient quantities of ergosterol, fungal membranes become destabilized. Mammalian cell membranes, in which cholesterol is the predominant sterol, are resistant. Can interfere with P450-dependent steroid biosynthesis (in humans) if given systemically.

**Clinical**
Topical treatment for candidiasis (e.g., cutaneous, oral, vulvovaginal) and dermatophytoes (including tinea infections and onychomycosis).

**Side Effects**
Topically: burning, irritation, erythema, itching, desquamation, pelvic cramps.

**Metabolism**
Used topically.

**Notes**
These agents share a common mechanism of action with triazoles (see voriconazole); however, imidazoles are generally too toxic to be given systemically, and their use is restricted to minor, superficial infections.

- _Butoconazole_ (Gynazole), _Clotrimazole_ (Gyn-Lotrimin), _Econazole_ (Spectazole), _Oxiconazole_ (Oxistat), _Sertaconazole_ (Ertaczo), and _Tioconazole_ (Monistat, Vagistat) are similar topical imidazole antifungals used to treat candidiasis and dermatophytoses.

- **Ketoconazole** (Nizoral) is the only imidazole antifungal that is still (rarely) used systemically, but it is a potent inhibitor of CYP3A4 → many drug interactions. At high doses, it can be used to inhibit P450-dependent adrenal steroid biosynthesis.
<table>
<thead>
<tr>
<th><strong>SPIRONOLACTONE (Aldactone)</strong></th>
<th><strong>diuretic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>A K⁺-sparing diuretic, this drug is a synthetic steroid that is a competitive antagonist of aldosterone at the aldosterone receptor in the distal convoluted tubule. Aldosterone enhances apical Na⁺ and K⁺ channel activity and basolateral Na⁺/K⁺ ATPase activity, leading to ↑ Na⁺ absorption and ↑ K⁺ excretion. The Na⁺ retention leads to hypertension and consequently accelerated atherosclerosis and ↑ risk of MI, stroke, and CHF. Aldosterone also has a direct effect on the heart, causing myocardial fibrosis. Inhibition of aldosterone → ↓ Na⁺ absorption and ↓ K⁺ excretion, ↓ BP, and possibly less cardiac fibrosis.</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td><strong>Edema</strong> secondary to CHF, cirrhosis, and the nephrotic syndrome. <strong>CHF</strong> (even without frank edema) to attenuate adverse cardiac remodeling and reduce mortality. Hypertension. Often added to other diuretic regimens to help minimize K⁺ loss. Primary hyperaldosteronism.</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td><strong>Hyperkalemia</strong> (especially in patients with renal impairment). Hyponatremia. Hypochloremic acidosis (blocks aldosterone’s effect on the Na⁺/H⁺ anti-porter). Gynecomastia (caused by binding to progesterone and androgen receptors).</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td><strong>TRIAMTERENE</strong> (Dyrenium) is similar but has a shorter half-life. <strong>EPLERENONE</strong> (Inspra) has a lower affinity for other steroid hormone receptors and therefore is less likely to cause gynecomastia. <strong>AMILORIDE</strong> (Midamor) is similar in effect to spironolactone, but it directly inhibits Na⁺ reabsorption in the collecting tubule, therefore working independent of the presence of aldosterone. Unlike spironolactone, it causes ↑ Ca²⁺ reabsorption and thus is used to treat Ca²⁺-based nephrolithiasis.</td>
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<td><strong>PRAZOSIN (Minipress)</strong></td>
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<tr>
<td><strong>Mechanism</strong></td>
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<tr>
<td>Reversible $\alpha_1$-adrenoceptor antagonist. Blockade on vascular smooth muscle $\rightarrow$ arteriolar and venous vasodilation $\rightarrow$ ↓ BP and ↓ venous return.</td>
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<td>Low affinity for $\alpha_2$-adrenoceptors may explain relative lack of reflex tachycardia compared with nonselective $\alpha$-blockers ($\alpha_1$-blockade would prevent negative feedback and thereby allow ↑ NE release, leading to $\beta$-stimulation of the heart).</td>
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<td>Inhibition of smooth muscle contraction in prostate $\rightarrow$ relief of urinary symptoms caused by benign prostatic hyperplasia (BPH).</td>
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<tr>
<td><strong>Clinical</strong></td>
<td></td>
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<tr>
<td>Hypertension.</td>
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<tr>
<td>BPH.</td>
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<tr>
<td>Treatment of Raynaud’s phenomenon (vasospasm that can lead to digital ischemia).</td>
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<tr>
<td><strong>Side Effects</strong></td>
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<tr>
<td>Orthostatic hypotension, syncpe. Dry mouth, nightmares, sexual dysfunction, lethargy.</td>
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<tr>
<td><strong>Metabolism</strong></td>
<td></td>
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<tr>
<td>PO. Short half-life necessitates twice-daily dosing.</td>
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<tr>
<td><strong>Notes</strong></td>
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<tr>
<td>TERAZOSIN (Hytrin) and DOXAZOSIN (Cardura) have longer half-lives and can be dosed once daily.</td>
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<tr>
<td><strong>TAMSULOSIN</strong> (Flomax) has greater selectivity for $\alpha_{1A}$ (blood vessels and prostate) over $\alpha_{1B}$ (blood vessels and heart) receptors; may explain why little effect on BP but particularly useful in BPH.</td>
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<tr>
<td>ALFUSZOSIN (Uroxatral) is another $\alpha_1$-blocker (no subtype selectivity) that is used primarily to treat BPH.</td>
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<tr>
<td>YOHIMBINE (Yocen) is an $\alpha_2$-adrenoceptor antagonist that causes ↑ NE release and has been used to treat erectile dysfunction, but it has largely been replaced by PDE inhibitors (see sildenafil).</td>
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<tr>
<td><strong>SILDENAFIL (Viagra, Revatio)</strong></td>
<td><strong>PDE Inhibitor</strong></td>
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<tr>
<td><strong>Mechanism</strong> Phosphodiesterase (PDE) V inhibitor. As PDE V inactivates cGMP, PDE V inhibitors → ↑ cGMP via ↓ degradation. ↑ cGMP → dephosphorylation of myosin light-chain → vascular smooth muscle relaxation. In the penis, this facilitates inflow of blood into the corpora cavernosa. In the pulmonary circulation, this ↓ vascular resistance.</td>
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<td><strong>Clinical</strong> Erectile dysfunction. Pulmonary arterial hypertension.</td>
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<tr>
<td><strong>Side Effects</strong> Headache, flushing, priapism. Potentiates vasodilation of nitroglycerin, which works through activation of guanylate cyclase, resulting in ↑ cGMP. Thus, concomitant blockade of cGMP degradation by sildenafil leads to greatly ↑ cGMP → marked vasodilation and hypotension. Alteration in color vision (blue tinge to vision) caused by inhibition of PDE6, which is involved in photoreceptor signal transduction. Reports of sudden visual loss caused by nonarteritic ischemic optic neuropathy, but causality not proven.</td>
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<tr>
<td><strong>Notes</strong> TADALAFIL (Cialis) and VARDENAFIL (Levitra) are similar compounds with longer half-lives.</td>
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</table>
**HYDRAZINE (Apresoline)**

**Mechanism**
Remains unclear. ↑ permeability to K⁺ (→ membrane hyperpolarization) and inhibition of sarcoplasmic release of Ca²⁺ are leading possibilities. Net effect is arteriol vasodilation. Also acts as an antioxidant that inhibits synthesis of superoxide (O₂⁻•). In conjunction with nitrates (which lead to the formation of NO), can help restore the "nitroso-redox" balance that can be disrupted in patients with CHF.

**Clinical**
Hypertension. Generally not first line, but useful in hypertensive urgency (because of the rapid onset of action when given IV), pregnancy (excellent safety record), and refractory hypertension.

*Congestive heart failure:* given with nitrates to ↓ afterload, ↓ preload, and help restore nitroso-redox balance. Often used in patients with renal failure who cannot tolerate ACEI. ↓ mortality when added to standard therapy (ACEI/ARB and β-blockers) in black patients with advanced CHF (who appear to have lower levels of NO and less activation of the renin–angiotensin system than white patients).

**Side Effects**
Headache, nausea, sweating, and flushing. Self-limited lupus-like syndrome in 10%.

Reflex ↑ HR, contractility, renin activity, and fluid retention in response to vasodilation, so often given with β-blocker, diuretic, or both.

**Metabolism**
PO or IV. Hepatic acetylation. Toxicity more likely in patients who are slow acetylators.

**Notes**
- **MINOXIDIL** (Rogaine) causes vasodilation by opening ATP-sensitive K⁺ channels → membrane hyperpolarization and relaxation of arteriol smooth muscle. Best known for its side effect, hypertrichosis, and its topical use to treat early male pattern baldness.

- **DIAZOXIDE** (Hyperstat, Proglycem) also opens K⁺ channels on vascular smooth muscle and pancreatic β cells, the latter effect leading to inhibition of insulin secretion and its use for refractory hypoglycemia (in contrast to sulfonylureas, which inhibit the K⁺ channel).
That’s All, Folks!