Urinary system

(URI-205)

Handout

Human Anatomy and Embryology	Medical Physiology
Medical Biochemistry	Histology and Cell Biology
Pathology	Pharmacology
Medical Microbiology and Immunology	Medical Parasitology

Level: 3

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Prepared by

Dr: Mohammed Elbadry
Professor of Human Anatomy and Embryology

Dr: Abeer Showman
Professor of Medical physiology

Dr: Dina Monir
Lecture of Medical Physiology

Dr: Ayda Abdeen
Professor of Medical Biochemistry

Dr: Safaa Said Hassan
Ass. Prof. of Histology and cell Biology, Faculty of Medicine

Dr: Samira Mahmoud Mohammed
Lecturer of Histology and cell Biology, Faculty of Medicine

Dr: Omnia Salim Farrag
Lecturer of Pathology, Faculty of Medicine

Dr: Lobna Aly Abdelzaher
Ass. professor of Pharmacology, Faculty of Medicine

Dr: Enas Mahmoud Amer
Lecturer of Medical Microbiology and Immunology, Faculty of Medicine

Dr: Noha Hammed Abdelgilil
Professor of Medical Parasitology, Faculty of Medicine

Dr: Nahed Ahmed Elossily
Professor of Medical Parasitology, Faculty of Medicine

Content

Overall Aims

Overall aim of the book

Integrative urinary system study provides comprehensive and integrated coverage of anatomy, physiology, histology and embryology of the urinary system. Microbiology, biochemistry, and pharmacology relating to the system are discussed. Pathology of the system is presented along with clinical presentations of diagnostic and treatment modalities.

Intended Learning Outcomes of the Block:

1. Recognize the general principles and major characteristics of endocrine glands. Describe the development, anatomical location, relation, parts, blood supply, nerve supply and lymphatic drainage and microscopic structure of pituitary, thyroid, parathyroid glands, adrenal glands.

2. Identify types of hormones, patterns of hormone secretion and their role as an integral part of the control system.

3. Recognize adenohypophyseal & neurohypophyseal hormones, regulation of pituitary hormones by the hypothalamus.

4. Describe functions, mechanisms of action regulation of growth hormones, antidiuretic hormone, oxytocin, thyroid, parathyroid, mineralocorticoids (aldosterone), and glucocorticoids, adrenal androgens ACTH, sex hormones, calcitonin and vitamin D.

5. Outline pharmacological uses of GnRh analogs and gonadotropins and therapeutic and diagnostic uses of ACTH preparations, TSH and posterior pituitary hormones

6. Outline the mechanism of action of drugs used in thyroid and parathyroid dysfunction, corticosteroids, mineralocorticosteroids. identify the mechanism of action, members, uses and their adverse effects

7. Describe etiology, pathogenesis, pathology and clinical features of dysfunction of endocrine glands and their tumors

8. Describe the development location, relation, blood and nerve supply and lymphatic drainage and microscopic structure of endocrine pancreas.

9. Discuss physiological effects and regulation of insulin, glucagon and somatostatin

10. Define, classify diabetes mellitus, discuss pathogenesis, difference between type I and II of diabetes mellitus and discuss complications of diabetes mellitus.

11. Explain the mechanism of action, adverse reactions and therapeutic uses of oral hypoglycemic IV agents and insulin.

12. Describe the development, location, structure, blood supply, lymphatic drainage and microscopic structures of the female and male pelves and reproductive system and their congenital malformations

13. Discuss the functions of the male and female reproductive organs and glands.

14. Identify and classify different types of inflammation and tumors of male and female genital systems and breast and causes of infertility

15. Identify preparations, therapeutic uses of synthetic androgens, antiandrogens, estrogens and progestins their adverse effects and contraindications.

16. Describe the biochemical nature, synthesis, transport, mechanism of action, metabolism and excretion of female steroid hormones.

17. Describe the function of placenta, physiological changes of different body systems during pregnancy and the stages of Parturition.

18. Identify the causative pathogens causing sexually transmitted diseases (STDs). List important prophylaxis of each STDs.

19. Differentiate congenital form non-congenital (post-natal) infections.

20. Demonstrate parasites causing sexually transmitted and congenital infections

Part 1
Human Anatomy and Embryology

Lecture 1:
ANATOMY OF THE KIDNEYS AND URETERS

Objectives of the Lecture:

By the end of the lecture the student should be able to:

1. What is the colour of the kidneys.
2. Enumerate the organs forming the urinary system.
3. Where is the site of the kidney?
4. Describe the coverings of the kidneys.
5. Describe the normal anatomy of the kidneys (position, dimensions, hilum, renal pelvis and sinus, gross structure, anatomical relations, blood supply, lymphatic drainage, renal vascular segments, nerve supply.
6. Describe the normal anatomy of the ureters; length, course, anatomical relations, anatomical narrowing's, blood supply, lymph drainage and lymph drainage.
7. Describe the surface markings of the kidneys.
8. Describe the surface anatomy of the ureters.

KIDNEYS

- One of the organs of the urinary system.
- Reddish-brown in colour.

Note: Urinary system consists of kidneys, ureters, urinary bladder and urethra.

Kidneys lie: Behind peritoneum on high up on posterior abdominal wall, largely under cover of costal margin.

Right kidney:

- Lies slightly lower than left kidney due to large size of right lobe of liver.
- With contraction of diaphragm during respiration, both kidneys move downward in vertical direction by about 1 inch.

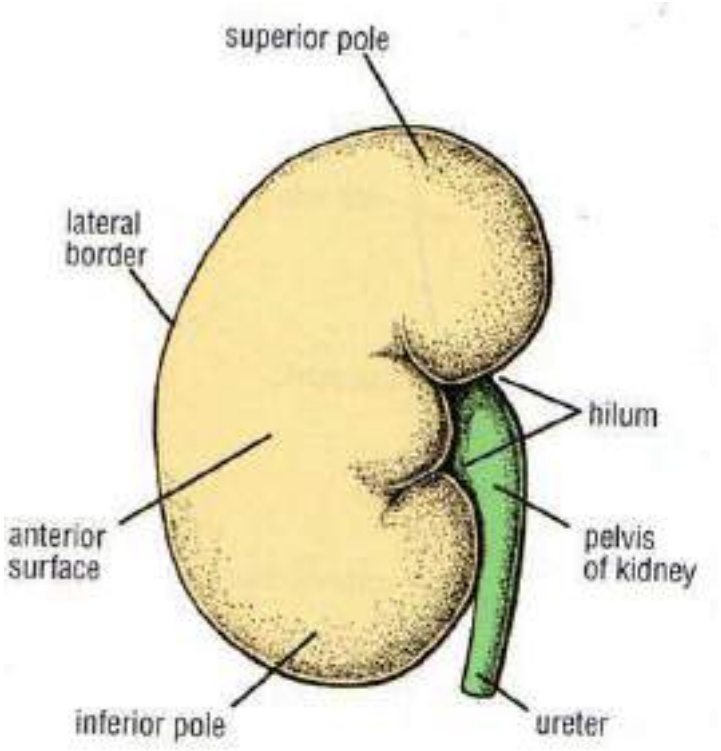


Figure 1: Right kidney. (Snell, 2019).

Coverings of the Kidneys:

1. Fibrous capsule: Surrounds the kidney and closely applied to its outer surface.

2. Perirenal fat: Covers fibrous capsule.

3. Renal fascia:

- Condensation of connective tissue outside perirenal fat.
- Encloses kidneys and suprarenal glands.
- Continuous laterally with fascia transversalis.

4. Pararenal fat: Lies external to renal fascia

- Often in large quantity.
- Forms part of retroperitoneal fat.

Note: Perirenal fat, renal fascia and pararenal fat support kidneys and hold them in position on posterior abdominal wall.

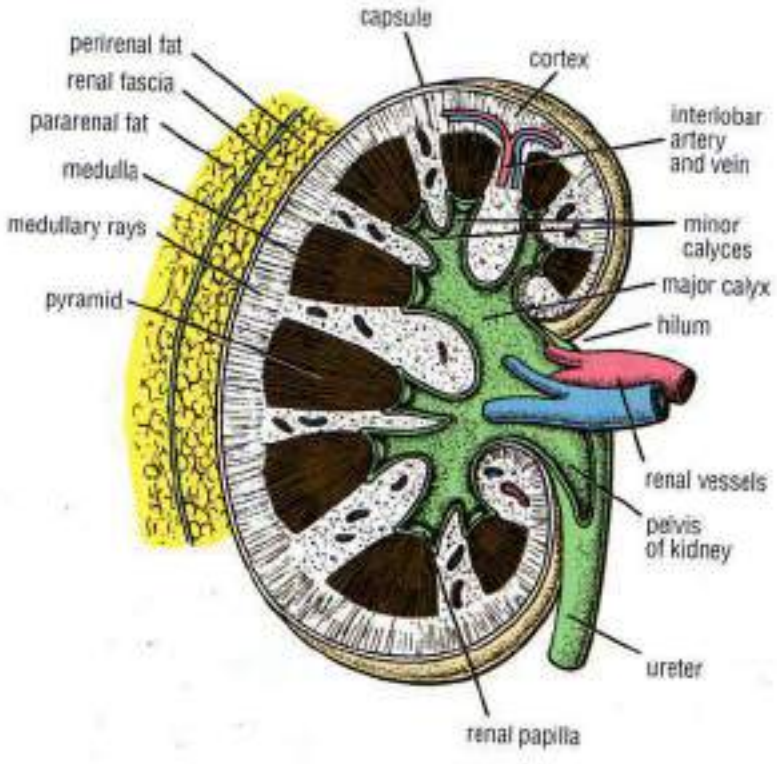


Figure 2: Coverings of the kidney. (Snell, 2019).

Hilum of the Kidney:

- Vertical slit on medial concave border of the kidney.
- Bounded by thick lips of renal substances.
- Extends into large cavity called renal sinus.

Hilum of the Kidney Transmits (V.A.U.A.):

1. Renal vein
2. Renal artery (2 branches)
3. Ureter
4. 3rd branch of renal artery
5. Lymph vessels
6. Sympathetic fibres

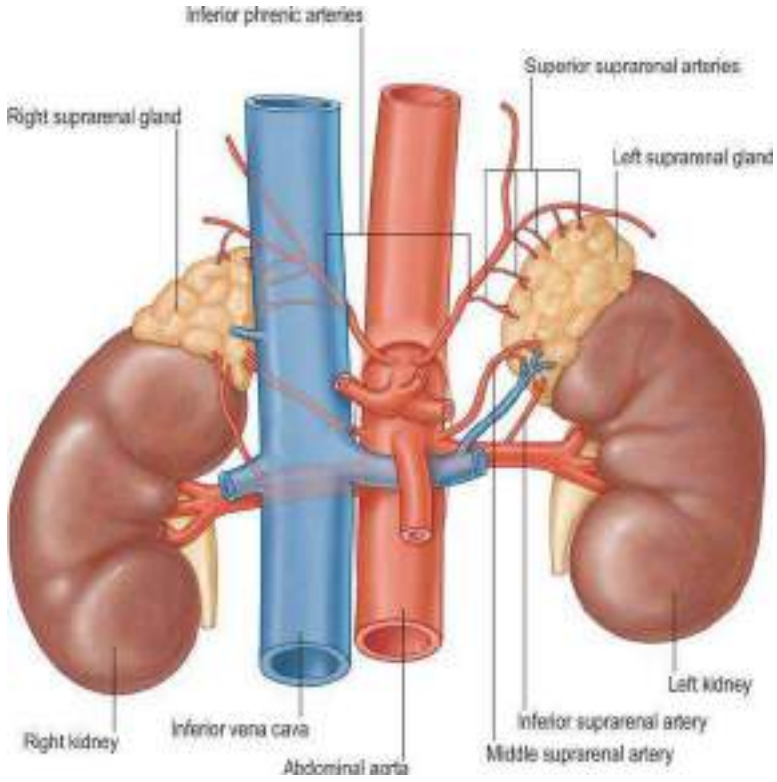


Figure 3: Blood supply of the kidney. (Snell, 2019).

Anterior Relations of the Kidneys

Anterior Relations of Right Kidney:

1. Right suprarenal gland.
2. Liver.
3. Second part of duodenum.
4. Right colic flexure.

Anterior Relations of Left Kidney:

1. Left suprarenal gland.
2. Spleen.
3. Stomach.
4. Pancreas.
5. Left colic flexure.
6. Coils of jejunum.

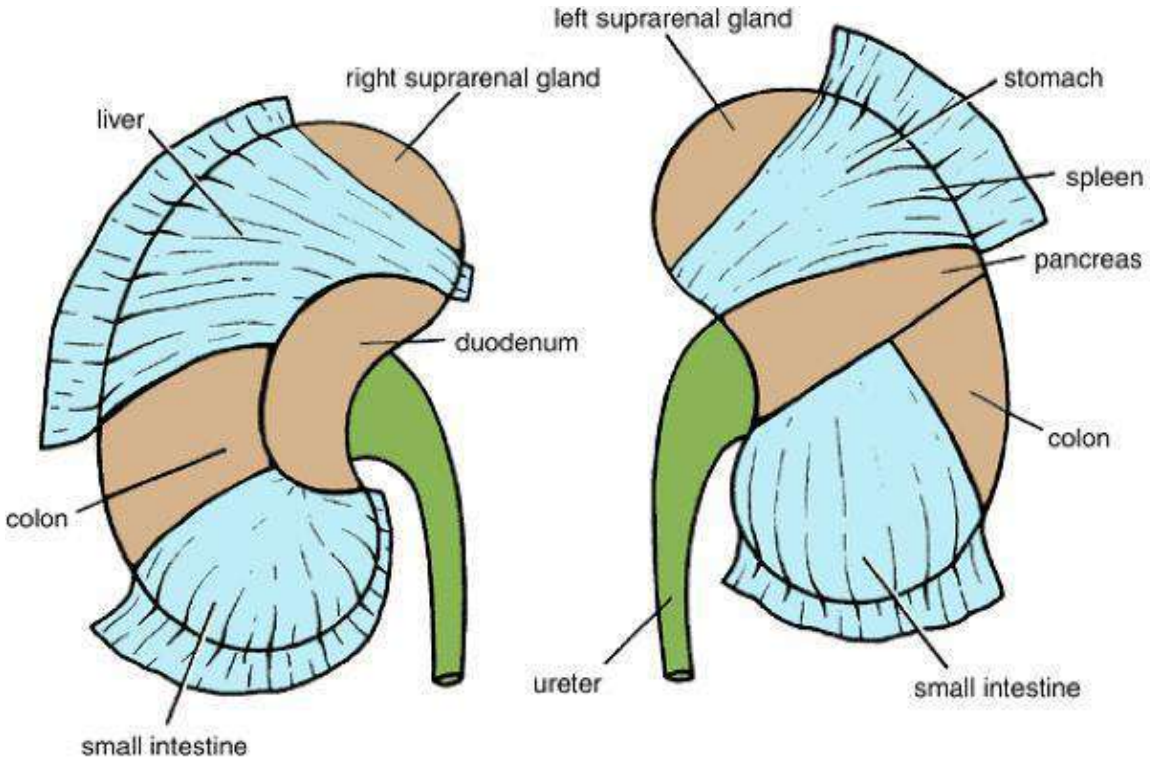


Figure 4: Relations of the kidneys. (Snell, 2019).

Posterior Relations of the Kidneys

Posterior Relations of the Right Kidney:

1. Diaphragm.
2. Costodiaphragmatic recess of right pleura.
3. Right 12th rib.
4. Right psoas muscle.
5. Right quadratus lumborum muscle.
6. Right transversus abdominis muscle.
7. Right subcostal nerve (T 12).
8. Right iliohypogastric nerve (L 1).
9. Right ilioinguinal nerve (L 1).

Posterior Relations of the Left Kidney:

1. Diaphragm.
2. Costodiaphragmatic recess of the left pleura.
3. Left 11^{th} and 12^{th} ribs.
4. Left psoas muscle.
5. Left quadratus lumborum muscle.

6. Left transversus abdominis muscle.
7. Left subcostal nerve (T 12).
8. Left iliohypogastric nerve (L 1).
9. Left ilioinguinal nerve (L 1).

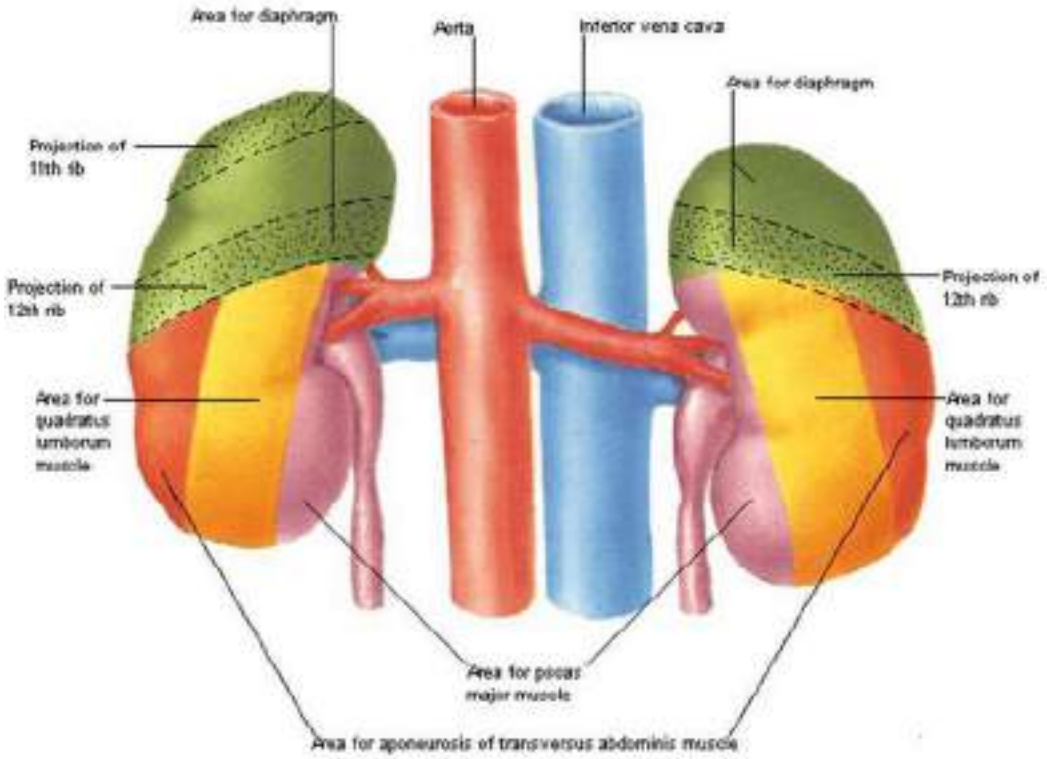


Figure 5: Posterior relations of the kidneys.

Blood Supply of the Kidneys

Arterial supply of the kidneys: Renal artery:

- From aorta at level of 2nd lumbar vertebra
- Each renal artery divides into: Segmental arteries that enter hilum of kidney, 4 front and 1 behind renal pelvis (distributed to different segments of kidney).
- Lobar arteries: Arise from each segmental artery, 1 for each renal pyramid.
- Each lobar artery gives: 2-3 interlobar arteries.
- Interlobar arteries run toward cortex on each side of renal pyramid, at junction of cortex and medulla they give off arcuate arteries (arch over bases of pyramids).
- Arcuate arteries give off: Interlobular arteries that ascend in the cortex.
- Afferent glomerular arteries: Branches of interlobular arteries.

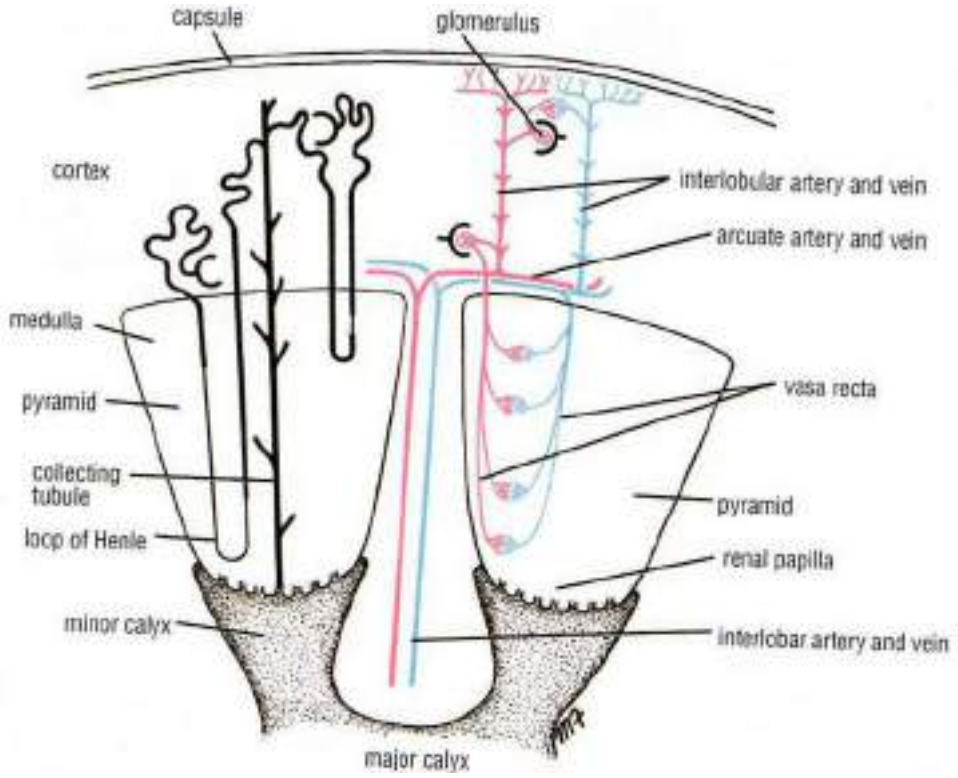


Figure 6: Arterial supply of the kidneys. (Snell, 2019).

Venous Drainage of the Kidneys:

Renal vein: Emerges from hilum front renal artery

- Drains into inferior vena cava

Left renal vein: Longer than right renal vein as it crosses the median plane.

Left Renal vein receives:

1. Left gonadal vein
2. Left suprarenal vein
3. Inferior hemiazygos vein

Lymph Drainage of the Kidneys:

- Lymph vessels follow renal artery to lateral aortic lymph nodes around origin of renal artery.

Nerve Supply of the Kidneys:

- Originate in renal sympathetic plexus and distributed along branches of renal vessels.
- Afferent fibres that travel through renal plexus enter spinal cord in 10th, 11th and 12th thoracic nerves.

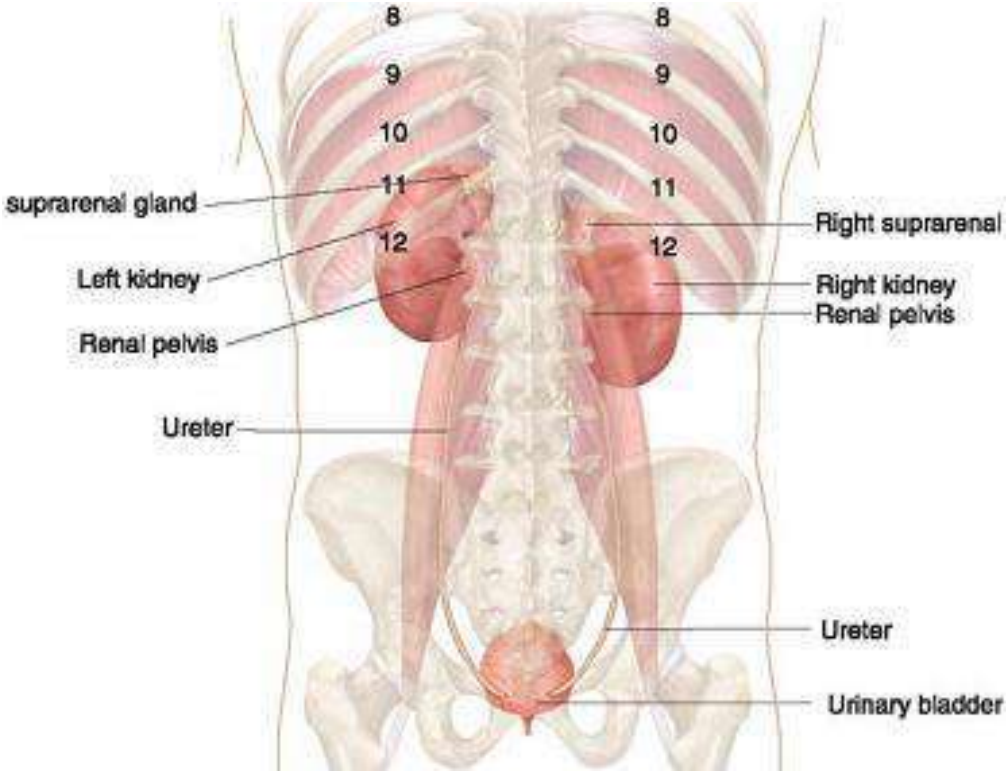


Figure 7: Surface anatomy of the kidneys.

URETERS

- Muscular tubes that extend from kidneys to posterior surface of urinary bladder.
- Each ureter is about 10 inches (25 Cm) long.

Constrictions of the Ureter:

1. Where renal pelvis joins the ureter.
2. Where it is kinked as it crosses pelvic brim.
3. Where it pierces the bladder wall.

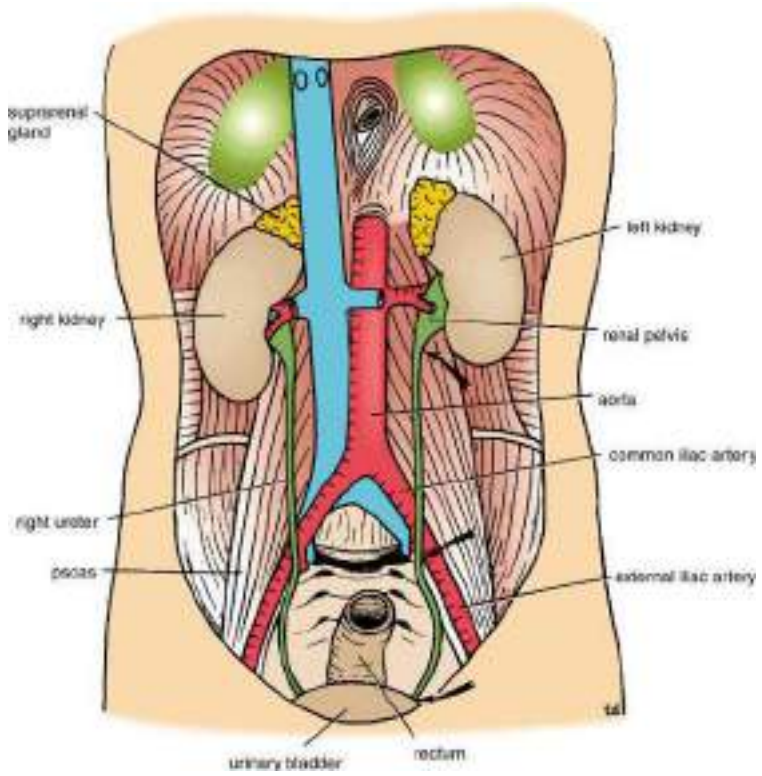


Figure 8: Constrictions of the ureter. (Snell, 2019).

Renal pelvis (pelvis of the ureter):

- Funnel-shaped expanded upper end of ureter.
- Lies within hilum of the kidney.
- Receives major calyces.

Course of the ureter:

- Ureter emerges from hilum of kidney.
- Runs vertically downward behind peritoneum on psoas muscle (separates it from tips of transverse processes of lumbar vertebrae).
- Enters the pelvis by crossing bifurcation of common iliac artery front sacroiliac joint.
- Then, runs down lateral wall of the pelvis to region of ischial spine and turns forward to enter lateral angle of the bladder.

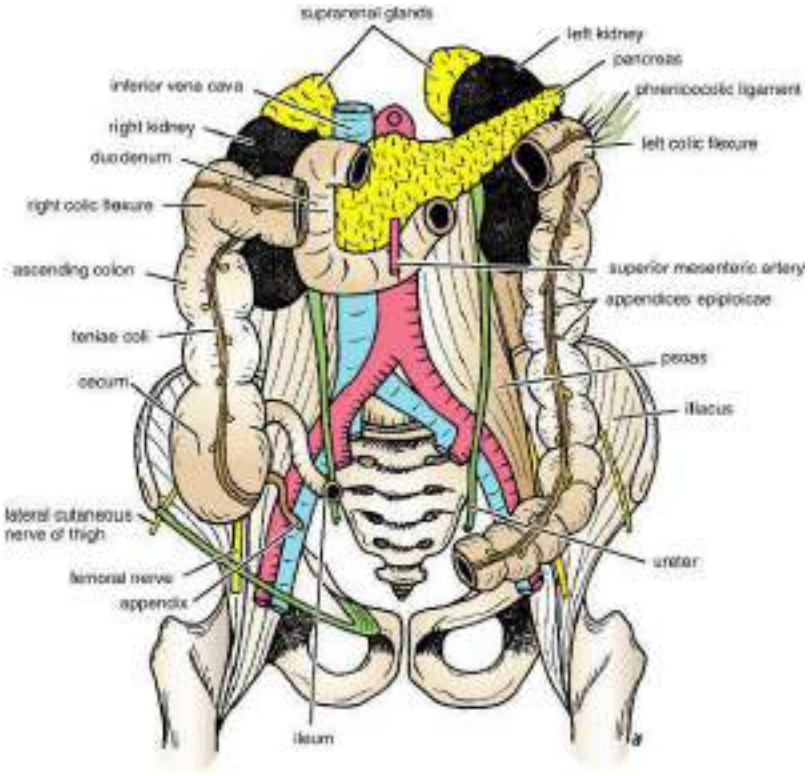


Figure 8: Course of the ureter. (Snell, 2019).

Pelvic Part of Ureter in Male

- Near its termination, crossed by vas deferens.
- Passes obliquely through wall of the bladder for about ¾ inches (1.9 Cm) before opening into the bladder.
- This provides valve like action which prevents reverse flow of urine toward the kidneys as the bladder fills.

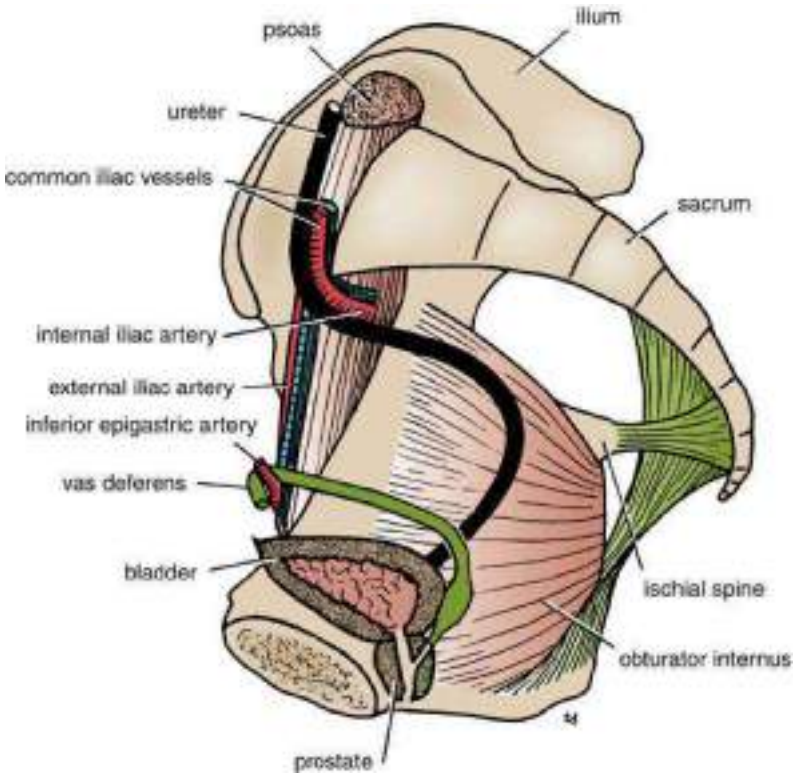


Figure 9: Pelvic part of the ureter in male. (Snell, 2019).

Pelvic Part of Ureters in Female

- Runs downward and backward in front of internal iliac artery and behind ovary until reaches region of ischial spine.
- turns forward and medially beneath base of the broad ligament.
- Crossed by the uterine artery.
- Runs forward lateral to lateral fornix of vagina to enter the bladder.

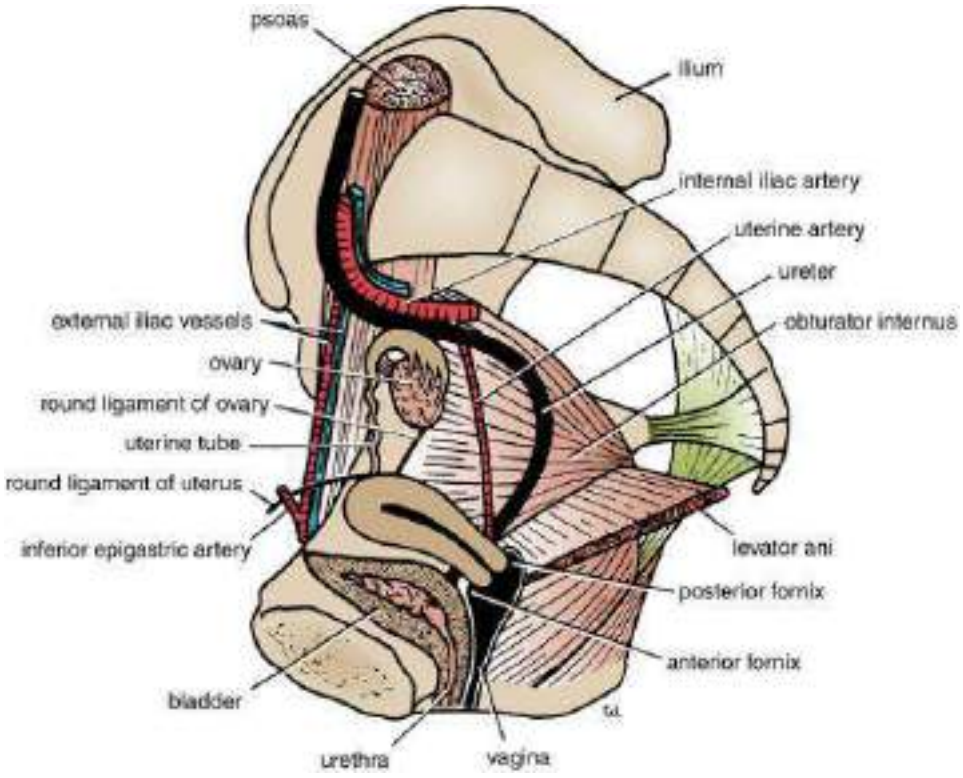


Figure 10: Pelvic part of the ureter in female. (Snell, 2019).

Relations of the Right Ureter:

Anteriorly:

1. Duodenum.
2. Terminal part of ileum.
3. Right colic vessels.
4. Ileocolic vessels.
5. Root of mesentery of small intestine.

Posteriorly:

1. Right psoas muscle.
2. Lumbar transverse processes.
3. Bifurcation of common iliac artery.

Relations of the Left Ureter:

Anteriorly:

1. Sigmoid colon
2. Sigmoid mesocolon
3. Left colic vessels
4. Left gonadal vessels

Posteriorly:

1. Left psoas muscle
2. Lumbar transverse processes
3. Bifurcation of left common iliac artery

Note: Inferior mesenteric vein lies along medial side of the left ureter

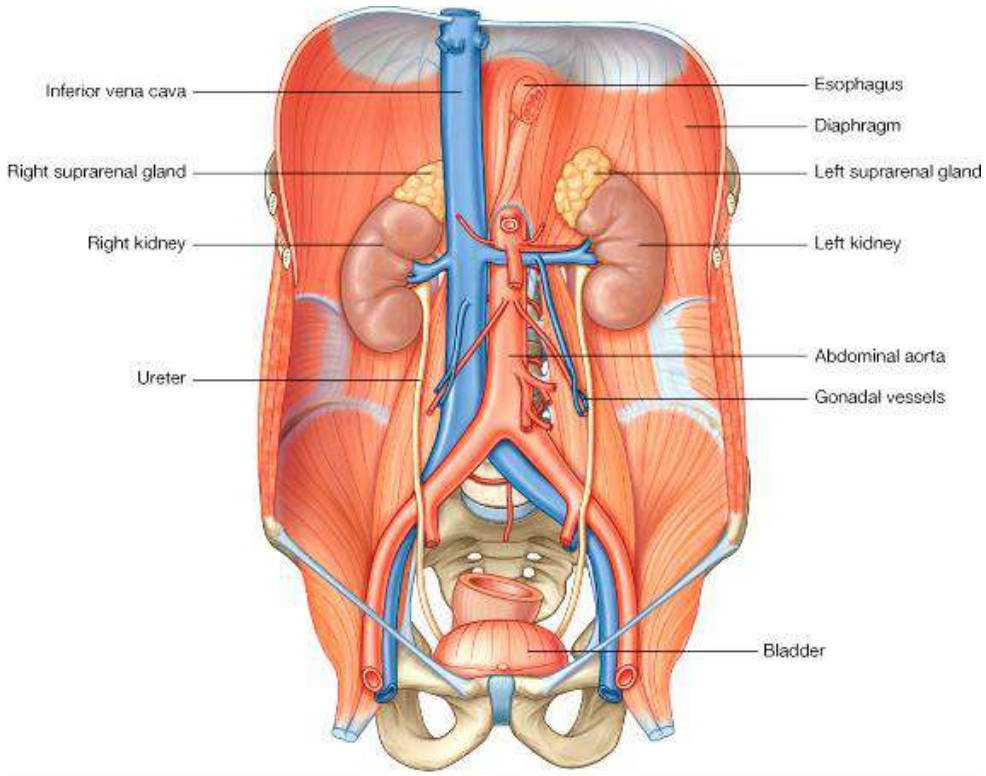


Figure 11: Posterior relations of the ureter. (Snell, 2019).

Blood Supply of the Ureter

ARTERIES:

Upper end: Renal artery

Middle part: Testicular (ovarian) artery

In pelvis: Superior vesical artery

VEINS:

Upper end: Renal vein

Middle part: Testicular (ovarian) vein

In pelvis: Superior vesical vein

Lymph Drainage of the Ureter

The lymph vessels drain into:

1. Lateral aortic lymph nodes
2. Iliac lymph nodes

Nerve Supply of the Ureter

Nerves of ureter are derived from:

Upper end: Renal plexus

Middle part: Testicular (ovarian) plexus

In pelvis: Superior vesical plexus

- Afferent fibres travel with sympathetic nerves
- Enter spinal cord in 1st and 2nd lumbar segments.

References:

1. Snell, R. S. (2019): Clinical Anatomy by Regions (Anatomy) 9th Edition. Lippincott Williams & Wilkins.
2. Moore, Keith L. and Dalley A. F. (2023): Clinically Oriented Anatomy, 9th Edition, Lippincott Williams & Wilkins.
3. KAPLAN Medical USMLE Step 1 Lecture Notes Anatomy (2021).

Lecture 2:

ANATOMY OF THE URINARY BLADDER AND URETHRAE

Objectives of the Lecture:

By the end of the lecture the student should be able to:

1. Describe the normal anatomy of the urinary bladder (position, shape, surfaces, relations, trigone and sphincters, peritoneal coverings, blood supply, lymphatic drainage and innervation).
2. Describe the normal anatomy of male and female urethra (length, parts and lymphatic drainage).
3. Describe the normal anatomy of the female urethra (Length and Lymphatic drainage).

Urinary Bladder:

- Situated immediately behind pubic bones within the pelvis.
- Receptacle for storage of urine.
- In adult, has maximum capacity of about 500 ml.
- Has strong muscular wall.
- Its shape and relations vary according to amount of urine it contains.
- **In adult,** empty bladder lies within pelvis.
- As the bladder fills, its superior wall rises up into hypogastric region.
- **In young child,** empty bladder projects above pelvic inlet.
- When pelvic cavity enlarges, the bladder sinks into the pelvis to take up the adult position.
- **Empty bladder:** Pyramidal in shape, having apex, base, superior, 2 inferolateral surfaces and neck.

Apex of the bladder:

- Points anteriorly and lies behind upper margin of symphysis pubis
- Fibrous cord: urachus (remains of allantois) passes upward in extraperitoneal fat to the umbilicus forming median umbilical ligament.

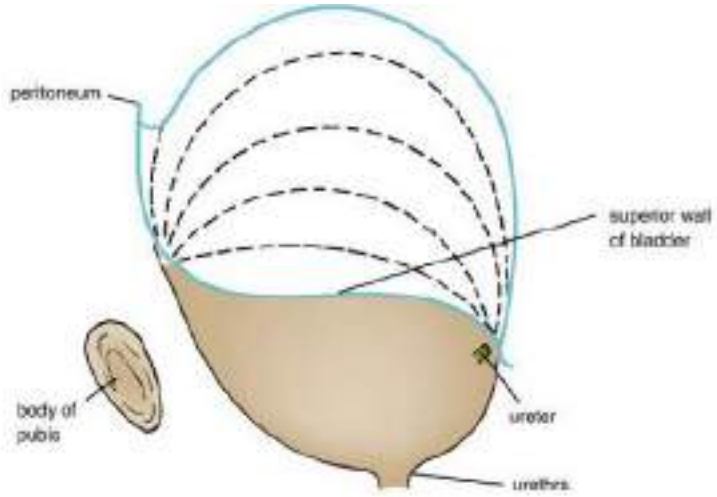


Figure 1: Urinary bladder, empty and full. (Snell, 2019).

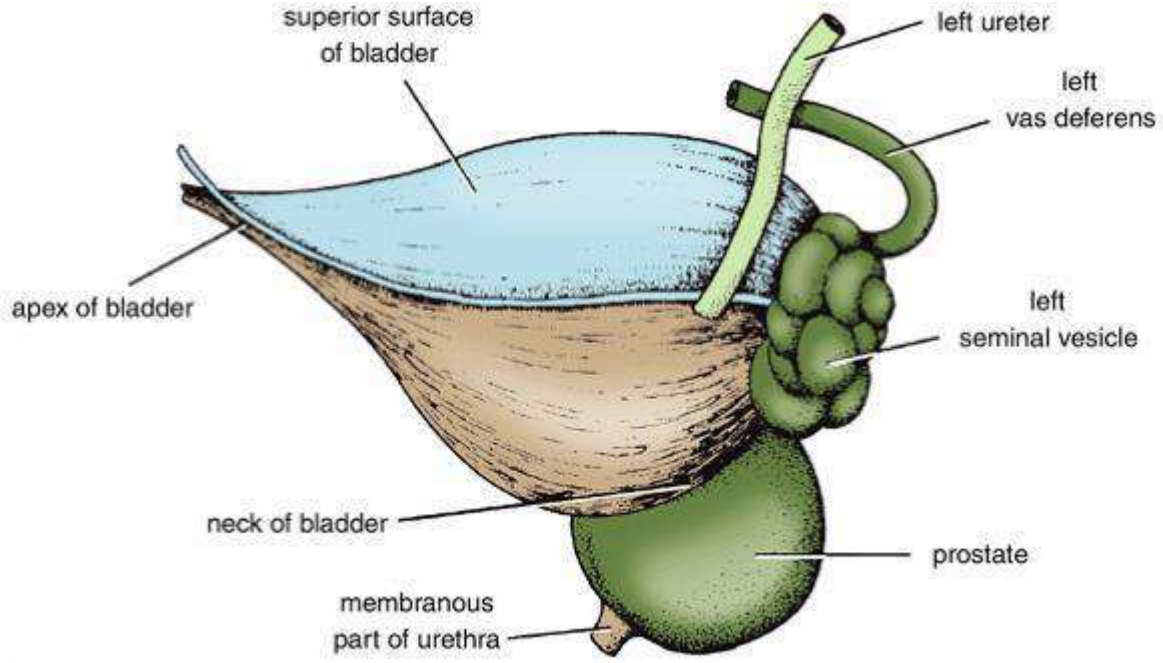


Figure 2: Urinary bladder, in male, lateral view. (Snell, 2019).

Base (posterior surface) of the bladder: (Figure 3).

- Faces posteriorly
- Triangular in shape

Superolateral angles: Joined by the ureters.

Inferior angle: Gives rise to urethra.

2 vasa deferentia: Lie side by side on posterior surface of the bladder and separate seminal vesicles from each other.

Upper part of posterior surface of the bladder: Covered by peritoneum forming anterior wall of rectovesical pouch.

Lower part of posterior surface separated from rectum by:

1. Vasa differentia.
2. Seminal vesicles.
3. Rectovesical pouch.

Superior surface of the bladder:

- Completely covered with peritoneum.
- Along lateral margins of superior surface, peritoneum reflected onto lateral pelvic walls.
- **Related to:** Coils of ilium, sigmoid colon.

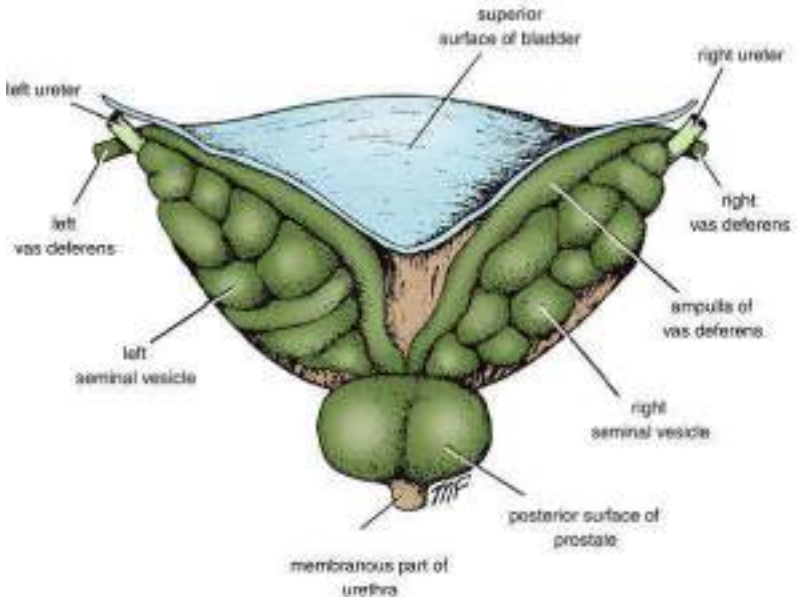


Figure 3: Base of urinary bladder, in male. (Snell, 2019).

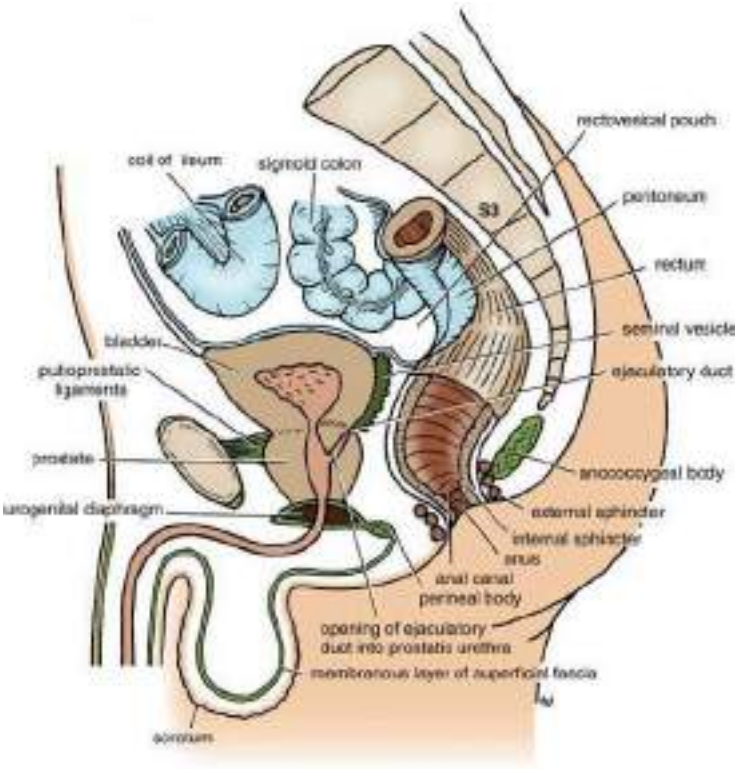


Figure 4: Superior surface of urinary bladder. (Snell, 2019).

Inferolateral surfaces of the bladder:

Related to:

In front

1. Retropubic pad of fat
2. Pubic bones

Posteriorly to:

1. Obturator internus muscle (above)
2. Levator ani muscle (below)

Neck of the bladder:

- Lies inferiorly
- Rests on upper surface of the prostate
- Here, smooth muscle fibres of bladder wall are continuous with those of the prostate
- Held in position by puboprostatic ligaments in male and pubovesical ligaments in female

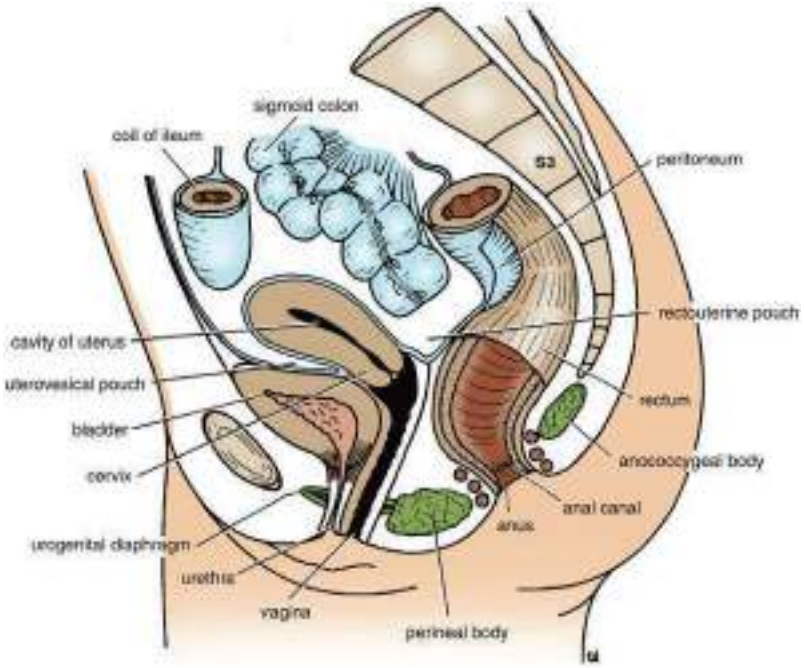


Figure 5: Superior surface of urinary bladder. (Snell, 2019).

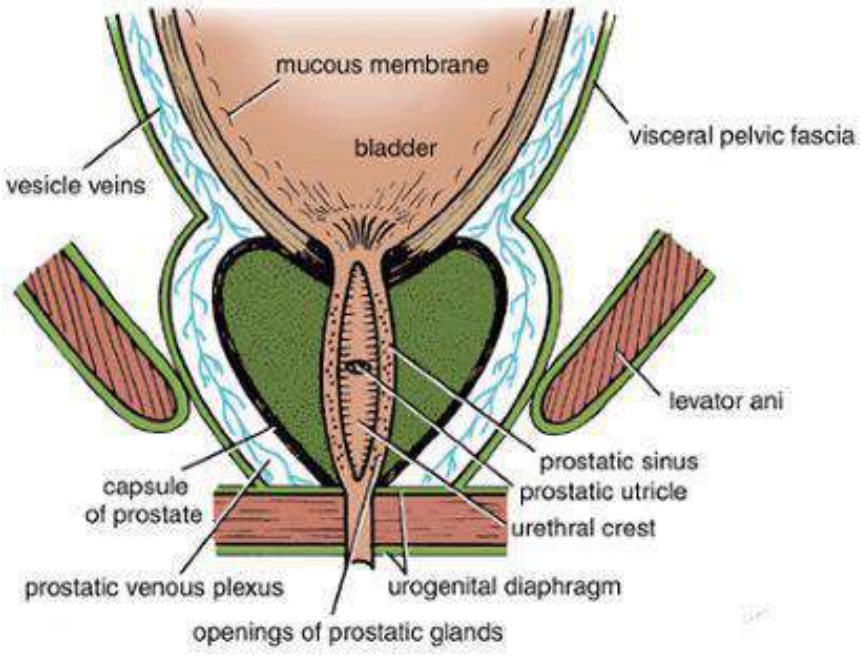


Figure 6: Superior surface of urinary bladder. (Snell, 2019).

Mucous membrane of greater part of empty bladder: (Figure 7).

- Thrown into folds, but these disappear when the bladder is full.

Trigone of the bladder:

- Area of mucous membrane covering internal surface of base of the bladder.
- Mucous membrane is always smooth, even when the viscus is empty, because mucous membrane over trigone is firmly adherent to underlying muscular coat.

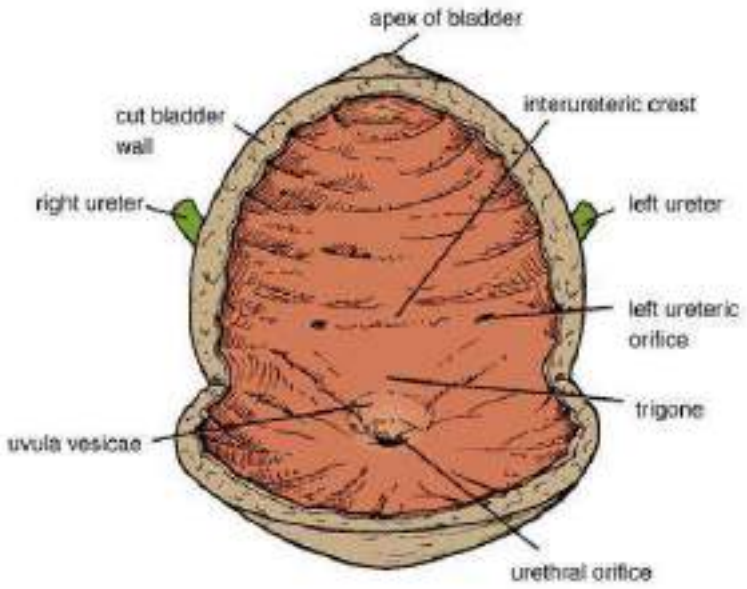


Figure 7: Mucous membrane and trigone of urinary bladder. (Snell, 2019).

Superior angles of the trigone: Correspond to openings of ureters.

Inferior angle of trigone: Corresponds to internal urethral orifice

Notes:

- Trigone limited above by interureteric ridge (muscular ridge between openings of the ureters).

  Uvula vesicae: Small elevation situated immediately behind urethral orifice, produced by underlying median lobe of prostate.

Muscular coat of the bladder: Composed of smooth muscle

- Arranged as 3 layers of interlacing bundles detrusor muscle.

Sphincter vesicae: Thickening of circular component of muscle coat at neck of the bladder.

URINARY BLADDER IN FEMALE: (Figure 5).

- Situated immediately behind pubic bones
- Lies at lower level than in male pelvis due to absence of the prostate

Neck: Rests directly on urogenital diaphragm

Apex: Behind symphysis pubis

Base (posterior surface):

Related to:

1. Vagina
2. Rectum

Superior surface of urinary bladder in female:

Related to:

1. Uterovesical pouch of peritoneum
2. Body of uterus

Inferolateral surfaces is related to:

1. Retropubic pad of fat
2. Pubic bones
3. Obturator internus
4. Levator ani

BLOOD SUPPLY OF THE URINARY BLADDER

Arteries: Branches of internal iliac artery

1. Superior vesical artery
2. Inferior vesical artery (in male).

Veins:

- The veins form vesical venous plexus communicates below with prostatic venous plexus and drain into internal iliac vein.

LYMPH DRAINAGE OF URINARY BLADDER

The lymph vessels drain into:

1. Internal iliac lymph nodes
2. External iliac lymph nodes

NERVE SUPPLY OF THE URINARY BLADDER

Inferior Hypogastric Plexuses:

Sympathetic postganglionic fibres:

- Originate in 1st and 2nd lumbar ganglia
- Descend to bladder via hypogastric plexuses

Parasympathetic Preganglionic Fibres:

- Arise as pelvic splanchnic nerves from 2nd, 3rd and 4th sacral nerves.
- They pass through inferior hypogastric plexuses to reach the bladder wall, where they synapse with postganglionic neurons.

Majority of Afferent Sensory Fibers:

- Arising in the bladder reach central nervous system via pelvic splanchnic nerves**.**

Some Afferent Fibers:

- Travel with sympathetic nerves via hypogastric plexuses and enter 1st and 2nd lumbar segments of spinal cord.

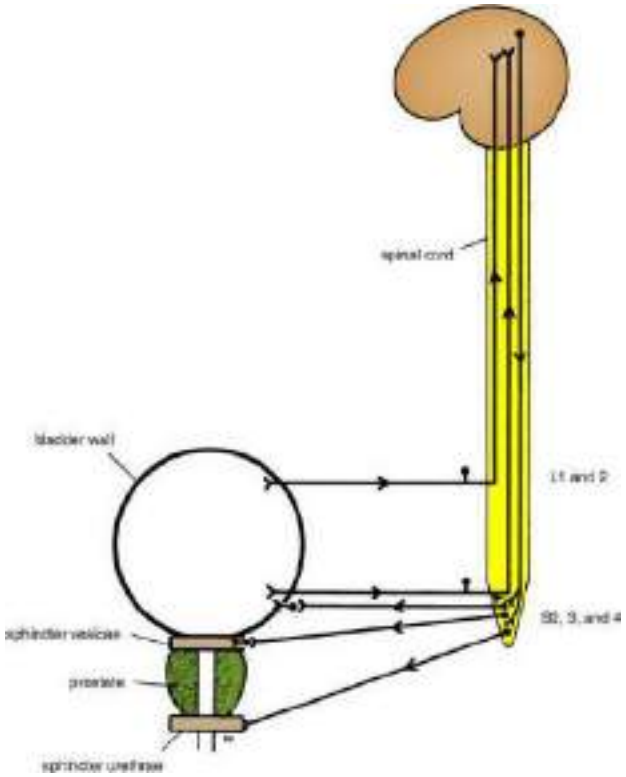


Figure 8: Nerve supply of the urinary bladder. (Snell, 2019).

MALE URETHRA (Figures 6 & 9).

Length: 8 inches (20 Cm) long.

Site: Extends from neck of the bladder to external urethral meatus on the glans penis.

Parts of Male Urethra:

1. Prostatic Urethra:

- About 1 ¼ inches (3 Cm) long.
- Begins at neck of the bladder.
- Passes through prostate from the base to the apex.
- Becomes continuous with the membranous part of urethra.
- The widest and the most dilatable part of the entire urethra.
- **Urethral crest:** Longitudinal ridge on its posterior wall.
- **Prostatic sinus:** Groove on each side of the ridge.
- **Prostatic glands:** Open into the prostatic sinuses.
- **Prostatic utricle:** Analogue of the uterus and vagina in females, depression on summit of urethral crest.
- **Ejaculatory ducts:** Open on edge of mouth of prostatic utricle.

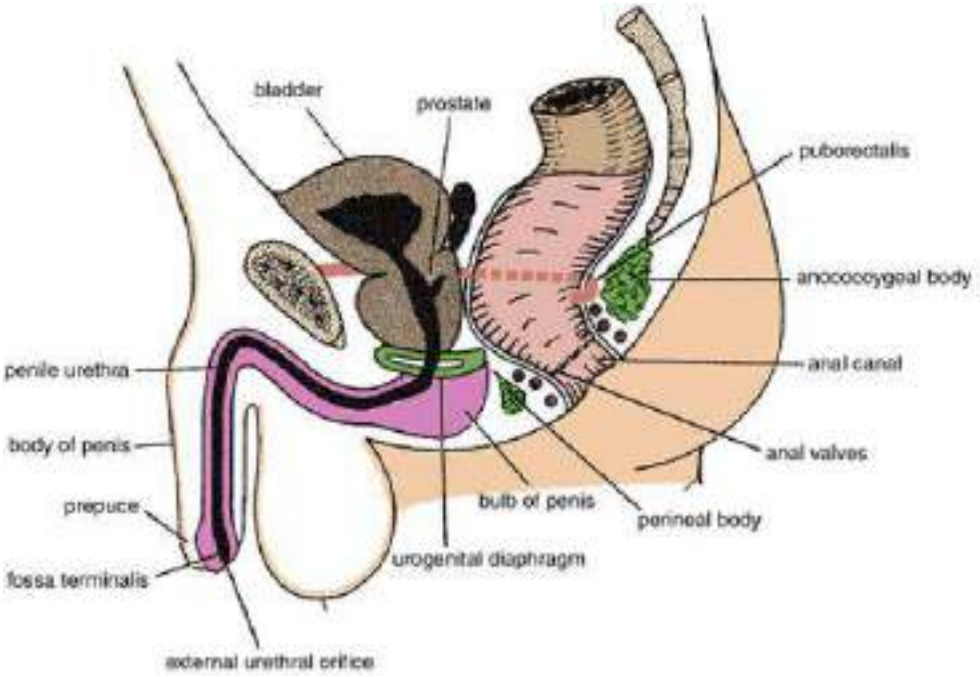


Figure 9: Male genital System, urethra. (Snell, 2019).

2. Membranous Urethra:

- About ½ inch (1.25 Cm) long
- Lies within urogenital diaphragm
- Surrounded by sphincter urethrae muscle
- The least dilatable portion of urethra.

3. Penile Urethra:

- About 6 inches (16 Cm) long
- Enclosed in bulb and corpus spongiosum of the penis
- The external meatus is the narrowest part of the entire urethra

Fossa terminalis (navicular fossa): Part of urethra that lies within the glans penis.

Bulbourethral glands (Figure 11): Open into penile urethra below the urogenital diaphragm.

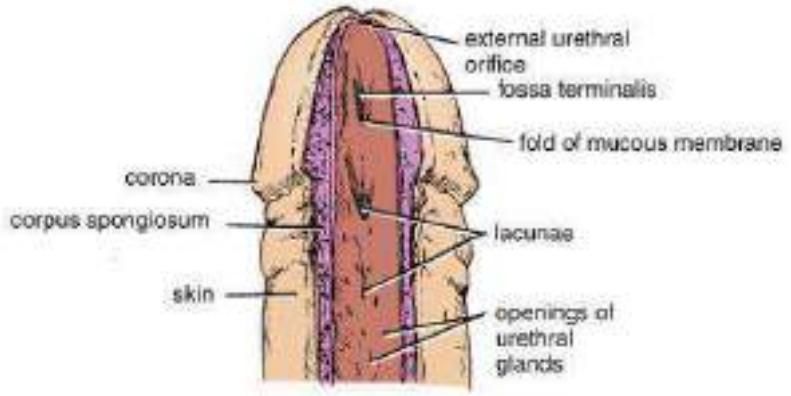


Figure 10: Male genital System, penile urethra. (Snell, 2019).

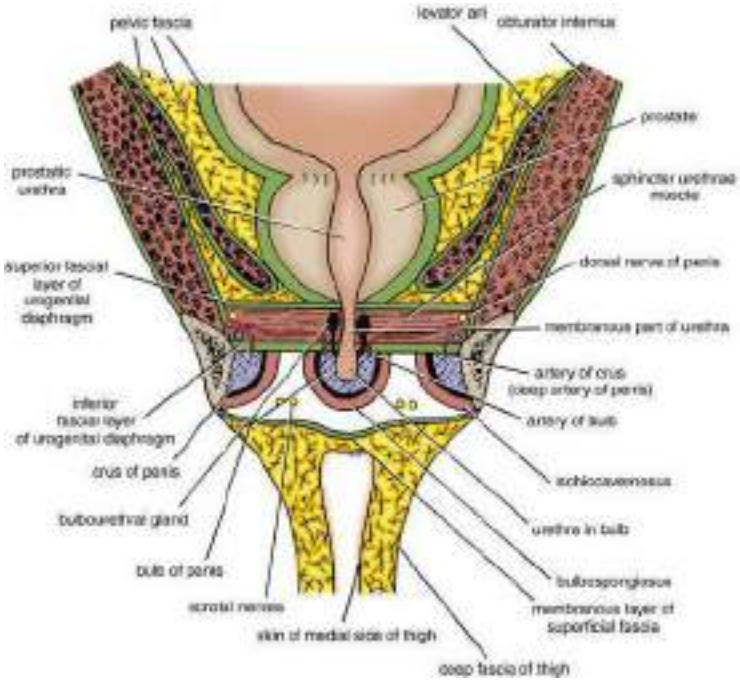


Figure 11: Male genital System, bulbourethral glands. (Snell, 2019).

FEMALE URETHRA (Figures 5 & 12)

Length: About 1 ½ inches (4 Cm) long

Site: From neck of the bladder to the external urethral meatus

- Opens into the vestibule about 1 inch (2.5 Cm) below the clitoris
- Traverses the sphincter urethrae.

Relation: Immediately in front of the vagina.

Ducts of paraurethral glands: Open at sides of external urethral orifice

Note: Female urethra can be dilated relatively easily.

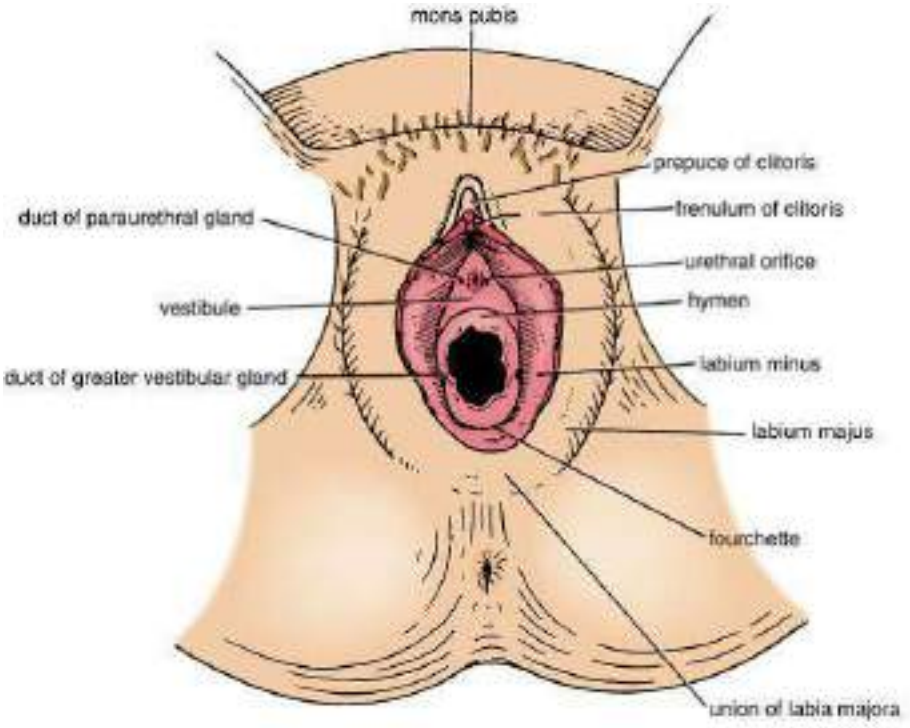


Figure 12: Female genital System, urethra. (Snell, 2019).

References:

1. Snell, R. S. (2019): Clinical Anatomy by Regions (Anatomy) 9th Edition. Lippincott Williams & Wilkins.
2. Moore, Keith L. and Dalley A. F. (2023): Clinically Oriented Anatomy, 9th Edition, Lippincott Williams & Wilkins.
3. KAPLAN Medical USMLE Step 1 Lecture Notes Anatomy (2021).

Lecture 3:

DEVELOPMENT AND CONGENITAL ANOMALIES OF THE KIDNEYS AND URETERS

ILOs:

1. Describe the different stages of development of the kidneys and ureters.
2. Describe the developmental defects of the kidneys.
3. Describe the developmental defects of the ureters.

DEVELOPMENT OF THE KIDNEYS

- **Develops from:** Intermediate mesoderm
- 3 successive kidneys are formed during intrauterine life in humans.

These are:

1. Pronephros
2. Mesonephros
3. Metanephros or permanent kidney

PRONEPHROS: (Figures 1 & 2).

At the beginning of the fourth week:

- Represented by 7 to 10 solid cell groups in the cervical region.
- These groups form vestigial excretory units, nephrotomes.
- Nephrotomes regress before more caudal ones are formed.

By the end of the fourth week: Pronephric system disappeared.

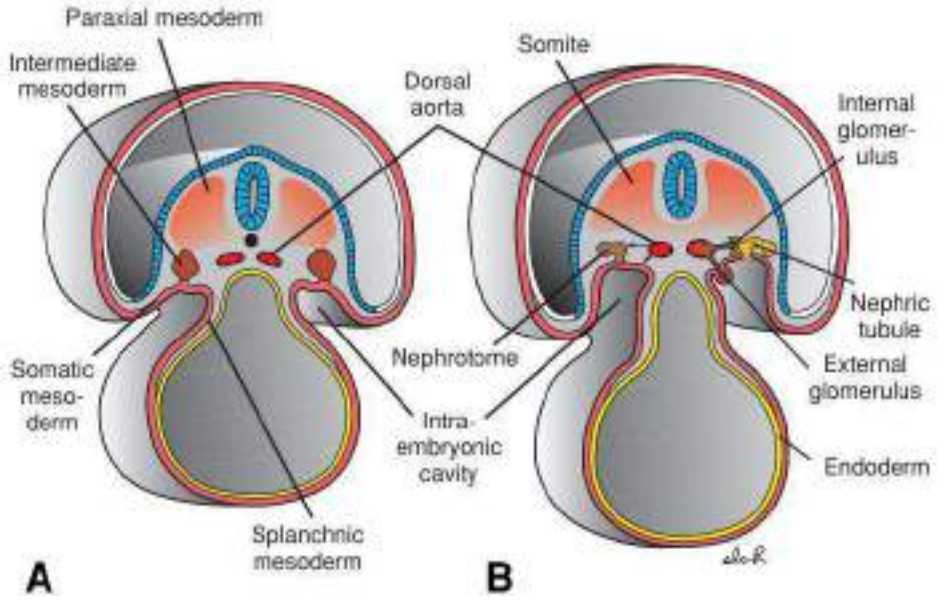


Figure 1: Transverse sections through embryos at various stages of development showing formation of nephric tubules. A. 21 days. B. 25 days. Formation of external and internal glomeruli and open connection between intraembryonic cavity and nephric tubule. (Sadler, 2018).

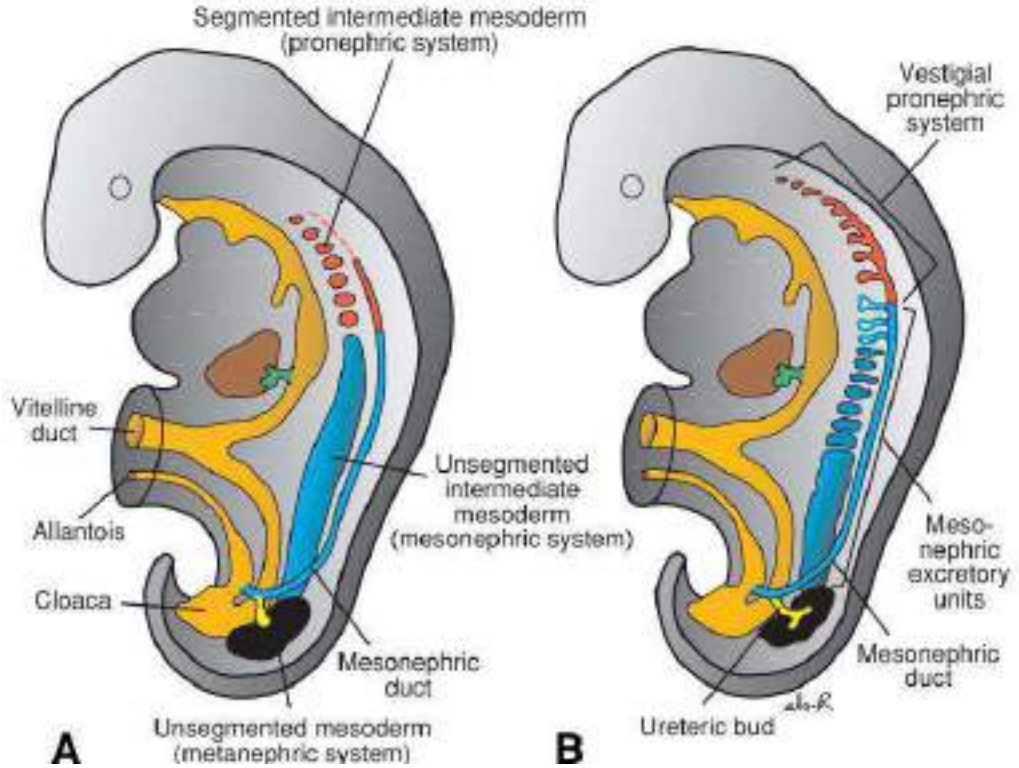


Figure 2: A. Relationship of the intermediate mesoderm of the pronephric, mesonephric, and metanephric systems. In cervical and upper thoracic regions intermediate mesoderm is segmented; in lower thoracic, lumbar, and sacral regions it forms unsegmented nephrogenic cord. Longitudinal collecting duct, formed initially by pronephros then by mesonephros.

B. Excretory tubules of pronephric and mesonephric systems in a 5-week-old embryo. (sadler, 2018).

MESONEPHROS (Figures 2 & 3)

- Mesonephros and mesonephric ducts are derived from intermediate mesoderm from upper thoracic to upper lumbar (L3) segments.

Early in the Fourth Week of Development:

- The first excretory tubules of the mesonephros appear.
- They lengthen rapidly, form an S-shaped loop, and acquire a tuft of capillaries that will form a glomerulus at their medial extremity.
- Around the glomerulus, the tubules form Bowman's capsule, and together constitute a renal corpuscle.
- Laterally the tubule enters the longitudinal collecting duct; mesonephric or wolffian duct.

In the Middle of the Second Month:

- Mesonephros forms a large ovoid organ on each side of the midline.
- Since the developing gonad is on its medial side, the ridge formed by both organs is known as the urogenital ridge.
- While caudal tubules are still differentiating, cranial tubules and glomeruli show degenerative changes.

By the End of the Second Month:

- Majority disappeared.
- In the male a few of the caudal tubules and the mesonephric duct persist and participate in formation of the genital system, but they disappear in the female.

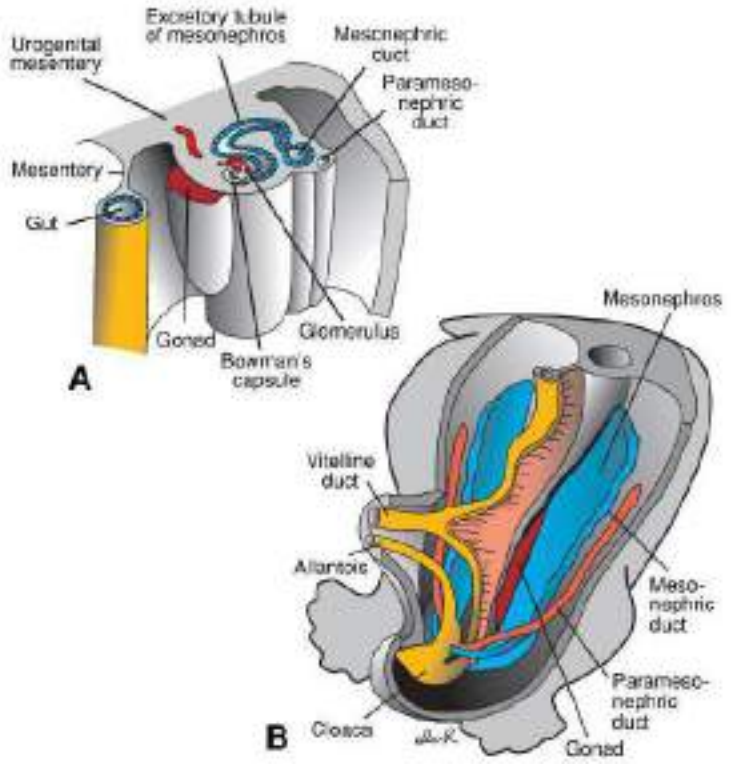


Figure 3: A. Transverse section through urogenital ridge in the lower thoracic region of a 5-week embryo showing formation of an excretory tubule of the mesonephric system. Appearance of Bowman's capsule and gonadal ridge. Mesonephros and gonad are attached to posterior abdominal wall by urogenital mesentery. B. Relation of the gonad and mesonephros. Mesonephric duct runs along the lateral side of mesonephros. (Sadler, 2018).

METANEPHROS (DEFINITIVE KIDNEY) (Figures 4, 5 &6).

- The third urinary organ, the metanephros, or permanent kidney.
- Appears in the fifth week.
- Its excretory units develop from metanephric mesoderm.

Development of the Collecting System of the Permanent Kidney:

1. Collecting ducts of the permanent kidney:

- Develop from the ureteric bud, an outgrowth of the mesonephric duct close to its entrance to the cloaca.
- The bud penetrates metanephric tissue, moulded over its distal end as a cap.
- Subsequently the bud dilates, forming the primitive renal pelvis, and splits into cranial and caudal portions, the future major calyces.
- Each calyx forms two new buds while penetrating the metanephric tissue.
- These buds continue to subdivide until 12 or more generations of tubules formed.

- At the periphery more tubules form until end of the fifth month.
- The tubules of the second order enlarge and absorb those of the third and fourth generations, forming the minor calyces of renal pelvis.
- Collecting tubules of the fifth and successive generations elongate and converge on the minor calyx, forming the renal pyramid.

Ureteric Bud: Gives rise to:

1. Ureter,
2. Renal pelvis.
3. Major calyces.
4. Minor calyces.
5. Collecting tubules (1 million to 3 million).

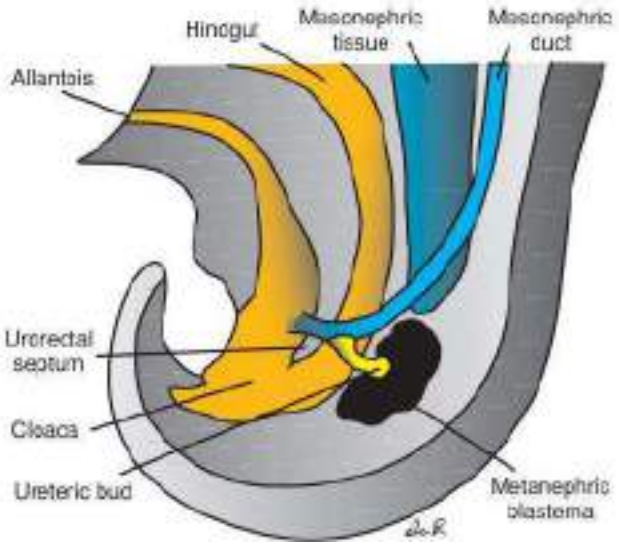


Figure 4: Relation of the hindgut and cloaca at end of the fifth week. Ureteric bud penetrates the metanephric mesoderm. (Sadler, 2018).

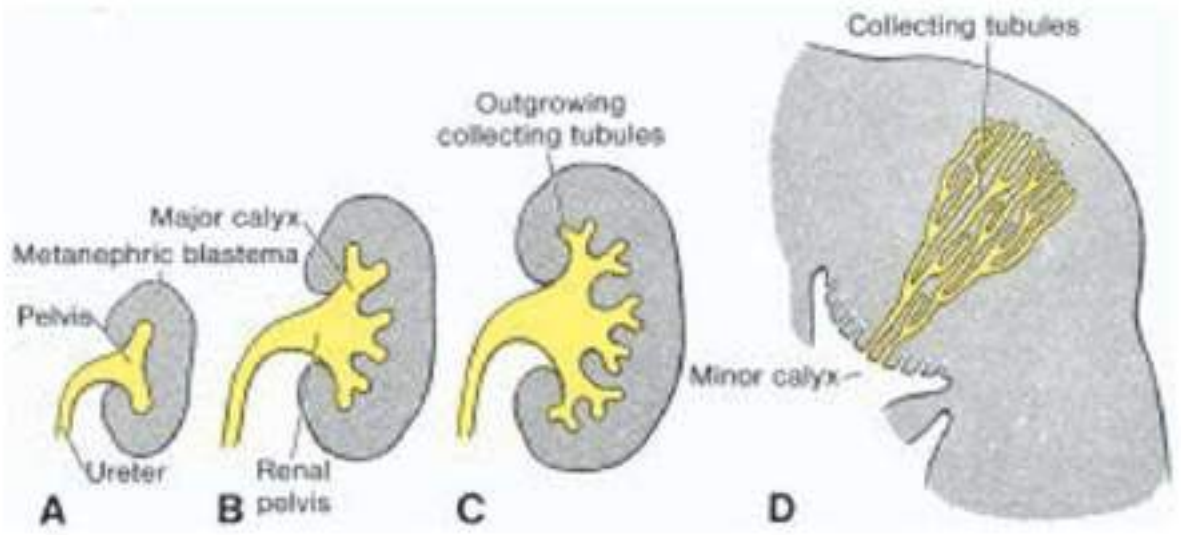


Figure 5: Development of the renal pelvis, calyces, and collecting tubules of the metanephros. A. 6 weeks. B. At the end of the sixth week. C. 7 weeks, D. Newborn.

The pyramid form of the collecting tubules entering the minor calyx. (Sadler, 2018).

2. Excretory System of the Permanent Kidney.

- Each formed collecting tubule is covered at its distal end by a metanephric tissue cap.
- Under influence of the tubule, cells of the tissue cap form renal vesicles, which in turn give rise to S-shaped tubules.
- Capillaries grow into the pocket at one end of the S and differentiate into glomeruli.
- These tubules, together with their glomeruli, form nephrons, or excretory units.
- Proximal end of each nephron forms Bowman's capsule, indented by a glomerulus.
- Distal end of each nephron forms an open connection with one of the collecting tubules, establishing a passageway from Bowman's capsule to the collecting unit.
- Continuous lengthening of the excretory tubule results in formation of the proximal convoluted tubule, loop of Henle, and distal convoluted tubule.

So, the kidney develops from two sources:

1. Metanephric mesoderm: Provides excretory units.
2. Ureteric bud, which gives rise to the collecting system.

Notes:

- **Nephrons:** Formed until birth, at which time there are 1 million in each kidney.
- **Urine production:** Begins early in gestation, soon after differentiation of the glomerular capillaries, which start to form by the 10th week.
- **At birth:** The kidneys have a lobulated appearance. the lobulation disappears during infancy because of further growth of the nephrons, no increase in their number.

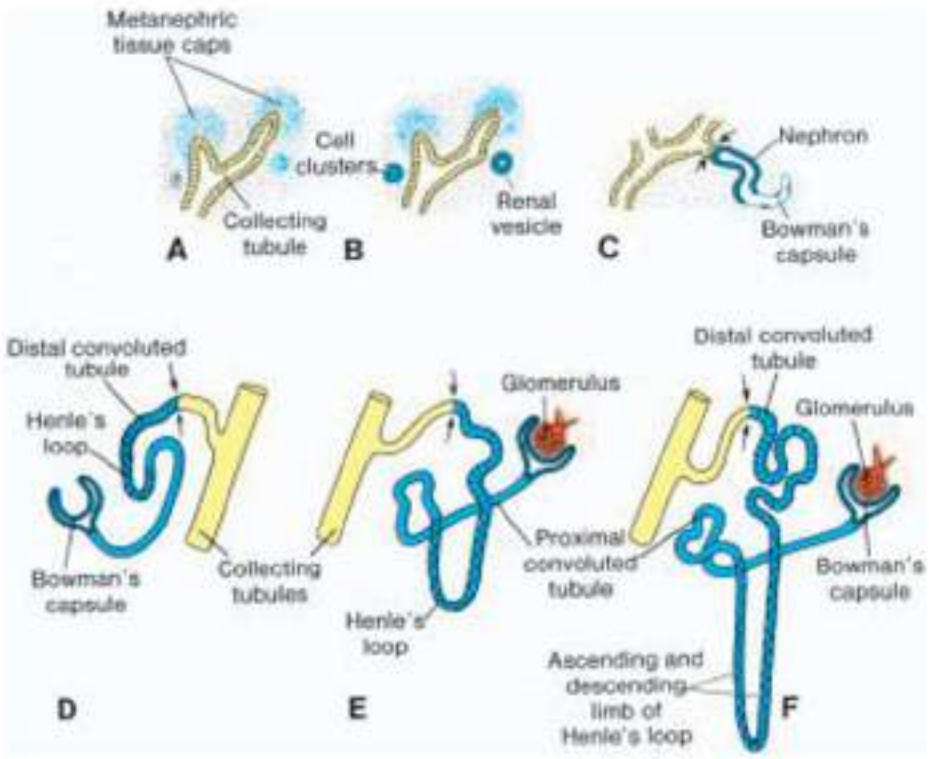


Figure 6: Development of a metanephric excretory unit. Arrows, the place where the excretory unit (blue) establishes an open communication with the collecting system (yellow), allowing flow of urine from the glomerulus into the collecting ducts. (Sadler, 2018).

Changes in the Developing Kidney:

1. Change in Shape: At birth the kidneys have a lobulated appearance which disappears during infancy as the result of growth of the nephrons.

2. Change in Position: At first the kidney is in the pelvis, later it shifts to the abdomen due to growth of the body in the lumbar and sacral regions.

3. Change in Blood Supply: In the pelvis, it receives its blood supply from the median sacral artery. During its ascent it is supplied by arteries from the common iliac artery then the aorta at successively higher levels. The lower vessels usually degenerate.

4. Change in Direction: At first the hilum looks forwards, then the kidney rotates so that the hilum looks medially.

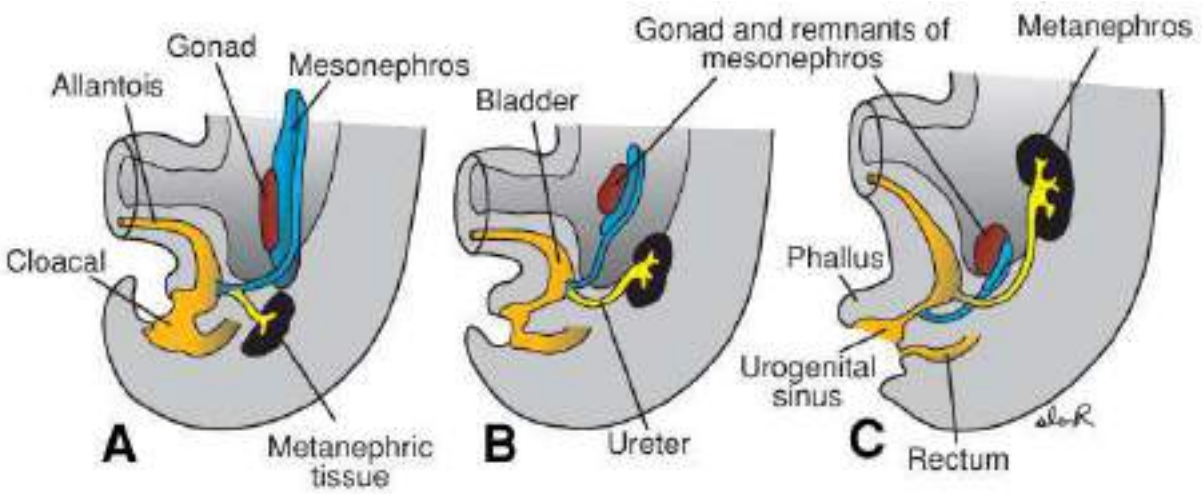


Figure 7: A to C. Ascent of the kidneys.
The change in position between the mesonephric and metanephric systems. (Sadler, 2018).

Congenital Anomalies of the Kidney:

1. Renal agenesis: May be unilateral or bilateral.

2- Congenital cystic kidney:

- Caused by failure of union between some collecting and excretory tubules.
- May be polycystic kidney or solitary cyst.

3. Double kidney: Caused by early splitting of ureteric bud.

4. Pelvic kidney: Caused by failure of the kidney to ascend.

5. Horseshoe kidney: The kidneys fuse at their lower poles.

6. Persistent fetal lobulation.

7. Aberrant renal artery: Caused by persistence of one or more transient arteries.

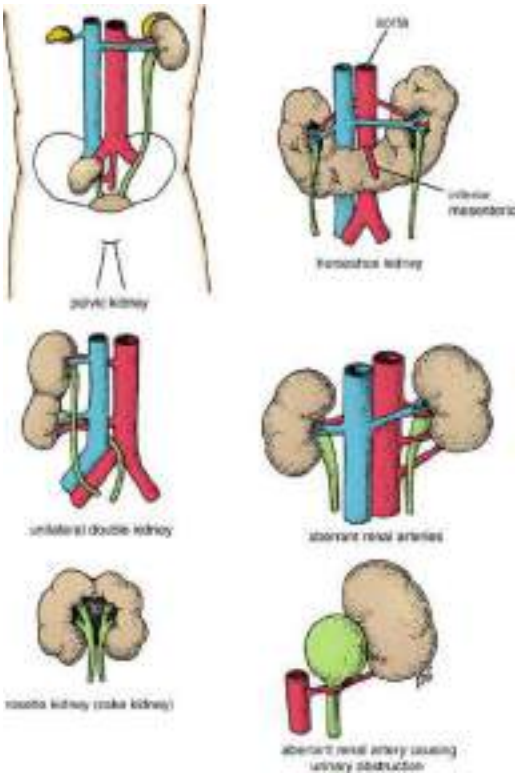


Figure 8: Some congenital anomalies of the kidney. (Snell, 2019).

URETER (Figures 7, 9, 10 & 11).

- Develops from the ureteric bud which arises from mesonephric duct.
- Caudal part of the mesonephric duct (below ureteric bud) is absorbed into ventral part of the cloaca to form trigone of the urinary bladder.
- As a result, the 2 ureteric buds and the 2 mesonephric ducts open separately into the urinary bladder.
- As the result of ascent of the kidneys, ureters elongate.

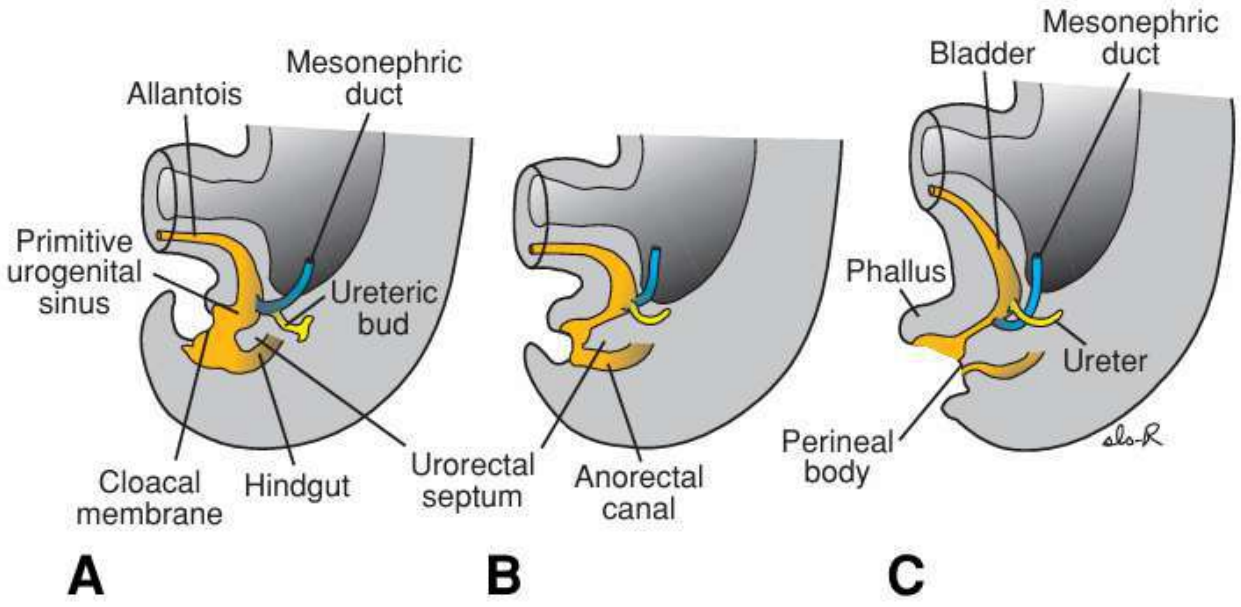


Figure 9: Divisions of the cloaca into the urogenital sinus and anorectal canal. Mesonephric duct is absorbed into the wall of urogenital sinus, and ureters enter separately. A. At the end of the fifth week. B. 7 weeks. C. 8 weeks. (Sadler, 2018).

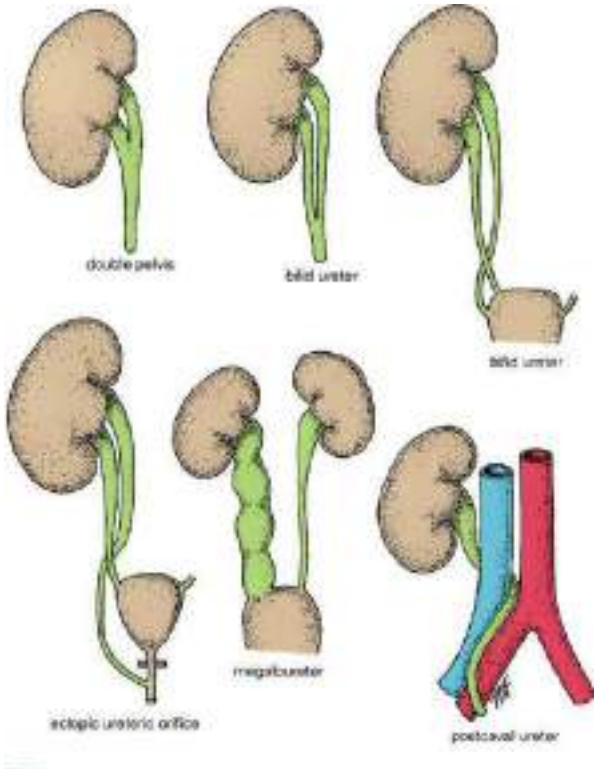


Figure 10: Some congenital anomalies of the ureter. (Snell, 2019).

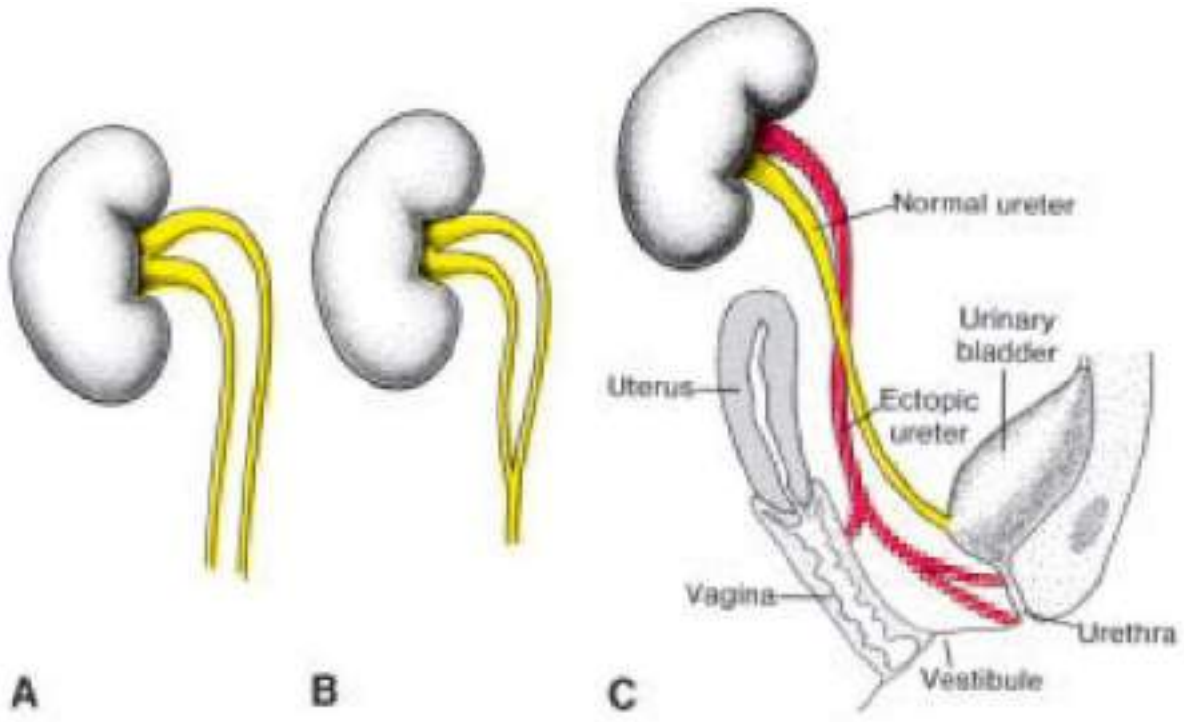


Figure 11: A. Complete double ureter B. Partial double ureter.
C. Sites of ectopic ureteral openings in the vagina, urethra and vestibule. (Sadler, 2018).

References:

1. Snell, R. S. (2019): Clinical Anatomy by Regions (Anatomy) 9th Edition. Lippincott Williams & Wilkins.
2. Moore, Keith L. and Dalley A. F. (2023): Clinically Oriented Anatomy, 9th Edition, Lippincott Williams & Wilkins.
3. KAPLAN Medical USMLE Step 1 Lecture Notes Anatomy (2021).

Lecture 4:
DEVELOPMENT AND CONGENITAL ANOMALIES OF THE URINARY BLADDER AND URETHRA

ILOs:

1. Describe the different stages of development of the urinary bladder and urethra.
2. Describe the developmental abnormalities of the urinary bladder.
3. Describe the developmental defects of the urethra.

DEVELOPMENT OF THE URINARY BLADDER

During the Fourth to Seventh Weeks of Development:

- The cloaca divides into urogenital sinus anteriorly and anal canal posteriorly.

Urorectal Septum:

- Layer of mesoderm between the primitive anal canal and urogenital sinus.
- Tip of the septum will form the perineal body.

Portions of the urogenital sinus:

1. **Urinary bladder:** Upper and largest part.

- Initially the bladder is continuous with the allantois, but when the lumen of the allantois is obliterated, a fibrous cord, urachus, remains and connects apex of the bladder with the umbilicus.
- **In the adult**: Urachus forms the median umbilical ligament.

2. **Pelvic part of the urogenital sinus:** Narrow canal, the, which in the male gives rise to the prostatic and membranous parts of the urethra.
3. **Phallic part of the urogenital sinus:** Flattened from side to side, and as the genital tubercle grows, this part of the sinus will be pulled ventrally.

During differentiation of the cloaca:

- Caudal portions of mesonephric ducts are absorbed into the wall of urinary bladder.
- The ureters, initially outgrowths from mesonephric ducts, enter the bladder separately.
- As a result of ascent of the kidneys, the orifices of ureters move cranially.

- Those of the mesonephric ducts move close together to enter the prostatic urethra and, in the male, become the ejaculatory ducts.
- Since both the mesonephric ducts and ureters originate in the mesoderm, the mucosa of the bladder formed by the ducts (trigone of the bladder) is also mesodermal.
- With time the mesodermal lining of the trigone is replaced by endodermal epithelium, so that finally the inside of the bladder is completely lined with endodermal epithelium.
- **Rest of bladder wall:** Derived from surrounding splanchnic mesoderm.
- **At birth**: Urinary bladder is an abdominal organ.
- **At puberty**: It becomes a pelvic organ.

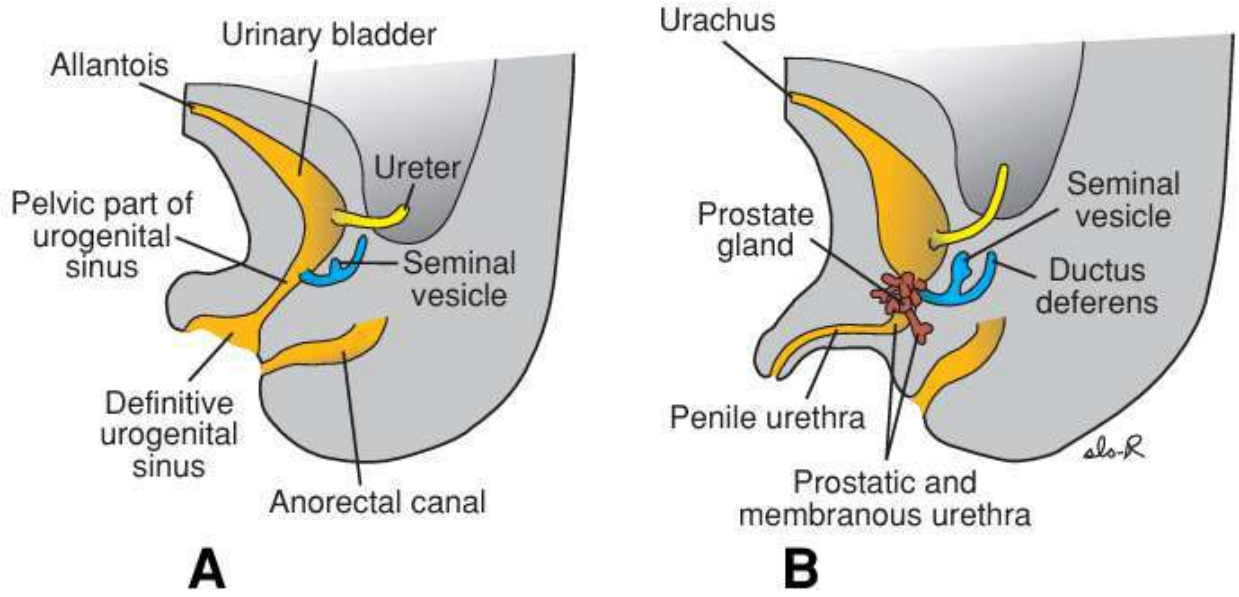


Figure 1: A. Development of the urogenital sinus into the urinary bladder and definitive urogenital sinus. B. In the male the definitive urogenital sinus develops into the penile urethra. (Sadler, 2018).

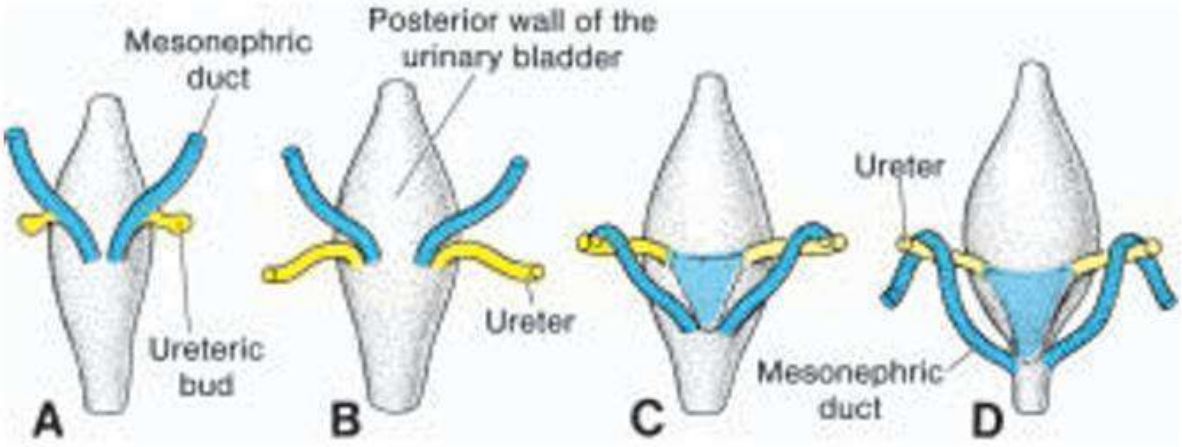


Figure 2: Dorsal views of the bladder showing relation of the ureters and mesonephric ducts during development. The ureters are formed by an outgrowth of the mesonephric duct (A), with time they assume a separate entrance into the urinary bladder (B–D). The trigone of the bladder formed by incorporation of the mesonephric ducts (C and D). (Sadler, 2018).

DEVELOPMENT OF THE URETHRA

Urethra:

- Epithelium of the urethra in both sexes originates in the endoderm.
- Surrounding connective and smooth muscle tissue is derived from splanchnic mesoderm.

At End of the Third Month:

- Epithelium of the prostatic urethra begins to proliferate and forms a few outgrowths that penetrate the surrounding mesenchyme.
- **In male:** The buds form the prostate gland.
- **In female**: Cranial part of the urethra gives rise to urethral and paraurethral glands.

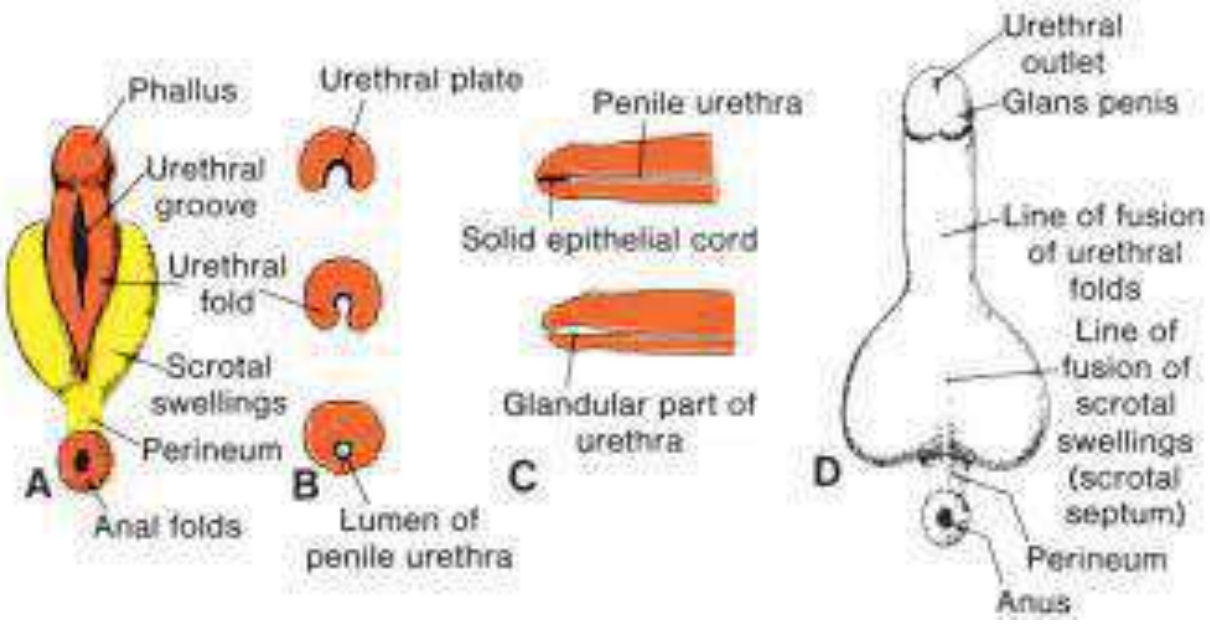


Figure 3: Development of the urethra. A. Development of external genitalia in the male at 10 weeks. Deep urethral groove flanked by urethral folds. B. Transverse sections through the phallus during formation of penile urethra. Urogenital groove is bridged by urethral folds.

C. Development of glandular portion of the penile urethra. D. Newborn. (Sadler, 2018).

CONGENITAL ANOMALIES OF URINARY BLADDER AND URETHRA

1. Ectopia vesical with epispadius:

- Mucosa of posterior bladder wall is exposed to the outside due to absence of the anterior wall together with overlying anterior abdominal wall.

2. Hypospadius; urethra is open on ventral surface of the penis.

3. Patent urachus:

a- Urachal fistula: Allantois does not constrict and urine flows from the umbilicus.

c- Urachal cyst: Cystic dilatation along course of urachus

b- Urachal sinus: Patent upper part of the urachus.

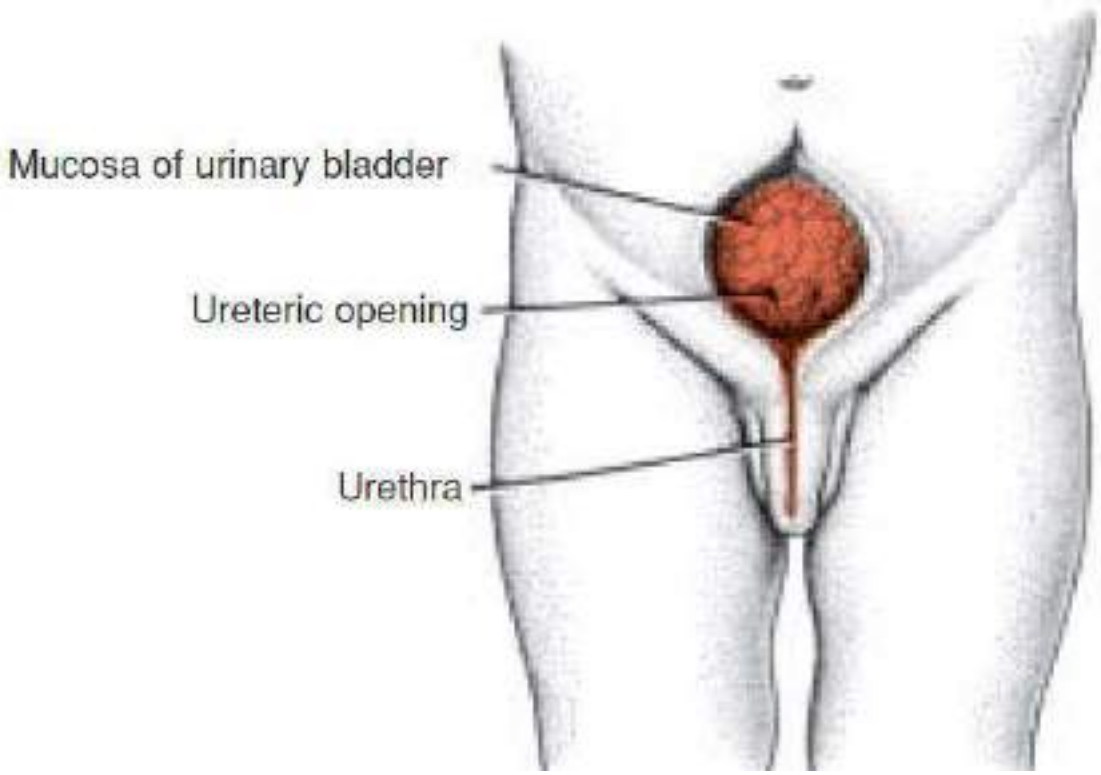


Figure 4: Epispadias with exstrophy of bladder. Bladder mucosa is exposed. (sadler, 2018).

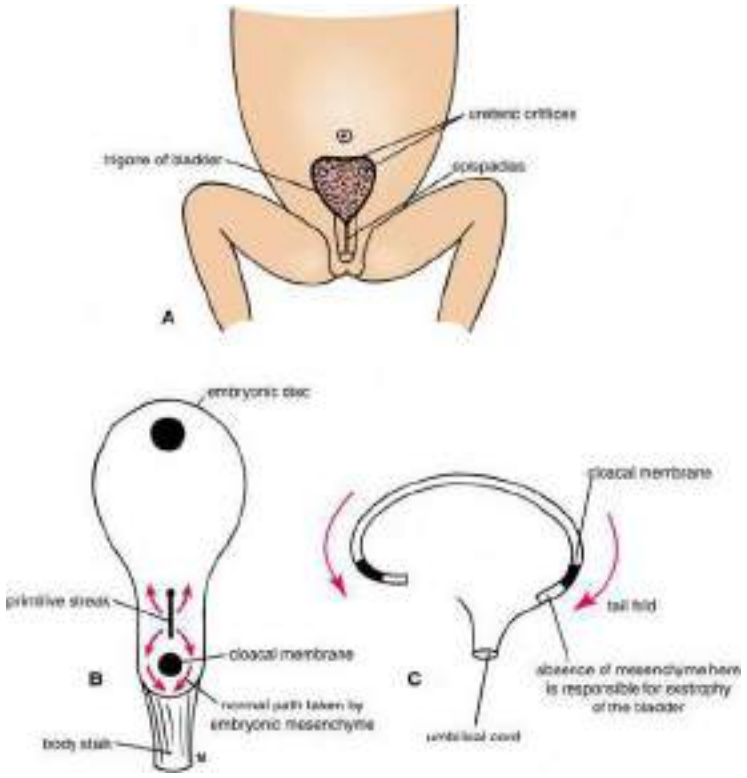


Figure 5: Ectopia vesica with epispadius: A. Exstrophy of bladder. B. Dorsal view of embryonic disc. Normal path by growing embryonic mesenchyme in region of cloaca. C. Fetus as seen from the side. Mesenchyme failed to enter ventral body wall between cloaca and umbilical cord. (Snell, 2019).

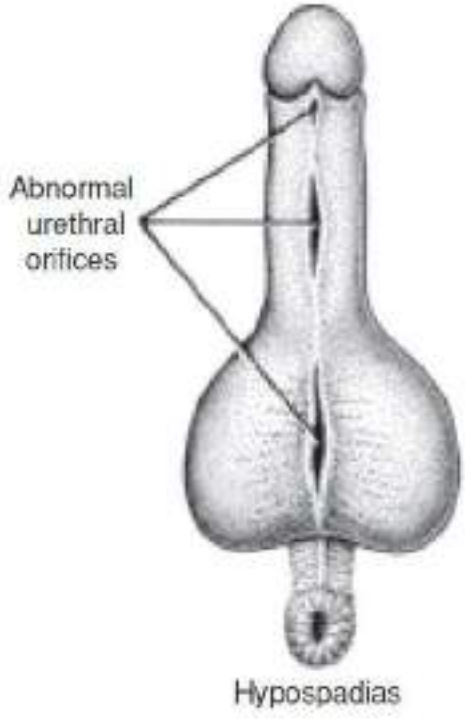


Figure 6: Hypospadius; urethra is open on ventral surface of the penis. (Sadler, 2018).

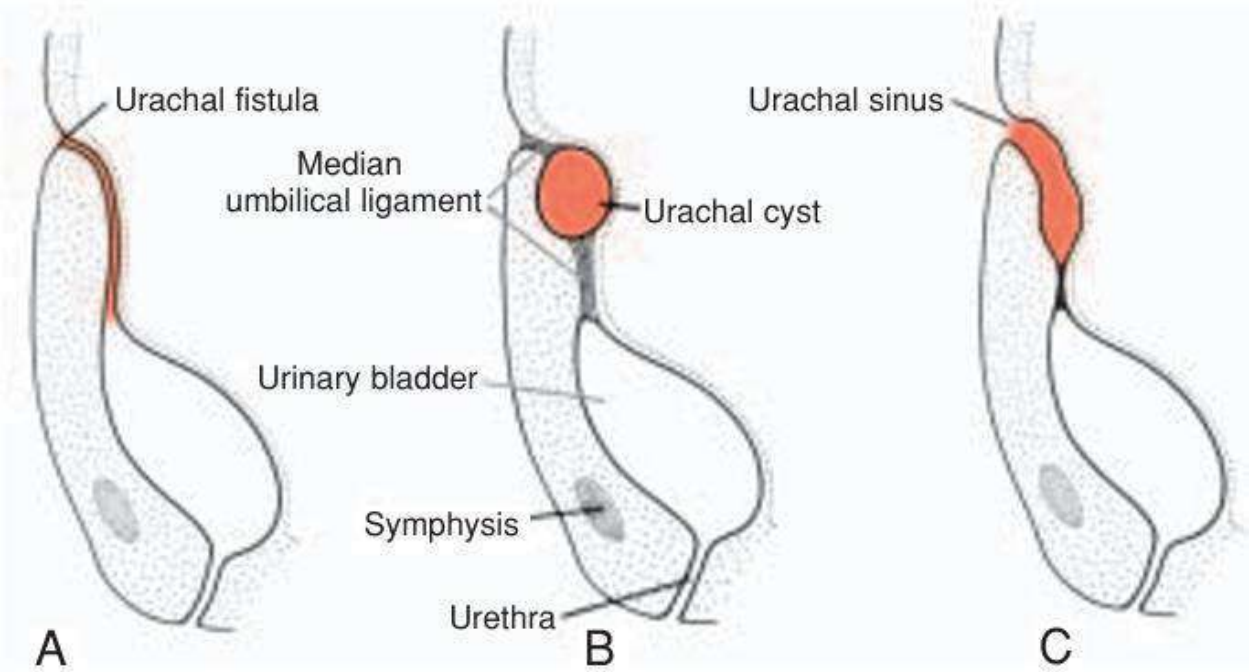


Figure 7: A. Urachal fistula. B. Urachal cyst. C. Urachal sinus. The sinus may or may not be in open communication with the urinary bladder. (Sadler, 2018).

References:

4. Snell, R. S. (2019): Clinical Anatomy by Regions (Anatomy) 9th Edition. Lippincott Williams & Wilkins.
5. Moore, Keith L. and Dalley A. F. (2023): Clinically Oriented Anatomy, 9th Edition, Lippincott Williams & Wilkins.
6. KAPLAN Medical USMLE Step 1 Lecture Notes Anatomy (2021).

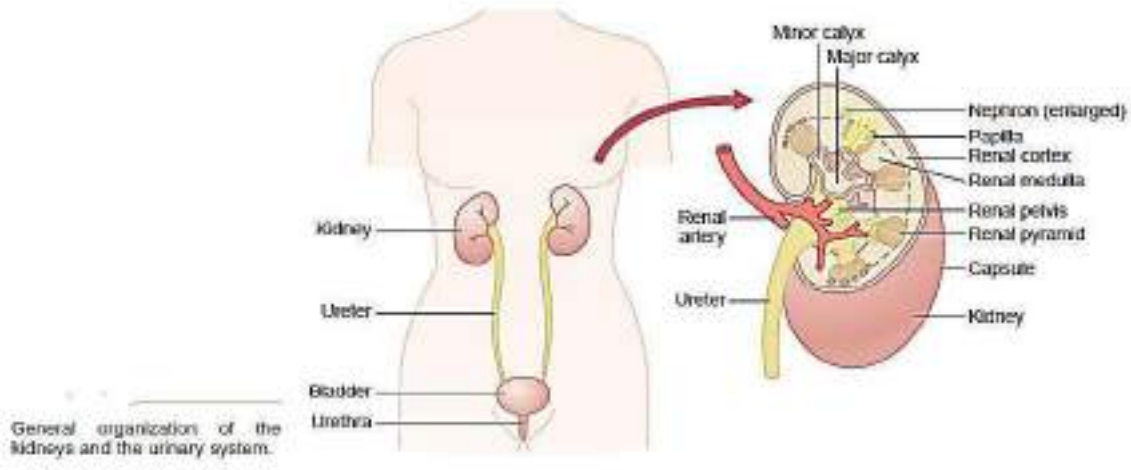
Part 2
Medical physiology

1- Functional organization of the Kidney and renal blood flow

ILOs:

1. Explain the process of glomerular filtration and state the composition of the glomerular filtrate.
2. Describe the main determinants of solute filterability across the glomerular membrane.
3. Define Glomerular Filtration Rate (GFR) and describe the Starling forces that determine its magnitude.
4. Define Renal Blood Flow (RBF), Renal Plasma Flow (RPF), and the Filtration Fraction (FF).
5. Describe the autoregulatory mechanisms (myogenic and tubuloglomerular feedback) that regulate RBF and GFR.

Kidney



General organization of the kidneys and the urinary system.

Kidney Functions :

The Kidney are largely responsible for maintenance of constant internal environment through:

- **Excretion of waste products**: Urea, creatinine and uric acid.
- **Control of** volume, osmotic pressure and electrolyte content of the extracellular fluid.

Endocrine functions:

a) Renin – Angiotensin mechanism which regulates ABP
b) Erythropoietin hormone which stimulates Erythropoeisis (so, there is anemia in Kidney diseases).
c) Formation of 1-25 dihydrocholecalciferol which control Ca^{++} and PO_4 Plasma levels
d) Secretion of prostaglandins (PGE, PGI2) & bradykinin: they are paracrine hormones that regulate renal blood flow.

Regulation of arterial blood pressure:

A. Short term: through renin angiotensin system.
B. Long term: excretion of Na+ & H_2O.

Regulation of acid base balance:

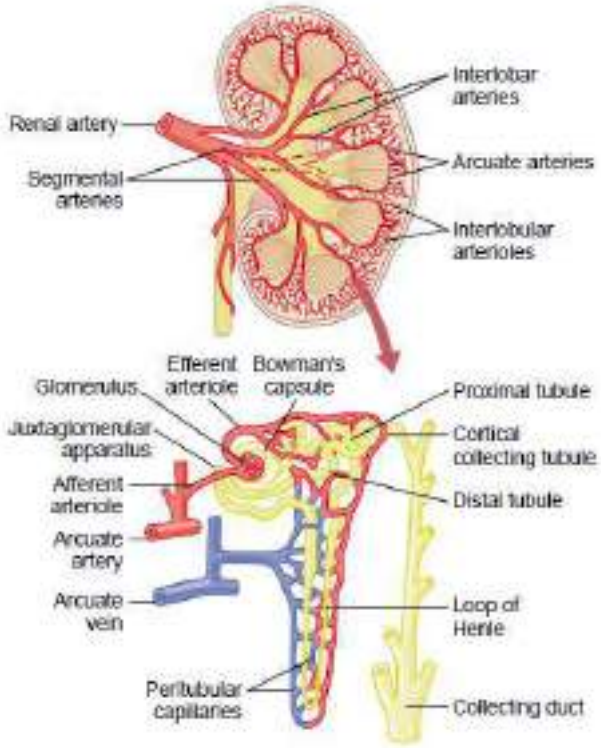
A. Elimination of acids e.g. sulphuric & phosphoric acids.
B. Regulation of buffer stores.

Gluconeogenesis: during prolonged fasting.

Physiological Anatomy of the Kidney :

The kidney is

- Paired organ lies on either side of the vertebral column.
- Below the diaphragm, just behind the peritoneum of the abdominal cavity.



Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the micro-circulation of each nephron.

Nephron is the functional unit of kidney. There are 1.3 million nephrons in each human kidney.

Structure of the kidney:

The kidney is formed of:

A. Cortex: Is the outer granular part because of its many capillary beds (glomeruli)
B. The Medulla: It is the deep part lighter in color formed of tubules and long blood vessels.

   The medulla consists of 8-15 renal pyramids. The apex of these pyramids drain urine into a small depression called minor calyx, several minor calyces unit to form major calyx. Major calyx unit to form the renal pelvis.

The **Nephron** consists of:

(1)Renal corpuscle	**(2) Renal tubule:**
It is formed of: Glomerulus & Bowman capsule	It is divided into: Proximal convoluted tub. Loop of Henle –distal convoluted tub.

Glomerular capillary is the only capillary lying between 2 arterioles.

There are two types of nephrons:

Cortical nephrons(85%)	**Juxta medullary nephrons(15%)**
*Their glomeruli lie close to surface	Their glomeruli lie deep near the medulla
*They have very short loop of Henle	*They have very long loop of Henle
*The tubule is surrounded by a network of peritubular capillaries	* The tubule is surrounded by a U shaped peritubular capillary that lie side by side with loop of Henle
*Its function is formation of urine	*play a role in urine cocentration

Renal Blood Flow (Blood supply of the kidney):

-Blood flow to kidney is 1200 ml/min (20% of Cardiac output)

-Renal artery arises directly from the abdominal aorta and enters the kidney at hilum dividing into: interlobar, arcuate, interlobular, afferent arterioles, glomerular capillaries, efferent arterioles, peritubular capillaries which give vasa recta

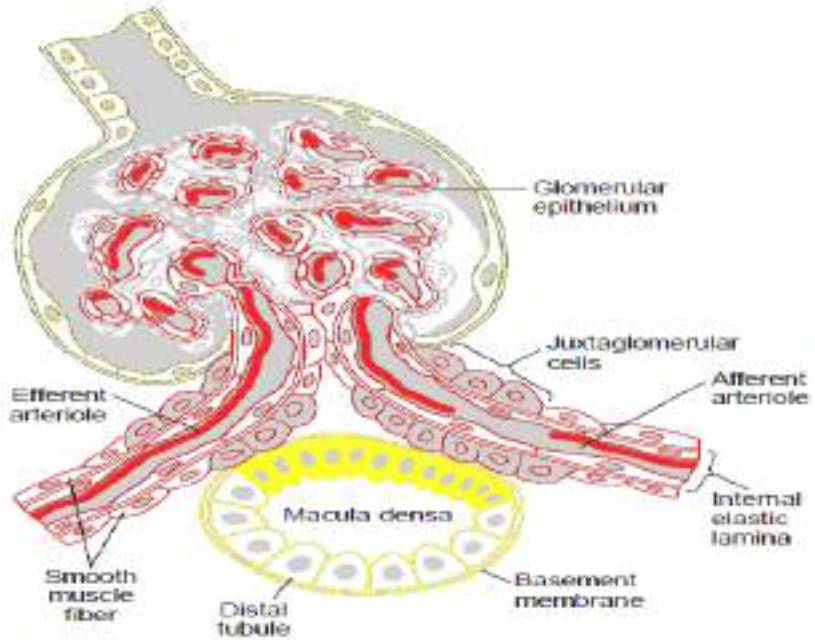
Vasa Recta:

These are capillaries that descend in medulla along juxtamedullary nephrons & reascend into cortex supplying lower part of loop of Henle & concerned with concentration of urine (with collecting duct) .
The great length of vasa recta results in a high resistance to blood flow and leads to low blood flow in the medulla (1-2% of blood flow). This sluggish blood flow in medulla allows urine concentration.

***There are two capillary beds associated with the nephron:**

Glomerular capillary	Peritubular Capillary
-Arises from afferent arteriole	-Arises from efferent arteriole
-High pressure bed	-Low pressure bed
- Capillary pressure=60 mmHg	-Capillary pressure=13 mmHg
-Plasma is filtered	-Filtrate is reabsorbed.

***Juxta glomerular apparatus:**

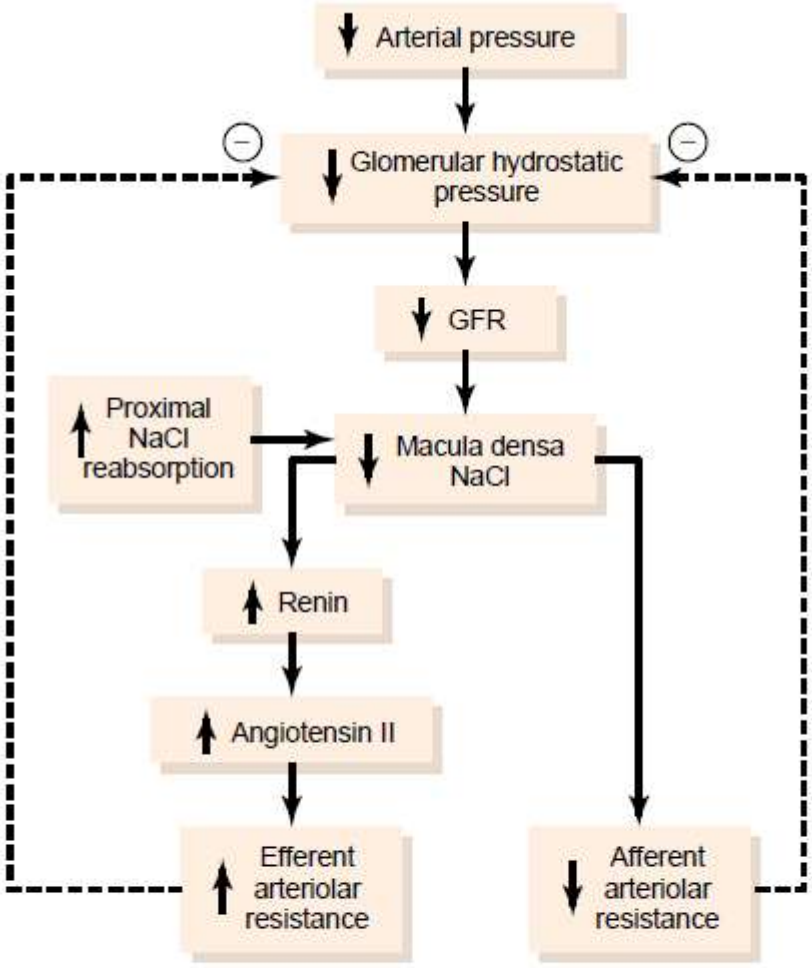


- It lies at the area of contact between distal convoluted tubule, and the afferent arteriole and efferent arteriole, formed of:

1-Macula densa: The tubular epithelium show dense crowding of cells & nuclei

2-Juxta glomerular cells: The smooth muscles of arterioles (afferent & to a lesser extent efferent) have an appearance like epithelial cells. They secrete renin.

3-Lacis cells: agranular cells between afferent & efferent arterioles. They contain renin.



Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during decreased renal arterial pressure.

Reference:

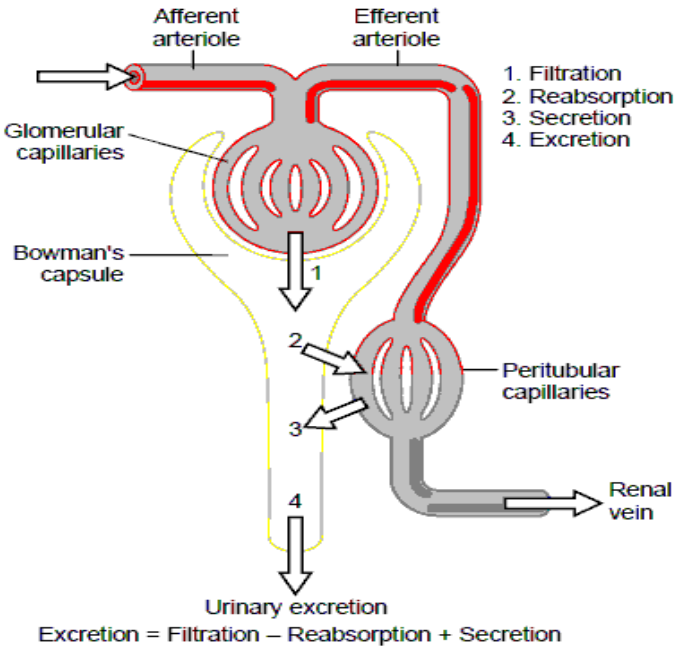
- First Aid for the Basic Sciences: Organ Systems, Third Edition, Page(s). 608

2- Mechanism of urine formation: I- Glomerular filtration II- Reabsorption and secretion

ILOs:

1- Describe the three layers of the glomerular filtration barrier and explain how size and charge selectivity prevent plasma protein filtration.
2- State the composition of glomerular filtrate and compare it to plasma.
3- Define the Starling forces (hydrostatic and osmotic pressures) that determine the Net Filtration Pressure (NFP).
4- Calculate the Net Filtration Pressure given the values of the individual forces.
5- Predict how changes in afferent or efferent arteriolar resistance will affect glomerular hydrostatic pressure and GFR.
6- Differentiate between passive, primary active, and secondary active transport mechanisms in the nephron with specific examples.
7- Distinguish between reabsorption (movement from tubule to blood) and secretion (movement from blood to tubule) and state their physiological importance.
8- Explain the concept of solvent drag and its role in paracellular reabsorption.
9- Predict whether a substance undergoes net reabsorption or net secretion by comparing its clearance to the clearance of inulin.

Formation of Urine



Urine is a result of three processes:

1- glomerular filtration
2- tubular reabsorption.
3- tubular secretion

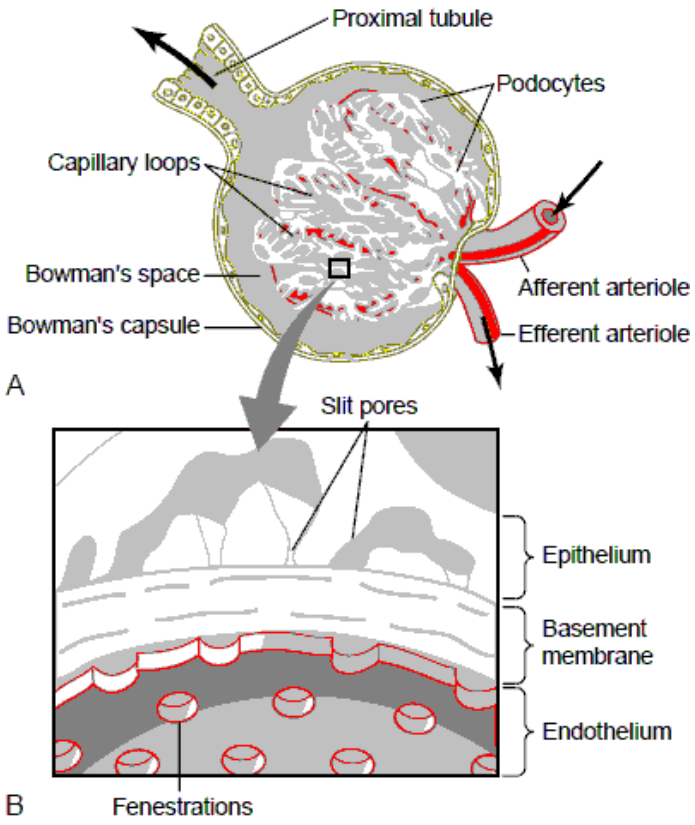
Glomerular Filtration Rate: GFR

Glomerular Filtrate: is the fluid that filters through glomeruli into Bowman's capsule, consists of plasma without plasma proteins.

Glomerular Filtration Rate: is the amount of glomerular filtrate formed each minute in all nephrons of both kidneys.

It equals: 125 ml/min - 180 litre/day (kidney filters in one day a volume of fluid that equals 60 times that of plasma volume)-

Glomerular Capillary Membrane : is formed of 3 layers:



1) **Capillary endothelium** : which have wide pores called fenestra 70-90 nm in diameter (not barrier for plasma protein)
2) **Basement membrane:** which has no pores, it is negatively charged forming anionic sites that repel anions of plasma (e.g. plasma proteins).
3) **Bowman's capsule epithelium:** formed of podocytes with slit pores (25nm)

Mesangial cells:

They are contractile stellate cells at bifurcation of the capillaries. They secrete various substances, involved in production of immune glomerular diseases & play a role in regulation of GFR.

The reasons for molecular selectivity:

1) **Size of pores:** They allow molecules up to 8 nm.

   - So substances < 4 nm freely filtered but > 8 nm not filtered.
   - But albumin although it is 7nm does not pass because of its negative charge.
   - Na^+ and glucose pass freely.

2) **Charge of the ion:** Because basement membrane has –ve charge, the neutral and +ve charged ions are filtered more than anions due their repulsion by the anionic sites.

   In kidney diseases, there is albuminuria because the negative charges on the basement membrane are lost without increase in size of pores.

Renal Blood Flow = 1200 ml/min, **plasma flow** = 650 ml/min so the **filtration Fraction** is the fraction of renal plasma that become filtrate.

It is equal $\frac{125}{650} = 20\%$

Forces causing glomerular filtration:

1) **Hydrostatic pressure of glomerular capillary** (HP_{GC})(**60** mmHg)

   - It helps filtration.
   - It is the highest capillary pressure all over the body because:

     a. The renal artery arises directly from the abdominal aorta at a right angle
     b. Afferent arterioles are short & straight branches.
     c. Diameter of the efferent arteriole is 1/3 that of the afferent, which raises the pressure & increase the resistance

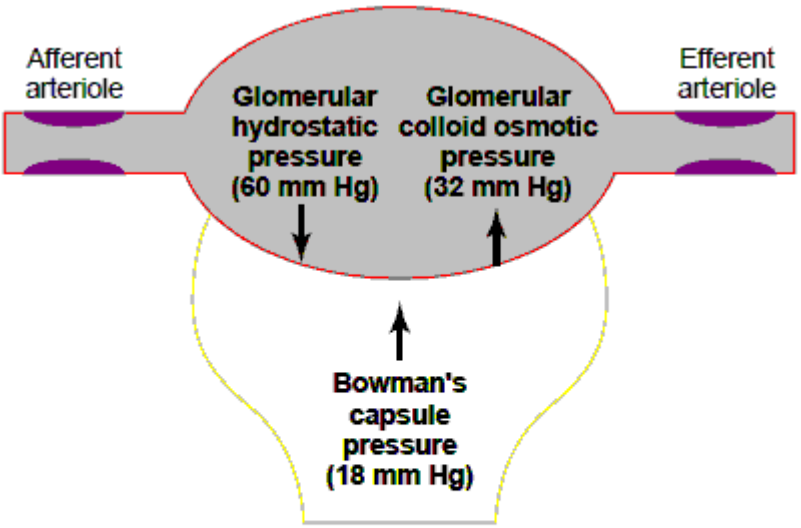
2) **Colloidal Osmotic Pressure of Bowman's capsule (CO_{BC})** (**zero**) as no protein in Bowman's capsule (protein is not filtered). It helps filtration.
3) **Colloidal Osmotic Pressure of Glomerular capillary (CO_{GC})** average=**32** mmHg. This force opposes filtration due to the osmotic power of plasma proteins.
4) **Hydrostatic pressure of Bowman's capsule** (HP_{BC})(**18** mmHg): It opposes filtration.

❖ **The Net filtering forces or the filtration pressure (NFF)**

NFF= CHP + COPB – (COPG + HPB)

= 60 + 0 - (32 + 18)

= 60 - 50 = 10 mmHg



Net filtration pressure (10 mm Hg)	=	Glomerular hydrostatic pressure (60 mm Hg)	–	Bowman's capsule pressure (18 mm Hg)	–	Glomerular oncotic pressure (32 mm Hg)

Starling Landis Equation :

GFR ∝ NFF

GFR = Kf (NFF)

Where GFR is the glomerular filtration rate

& Kf is the glomerular filtration coefficient

$$Kf = \frac{GFR}{NFF} = \frac{125 \text{ ml/min}}{10 \text{ mmHg}} = 12.5 \text{ ml/min/mmHg}$$

So KF is the glomerular filtration rate in both kidneys per millimetre of mercury of filtration pressure. KF depends on permeability of glomerular membrane and surface area of glomerular capillaries.

Factors affecting GFR:

1. **Changes in glomerular hydrostatic pressure (GHP):**

   Glomerular Hydrostatic Pressure is affected by:

   A. Afferent arteriolar dilatation (by prostaglandin & bradykinin) leads to increase $HP_{GC} \rightarrow$ increase GFR
   B. Afferent arteriolar constriction (by sympathetic & adenosine) leads to decrease HP_{GC} → decrease GFR.
   C. Moderate Efferent arteriolar constriction leads to increase HP_{GC} → slight increase of GFR
   D. Severe efferent arteriolar constriction→plasma remains for a longer time in glomerulus with more filtration with more increase in colloidal osmotic pressure (O.P)→ decrease GFR. It is called paradoxical decrease in GFR despite elevated HP_{GC}.

2. **Changes in glomerular colloidal osmotic pressure (OP_{GC})**
   A. Increase in OP_{GC} (as in dehydration) leads to decrease GFR.
   B. Decrease in OP_{GC} (as in hypoproteinemia) leads to increase GFR

3. **Increase hydrostatic pressure in Bowman's capsule (HP_{BC}):**

   As in urinary tract obstruction →decrease GFR.

4. **Increase colloidal osmotic pressure in Bowman's capsule (OP_{BC}):**

   As in increased glomerular membrane permeability → increase GFR

5. **Conditions affecting Kf:**

   A. Membrane permeability: Increase thickness of glomerular membrane →decrease membrane permeability→ decrease Kf → decrease GFR.
   B. Surface area of glomerular capillaries: it is affected by:

Contraction of mesangial cell which reduce surface area and decrease GFR. It is caused by: Angiotensin II, Nor epinephrine, Vasopressin & Endothelins.

Relaxation of mesangial cells which increase surface area and increase GFR. It is caused by: ANP**,** CAMP**,** PGE2 & Dopamine.

6. <u>Changes in Arterial blood pressure ABP & or renal blood flow</u> :

GFR is kept constant despite of changing ABP between 90 - 200 mmHg. This is called **autoregulation** of GFR. The mechanisms involved in autoregulation of GFR are:

A. Tubuloglomerular balance:

It is an efficient specific feedback mechanism to buffer effect of changes in arterial blood pressure (ABP) on GFR.

Decrease ABP → decrease GFR → decrease Na^+, cl^- concentration at macula densa leading to:

Efferent arteriolar V.C. feedback	**afferent arteriolar VD feedback**
Macula densa send signals to release Renin →increase angiotensin II→ VC of efferent arteriole → increase Glomerular pressure→ increase GFR	Macula densa send signals to cause VD of afferent arteriole → increase GFR

Increase ABP → increase GFR → increase Na+, cl- concentration at macula densa leading to release of vasoactive substances (prostaglandins & adenosine)→afferent arteriolar vasoconstriction reducing RBF and GFR.

B. Myogenic autoregulation:

It is a rapid mechanism and the first line of defense against rapid change in blood pressure.

Increase ABP → stretch wall of arteriole→ increase tension → contraction of plain muscle of arteriole → decrease diameter → decrease blood flow.

Conversely, a decrease in ABP results in relaxation of smooth muscles.

N.B. Determination of GFR By inulin clearance or creatinine clearance test

Plasma Clearance

*__Definition__: The volume of plasma (in ml) that is cleared from a certain substance which is excreted in urine/min.

* **Calculation:**

Amount of substance cleared/min= amount of substance excreted in urine/min

$$C \times P = U \times V$$

Where: C is volume of cleared plasma/min

P is the concentration of the substance in plasma

U is the concentration of substance in urine

V is the volume of urine/min.

$$C = \frac{U \times V}{P}$$

1) A Substance that is filtered freely and neither reabsorbed nor secreted by the renal tubules will be cleared from plasma only by glomerular filtration. Its clearance equal GFR. For example : inulin
2) A substance that is reabsorbed by the renal tubules will have clearance below GFR. Since tubular reabsorbtion returns the filtered substance back to the blood, it decreases its removal (clearance) from the plasma e.g. urea and K^{+}.
3) A substance that is secreted by the renal tubules will have clearance above GFR. Since tubular secretion increases its removal (clearance) from the plasma e.g. creatinine.

** **Importance**:

1- It is an early index of renal disease.
2- It is used for measurement of GFR using inulin or Mannitol
3- It is used for study of behavior of different substances.

Substance	Clearance	Behaviour
Inulin	125 ml/min	Neither reabsorbed nor secreted
Urea, K+	< 125	Partially reabsorbed
Creatinine (140)	125 – 650	Partially secreted
PAHA	650	Completely secreted
Ammonia	>650	Completely secreted + manufactured by kidney
Glucose	Zero	Completely reabsorbed

4- Determination of effective renal plasma flow ERPF: A substance as Para Amino Hippuric Acid ”PAHA” [diodrast] is completely secreted through a single circulation in kidneys. Its clearance = 650 ml/min
5- Clearance of endogenous substance as that of urea & creatinine: is preferred in investigating renal functions to avoid administration of exogenous substances.

**** Disadvantage:**

It gives the net effect and not the detailed study of renal tubule e.g. K+ clearance = 75 ml/min which suggests that K+ is partially reabsorbed but K+ is 65% reabsorbed in Proximal Convoluted Tubules “PCT” & then secreted in Distal Convoluted Tubules “DCT”.

Measurement of GFR:

1]inulin clearance test:

- Large dose of inulin is injected intravenously & followed by sustained infusion to keep arterial plasma level constant

Inulin is:

a) A polymer of fructose MW = 5200
b) Neither reasbsorped, nor secreted by renal tubule, i.e amount filtered = amount excreted.
c) Non toxic.
d) Not metabolized.
e) Not stored by kidney and not affect GFR.
f) Can be easily measured in urine & plasma.

Amount filtered = Amount Excreted

$$C \times P = U \times V$$

C is the volume of glomerular filtrate/min (unknown)

P is the concentration in plasma which is equal to that in filtrate

U is the concentration in urine.

V is the volume of urine/min.

$$GFR = \frac{U \times V}{P} = 125 \text{ ml/min}$$

2] Creatinine Clearance

Creatinine is an endogenous substance that is formed from creatine in muscle. It is easily measured.

a) Freely filtered

b) Not reabsorbed.

c) Partially secreted by the renal tubule.

Reference:

- First Aid for the Basic Sciences: Organ Systems, Third Edition Page(s) 610-611 616-620-622

3- Tubular load, tubular transport maximum (Tm) and gradient time transport & Functions of the different parts of the nephron

ILOs

1- Define the terms "tubular load" and "renal threshold" and explain their relationship using glucose as an example.
2- Explain the concept of transport maximum (Tm) and how it leads to the splay phenomenon and eventual excretion of substances when the tubular load is exceeded.
3- Differentiate between Tm-limited transport (e.g., glucose, PAH) and gradient-time limited transport (e.g., sodium, water).
4- Interpret a graph showing the relationship between plasma concentration, tubular load, reabsorption, and excretion for a Tm-limited substance.
5- Describe the mechanism of glucose reabsorption and define the concepts of Transport Maximum (Tm) and renal threshold.
6- Explain the phenomenon of "splay."
7- Describe the reabsorption mechanisms for urea and phosphate.
8- Explain gradient-time limited transport and contrast it with Tm-limited transport.
9- Summarize the functions of the Loop of Henle and early distal tubule.

Specific functions of Different Tubular Segments

Functions of Proximal Convoluted tubules:

The tubular epithelium of proximal tubules:

A. Are highly metabolic, having a large number of mitochondria.
B. Have extensive surface area on both luminal (brush border) & basal (extensive channels) borders. Both a & b facilitate proximal tubular function.

[1] <u>Reabsorption of</u>: 65 % of filtered Na^+, H_2O, Cl, K**,** Most of HCO3-

Na^+: primary active transport:

- In upper half of proximal tubules: it is coupled by active transport of glucose, amino acids (a.a.).
- In lower half of proximal convoluted tubule : it is accompanied by passive diffusion of cl

Cl^-, H_2O: Passive reabsorption secondary to Na^+

- Partial reabsorption of urea: back diffusion secondary to H_2O reasborption.

[2] <u>Secretion of</u> :

- H^+: Counter transported with Na^+ at luminal border.
- Organic substances: as bile salts, oxalate, urate, catecholamines
- Drugs: as penicillin, salicylate & PAH acid.
- Uric acid & creatinine

NB: Fanconi Syndrome: is due reduction of ATP in proximal convoluted tubules (due to toxins or vit.D deficiency → decrease reasborption of Na^+, glucose, a.a. resulting in metabolic acidosis, glucosuria, amino aciduria.

[3] **<u>Synthesis of :</u>** Ammonium from glutamine.

<u>Functions of loop of Henle:</u>

1) Thick ascending limb:

- Reabsorption of 25% of filtered Na, K, cl, some Ca & Mg & few HCO_3
- Secretion of H So, the fluid entering the tubule is hypotonic

2) Thin descending limb

- Reabsorption of 20% of filtered water
- So, fluid reaching the tip is hypertonic.

Functions of Distal convoluted tubules (DCT) & cortical collecting tubules (CT):

[1] First half of DCT(diluting segment) :

a) Absorption of Na^+, K^+, cl^-

b) Impermeable to H_2O , Urea (like thick ascending limb)

c) H+ secretion

[2] Second half of DCT & cortical CT:

a) absorption of Na^+ in exchange with K^+ secretion under effect of aldosterone (active by Na^+-K^+ ATPase pump at the basal border) These cells are called **principal** cells
b) Secrete H^+ & reabsorb HCO_3 using H^+ ATPase transport mechanism (independent on Na+). These cells are called **intercalated** cells (I cells).
c) Impermeable to urea.

[3] Facultative H_2O reabsorption under effect of ADH (5%).

[4] Increase reabsorption of Ca++ by primary active transport (under parathormone effect).

[5] Ammonium synthesis from glutamine.

Functions of Medullary collecting duct:

1) Concentration of urine : together with action of loop of Henle by facultative H_2O reabsorption under effect of ADH.
2) Back diffusion of urea to interstitium maintaining hyperosmolarity of medullary interstitium.
3) Na+ reabsorption
4) H+ secretion by primary active transport.
5) Synthesis of ammonia from glutamine.

Glutamine $\xrightarrow{\text{glutaminase}}$ NH_3 + glutamic acid

Glumatic acid $\xrightarrow{\text{glutamic dehydrogenase}}$ NH_3

NH_3 acts as hydrogen acceptor and then transformed into NH_4 excreted in urine until pH of tubular fluid becomes 6.9 (max. acidifying power of Proximal convoluted tubules).

Na^+ reabsorption

Na^+ accounts for over 90% of osmotically active particles in extracellular fluid “ECF” so, determine extracellular fluid volume.

***Mechanism:**

1) At basal border: primary active, against electrochemical gradients. Na^+ is actively pumped, by Na^+-K^+ ATPase from inside tubular cells of P.C.T across basal border to intercellular space

    - 3 Na^+ are pumped out
    - 2 K^+ are pumped inside the cell.

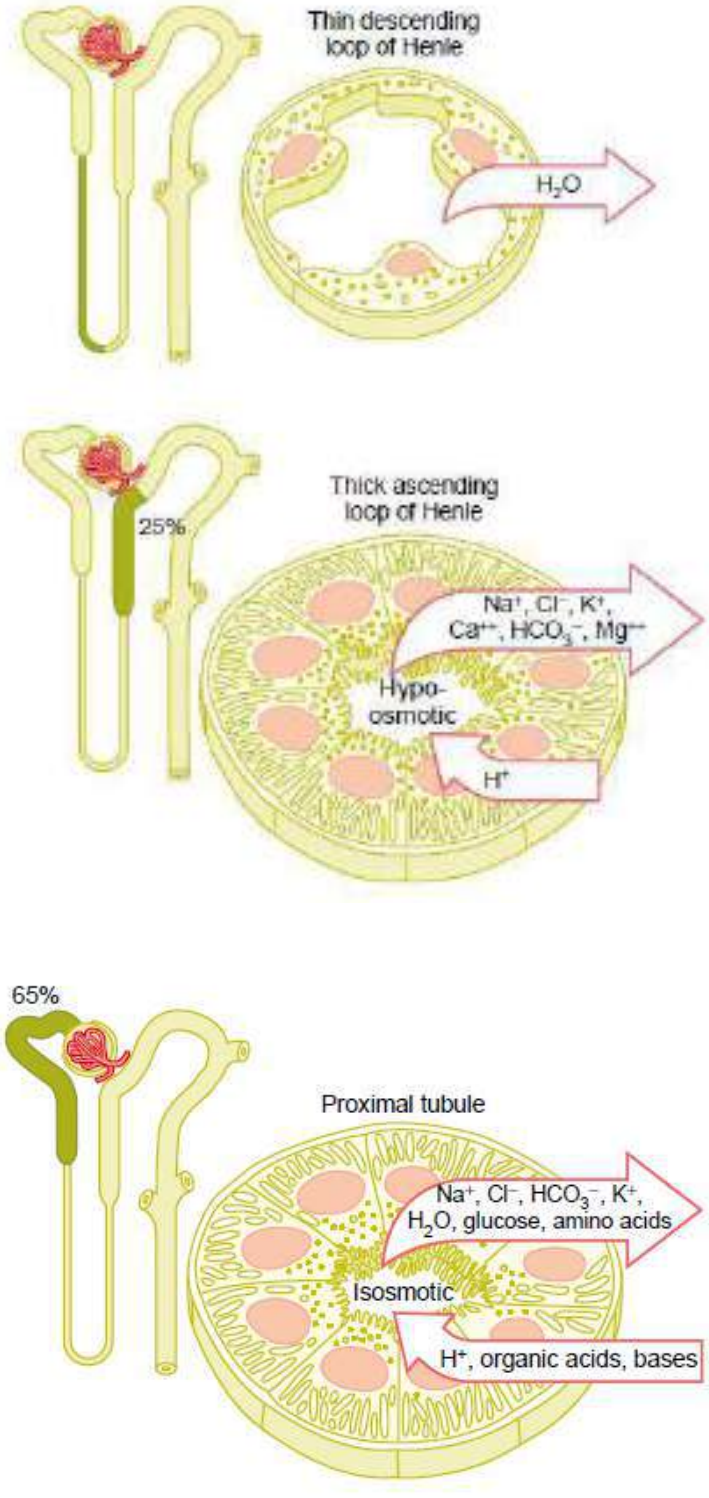
    This creates a negativity inside the cell (-70 mv)

2) At luminal border : passive

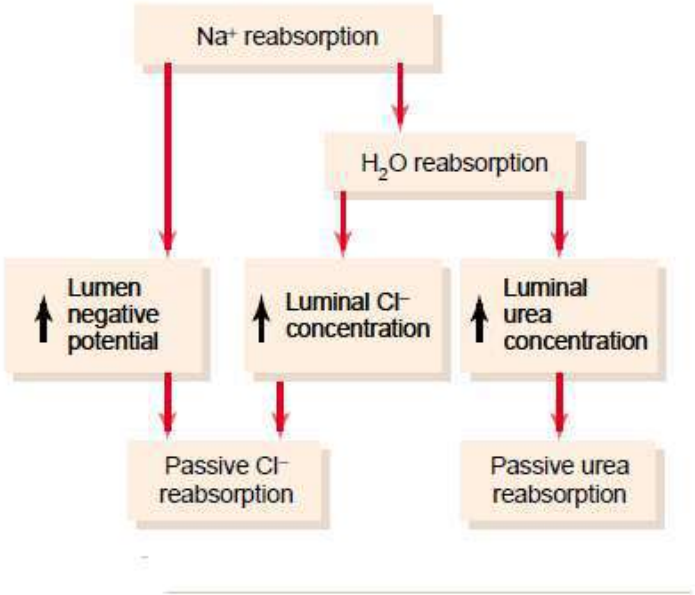
The pump creates passive diffusion of Na^+ from tubular lumen into

Tubular cells down an electrochemical gradient.

- **Sites of Na^+ reabsorption** in the nephrone :96-99% of Na^+ is reabsorbed.



Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65 per cent of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, bases, and hydrogen ions into the tubular lumen.



Mechanisms by which water, chloride, and urea reabsorption are coupled with sodium reabsorption.

1) At proximal tubules: Primary active reabsorption of Na^+

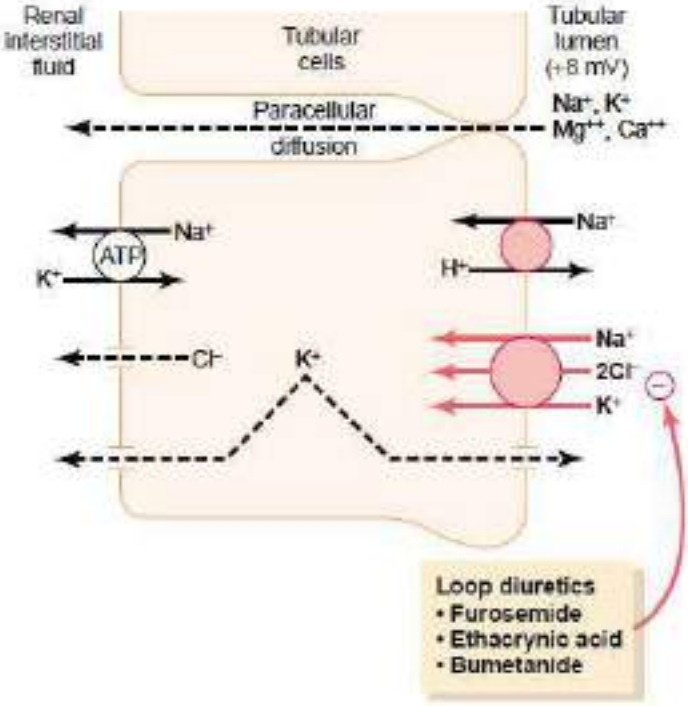
In upper half: coupled by co-transport of glucose & a..a & organic acids (lactate & citrate) & HCO_3 , and H^+ secretion by Counter transport

- in lower half : - Na^+ is reabsorbed, accompanied with:

*Cl-, HCO_3 reabsorption , passive by electrical gradient.

* H_2O reabsorption, passive by osmotic gradient

2) At loop of Henle: Only in ascending limb, 30% of filtered Na^+ is reabsorbed (No Na^+ channels in descending limb)



Mechanisms of sodium, chloride, and potassium transport in the thick ascending loop of Henle. The sodium-potassium ATPase pump in the basolateral cell membrane maintains a low intracellular sodium concentration and a negative electrical potential in the cell. The 1-sodium, 2-chloride, 1-potassium co-transporter in the luminal membrane transports these three ions from the tubular lumen into the cells, using the potential energy released by diffusion of sodium down an electrochemical gradient into the cells. Sodium is also transported into the tubular cell by sodium-hydrogen counter-transport. The positive charge (+8 mV) of the tubular lumen relative to the interstitial fluid forces cations such as Mg^{++} and Ca^{++} to diffuse from the lumen to the interstitial fluid via the paracellular pathway.

→ In the thin part, Na^+ reabsorption is limited (Passive)

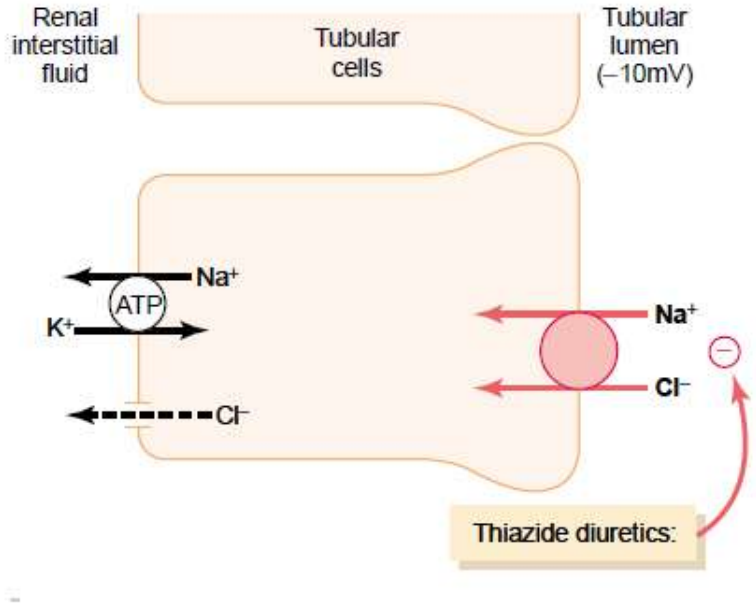
→ In the thick part, Na^+ reabsorption (25%) is active; Cl^- is secondary to it

[1 Na^+, 2Cl^-, 1K^+ (co-transport)].

3) At distal convoluted tubules + collecting tubules: 3%

- Under the control of aldosterone, variable amounts of Na^+ are reabsorbed and associated with →Cl^-, HCO_3 reabsorption passively

→ K^+, H^+ secretion (counter transport)



Mechanism of sodium chloride transport in the early distal tubule. Sodium and chloride are transported from the tubular lumen into the cell by a co-transporter that is inhibited by thiazide diuretics. Sodium is pumped out of the cell by sodium-potassium ATPase and chloride diffuses into the interstitial fluid via chloride channels.

**** Regulation of Na^+ excretion** :

(1) Rate of tubular flow & GFR :

Slow rate of flow → increase tubular reabsorption of Na^+.

As in decrease GFR which initiates tubuloglomerular feedback mechanism (as discussed before).

Increase GFR →increase Na^+ filtered-→increase Na^+ reabsorbed--→slight increase in Na^+ excretion i.e. proximal tubules reabsorb constant % of filtered load of Na^+ & H_2O.

(2) Pressure Naturesis (Effect of increased Arterial Blood Pressure "ABP" on Na^+ excretion) :

Increase ABP → increase Na^+, H_2O excretion to regulate ABP & return it to normal. It is compensatory mechanism independent of nerves or hormones.

(3) Concentration gradient:

Na^+ reabsorption has no transport maximum (Tm) in proximal convoluted tubules. So, reabsorption is determined by 2 factors:

- Concentration gradient → increase Na^+ in proximal tubules→ increase reabsorption of Na^+
- The time that the fluid remains in the tubule: The more the time, the more the reabsorption

However, in the distal tubule, Na^+ transport exhibits a transport maximum "Tm".

(4) Sympathetic stimulation: increase Na+ reabsorption

-direct on PCT & thick ascending loop of Henle

-increase renin & angiotensin II

(5) Hormones:

- **Aldosterone**: Acts on distal tubules & cortical collecting tubules
  - Increases Na^+ reabsorption, Cl^- reabsorption
  - Increases K^+ & H^+ secretion.
  - Mechanism : induces synthesis of protein that increase number of open channels in luminal border & increase Na^+--K^+ATPase at base.
- **Angiotensin II:** leads to Na^+ retention

  ++ aldosterone

  Direct effect on PCT (++ Na-K pump & H^+ pump)

  Constrict efferent arteriole (-- hydrostatic press & ++ osmotic

  Pressure of peritubular capillaries)
- **Glucocorticoids:** ↑ Na^+ reabsorption through their weak mineralocorticoid effect.

- **Sex hormones** especially Estrogen: ↑ Na^+ reabsorption as they have mineralocorticoid effect (before menses)
- **Atrial Natriuretic peptide** "ANP": Na^+ excretion

  - increase GFR by relaxation of mesangial cells & VD of Afferent arteriole & VC of efferent arteriole
  - inhibits renin secretion.
  - direct on collecting duct (inhibits Na-K^+ pump & Na^+ channels)

(6) Effect of diuretics:

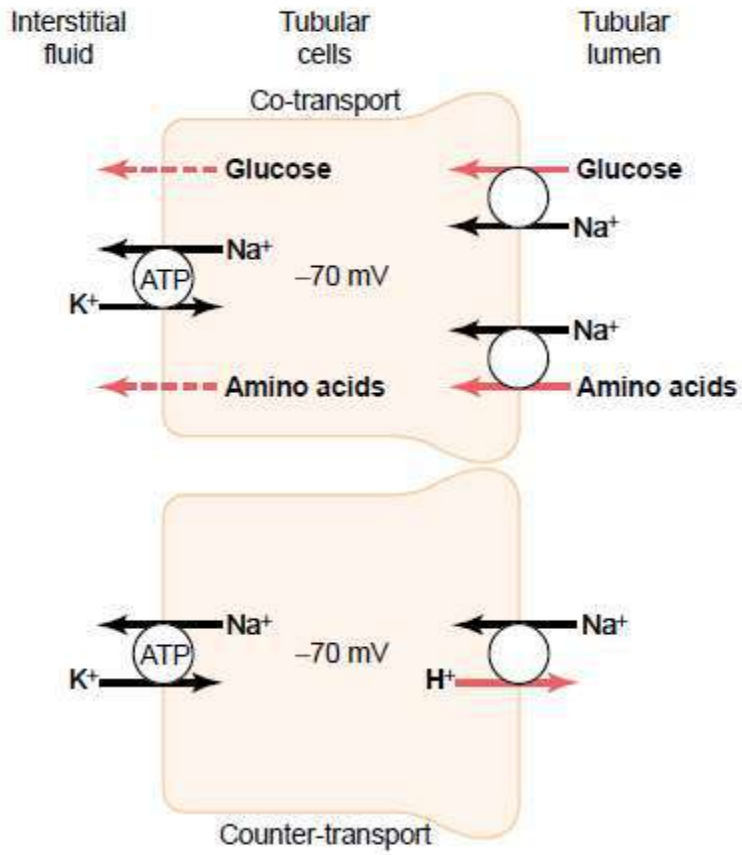
Diuretics are substances which increase urine volume

a) Osmotic diuretics: which decreases Na^+ & H_2O reabsorption at proximal convoluted tubules.

   E.g. Mannitol & glucose which are not absorbed→ they will retain water & increase volume of urine & increase excretion of Na^+ in urine→they are primary diuretics & secondary naturetic

b) Diuretic drugs (loop diuretics) : which decreases Na^+ reabsorption at thick part of loop of Henle e.g. lasix (Furosemide)→ the excreted Na^+ retains H_2O with it → They are primary naturetic & secondary diuretics
c) Diuretics that inhibit aldosterone as Spironolactone or aldactone . It decreases Na^+ reabsorption from DCT & CD → Na^+ loss & K^+ retaining (it acts on Na^+-K^+ exchange mechanism)

Glucose reabsorption



Mechanisms of secondary active transport. The upper cell shows the *co-transport* of glucose and amino acids along with sodium ions through the apical side of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The lower cell shows the *counter-transport* of hydrogen ions from the interior of the cell across the apical membrane and into the tubular lumen; movement of sodium ions into the cell, down an electrochemical gradient established by the sodium-potassium pump on the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen.

Glucose is: 1-Completely reabsorbed.

2- In proximal convoluted tubule (upper half)

3-By an active process (secondary active)

Glucose to be reabsorbed via tubular cells, it has to cross its luminal and basal borders.

(1) **At luminal border**:

- By secondary active mechanism (no energy is used directly from ATP)
- It enters the cell against concentration gradient
- A carrier (termed SGLT-2 = sodium dependant glucose transporter) binds both Na^+ & glucose at the luminal brush border where Na^+ diffuses along electrochemical gradient & glucose actively against concentration gradient.

(2) **At basal border**:

- By facilitated diffusion, passive, the glucose passes to the extra cellular fluid & blood.
- The carrier needed here is not Na^+ dependent. It is termed (GLT-2) glucose transporter.

** **Study of glucose reabsorption**:-

- **Tubular load "TL"of glucose**, is the total amount of glucose that is filtered in glomerular filtrate/min = (**125** mg/min)

"TL" = GFR X concentration of glucose/ml plasma

125 ml/min X 1 mg glucose/ml plasma [100 mg/100 ml]

- **Glucose Renal Threshold**:

  - This is the maximal concentration of glucose in plasma above which glucose appears in urine.
  - **Normal glucose plasma level = 70-110 mg%**; Up to 180 mg%, all glucose filtered is reabsorbed. The glucose appears in urine at a plasma concentration above **180 mg%** in venous blood & **200 mg %** in arterial blood.

- **Tubular Maximum of Glucose "TMG"** :

- Is the maximal amount of glucose which can be reabsorbed/min = **300** mg/min in female & **375** mg/min in male.

- Above the renal threshold, glucose excretion rises. Finally, glucose reabsorption reaches a maximum rate called Transport Maximum for glucose (TMG) when the carrier for glucose is completely saturated. TMG depends on reabsorbed power of different nephrons which depends on amount of carrier protein.

** **Glucosuria** : is appearance of glucose in urine.

Causes:

1- Diabetes Mellitus: decrease insulin→increase blood glucose above 180 mg%→increase tubular load of glucose above TMG.
2- Renal Glucosuria : This is a hereditary disease in which the number of glucose carrier decreases or the affinity of the carrier towards glucose is reduced. This lower renal threshold &TM to about 100 mg%. Thus glucosuria occurs at normal fasting glucose level
3- Other monosacchrides as galactose , xylose & fructose, when present simultaneously with glucose they depress its transport. This is called "competition for transport"
4- Oubain which block Na^+ -K^+ ATPase
5- Phlorizin which blocks sugar access to the carrier protein.

H_2O Reabsorption

About 180 liter/day of fluid filtered by both kidneys & Urine volume is about 1 liter/day. I.e.179 liter of H_2O are reabsorbed / day (99%)

H_2O reabsorption in kidney is 2 types.

	Obligatory	**Facultative**
Amount:	70%	Variable
Mechanism	secondary to solutes reabsorbed e.g.Na^+	Na^+ independent
Effect on urine	Not affect urine concentration	Can affect urine concentration
ADH	Not affect it	It depends on it

** **Reabsorption of H_2O in different tubular segments** :

(1) Proximal convoluted tubules :

- 60-70 % is obligatory reabsorbed secondary to active transport of solutes as Nacl, glucose, amino acids.
- It occurs through H_2O channels called aquaporin-1(protein in nature) located at luminal border of tubular cells of PCT.

(2) Loop of Henle:

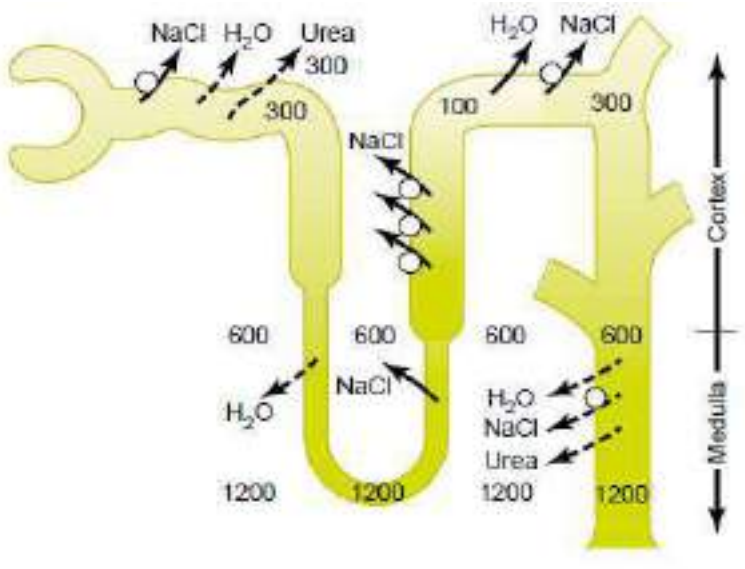
- 15% of H_2O is reabsorbed by descending limb.

(3) Distsal convoluted tubule :

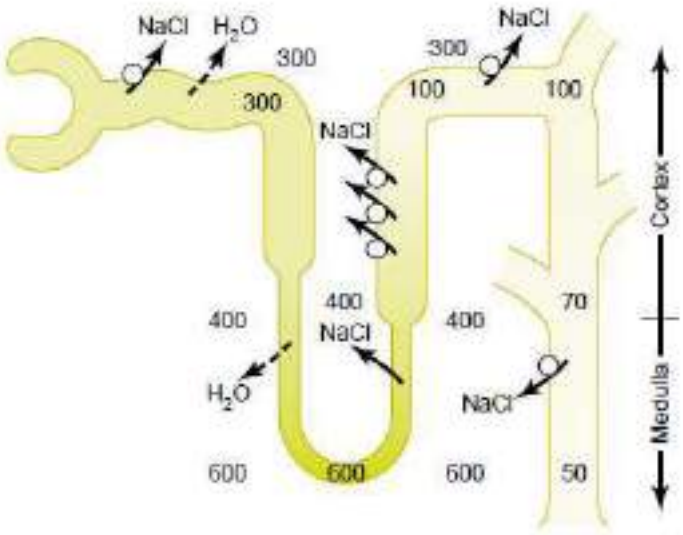
- 5% of H_2O is reabsorbed.

(4) Late distal tubule & collecting duct [cortical & medullary]:

- Under effect of antiduretic hormone (ADH)



Formation of a concentrated urine when antidiuretic hormone (ADH) levels are high. Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is absorbed from the distal tubules and collecting tubules. With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the papilla, which is about 1200 mOsm/L. (Numerical values are in milliosmoles per liter.)



Formation of a dilute urine when antidiuretic hormone (ADH) levels are very low. Note that in the ascending loop of Henle, the tubular fluid becomes very dilute. In the distal tubules and collecting tubules, the tubular fluid is further diluted by the reabsorption of sodium chloride and the failure to reabsorb water when ADH levels are very low. The failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine. (Numerical values are in milliosmoles per liter.)

- It acts on H_2O channels called aquaporin-2 located in the principal cells at luminal border.
- N.B> Aquaporin-3 is located at basolateral membrane of collecting duct for transport of urea, glycerol & water.

****Mechanism of water reabsorption** in collecting tubules depends on:

1) Counter current mechanism: done by loop of Henle-→this creates high osmotic pressure in interstitium of renal medulla which pulls water from collecting tubules.
2) Antidiuretic hormone (ADH)

Reference:

- First Aid for the Basic Sciences: Organ Systems, Third Edition Page(s) 620,622,624
- Lippincott illustrated reviews: Integrated system Page(s).268, 269,270,271,272
- Oxford Handbook for Medical Sciences Page(s). 490-492

4- Urine Concentration and Dilution & Regulation of Tubular Function

ILOs:

1. Explain the mechanisms by which the kidneys produce dilute or concentrated urine.
2. Describe the role of the countercurrent multiplier system and the countercurrent exchanger in establishing the medullary osmotic gradient.
3. Summarize the role of the distal nephron (late DCT and Collecting Duct) in regulated reabsorption and secretion.
4. Describe local (intrarenal) mechanisms that regulate tubular function.
5. Explain the role of the renal sympathetic nerves in regulating tubular function.
6. Describe the hormonal mechanisms (RAAS, Aldosterone, ADH, ANP) that regulate tubular function.

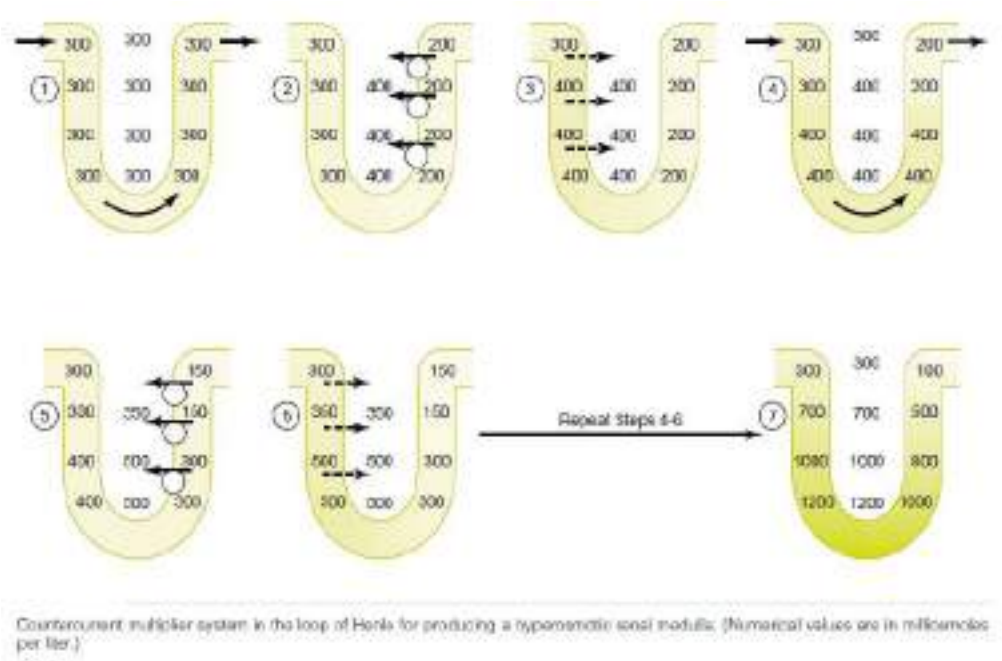
Mechanism of Urine concentration

"Counter Current Mechanism"

This involves 2 main mechanisms:

1) Counter Current multiplier mechanism of loop of Henle.
2) Counter Current exchanger mechanism of Vasa Recta.

[1] Counter Current Multiplier = function of loop of Henle.



Countercurrent multiplier system in the loop of Henle for producing a hyperosmotic renal medulla. (Numerical values are in milliosmoles per liter.)

(1)The thick part of the ascending limb:

- It is lined by cuboidal epithelium rich in mitochondria.
- Na^+ is actively pumped from the lumen to the interstitium.
- Cl^- is passively reabsorbed secondary to Na^+ (cotransport with sodium).
- [1Na - 2Cl - 1K]
- The wall is impermeable to water being lined by cuboidal epithelium.
- The result is increased osmotic pressure of the interstitial fluid while the tubular fluid delivered to distal convoluted tubules becomes hypo-osmotic.

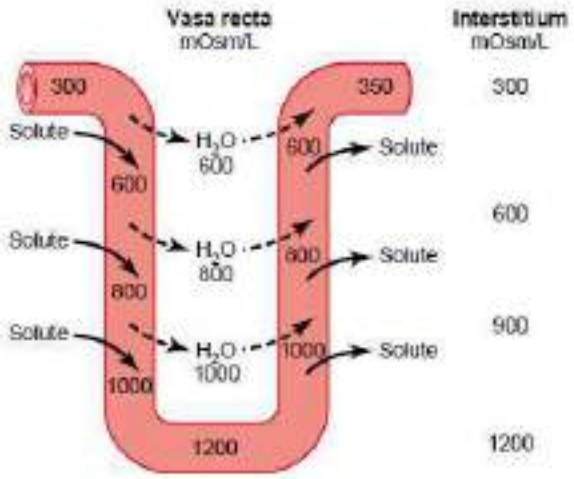
(2)The thin part of the ascending limb:

- It is permeable to Na^+ and Cl^-, so Nacl diffuses passively from the lumen to the interstitium.
- It is impermeable to water.
- The net result of the previous two steps is the creation of the high osmotic pressure in the interstitium of the renal medulla due to passive reabsorbtion of Nacl from the thin part and active reabsorbtion of Nacl from the thick part of the ascending limb.

(3)The descending limb :

- It is lined by simple squamous epithelium.
- It is relatively impermeable to Nacl and urea.
- It is freely permeable to water which diffuses from the lumen to the interstitium under the effect of hypertonic interstitium.
- The result is that the fluid passing down the descending limb becomes more and more hypertonic until it reaches the maximum concentration at the tip of the loop (1200 m.osmole)

Vasa Recta as Counter-Current Exchanger:



Countercurrent exchange in the vasa recta. Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood. In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid and water diffuses back into the vasa recta. Large amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries. (Numerical values are in milliosmoles per liter.)

(A) **Descending limb of Vasa Recta** :

1- Nacl and urea diffuses from the interstitial fluid to the blood along concentration gradient.

2- H_2O diffuses from blood to the interstitium as :

(a) The interstitial fluid is hyperosmotic.

(b) The capillary blood pressure (35 mmHg) is higher than the osmotic pressure of plasma proteins (25 mmHg).

Net result: blood now is hypertonic at the tip of vasa recta.

(B) **Ascending limb of Vasa Recta** :

1- Nacl and urea diffuse from the blood to the interstitium as the blood now is more concentrated than the interstitium

2- However, water coming from collecting tubules, descending limb of vasa recta and loop of Henle diffuse from the interstitium to the blood of the general circulation as → a) blood becomes more concentrated than interstitium b) Plasma protein becomes more concentrated → higher osmotic pressure than capillary pressure.

3- The net result: Solutes (Nacl and urea tend to recirculate in the medullary interstitium →(Nacl and urea cycle) while water tends to leave the interstitium and passes to the general circulation. This maintains the hyperosmolarity of the medullary interstitium.

** Thus, the Vasa recta perform two important functions:

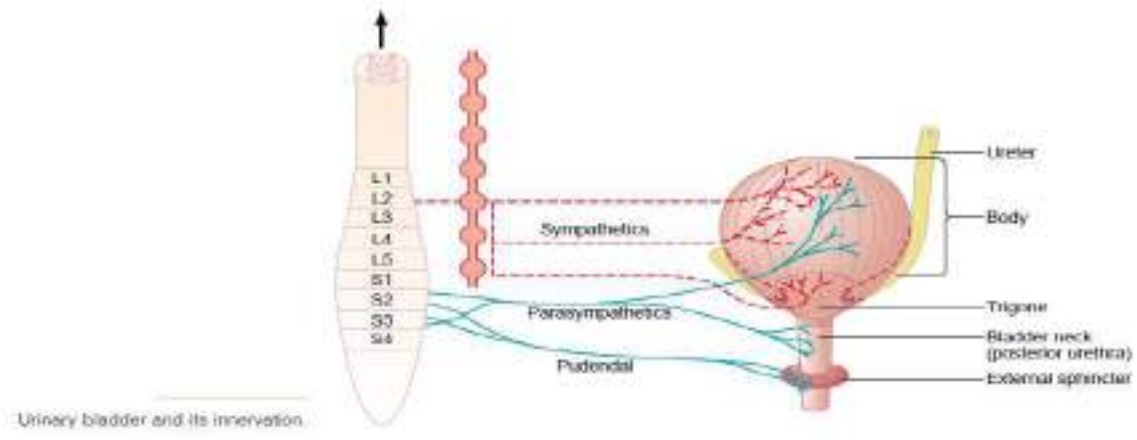
1- Trapping solutes (Nacl and urea) in the renal medulla.
2- Removing the absorbed water from the medulla to the general circulation.

The role of urea in concentration of urine:

Absorption of urea in the medullary collecting duct (which is highly permeable to urea in the presence of ADH) , adds much to the osmolarity of lower medulla, which in turn increases the rate of H2O reabsorption by descending limb of loop of Henle so increasing NacL concentration in the tubular fluid that reach ascending limb.

Urea diffuses from medullary interstitium to the thin ascending limb and to the descending limb of L.H till reaches inner medullary collecting duct to be reabsorbed again by ADH which is known as **urea trapping** or **urea cycling**.

Micturition



Urinary bladder and its innervation

Innervation of urinary bladder:

	Parasympathetic	Sympathetic	Somatic
Origin	S 2, 3, 4	L 1, 2, 3	S 1, 2
Afferent	-Detection of degree of bladder stretch	-Sensation of fullness -Pain sensation due to overstretch	Stretch receptors in posterior urethra
Efferent	Pelvic nerve	Lesser splanchnic nerve→ presacral → hypogastric nerve.	Pudendal nerve
Ganglion	Terminal	Inf. Mesenteric	
Function	Contraction of wall & relaxation of internal sphincter.	Relaxation of wall & contraction of internal sphincter	Voluntary contraction or relaxation of external urethral sphincter.
Role in micturition	Essential for reflex micturition	No role It prevents semen reflux into bladder during ejaculation	Voluntary control of micturition

Reference:

- First Aid for the basic Sciences: organ systems, Thirdedition, Page(s) 624,625,626,630
- Lippincott illustrated reviews: Integrated system Page(s).265,266,267,272,273

5- Renal regulation of acid-base balance and the micturition reflex

ILOs:

1. State the normal range for plasma pH.
2. Explain the kidney's role in the daily excretion of metabolic acid.
3. Outline the body's three major defense mechanisms (chemical buffers, respiratory, renal) against pH changes.
4. Describe the mechanisms of H+ secretion and bicarbonate handling in different nephron segments.

Acid Base balance:

Regulation of H+ concentration is very important because it affects the function of all enzyme systems of the body, as any change in H+ concentration may alter most of cellular functions.

Normal H+ concentration = 0.00004 m Eq / L

PH= - log H^+= log 1/ [H^+]

Normal PH = 7.4

Sources of H+:

1- Ingested: Some H+ is ingested in food.

2- Metabolism of food:

a-Metabolism of carbohydrates: generate volatile acids

$CHO + O_2 \rightarrow CO_2 + H_2O$.

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3$

b-Metabolism of proteins and lipids: give fixed acids (H_2SO_4 & H_3PO_4)

c-Lactic acids in muscles in sever exercise.

d-Ketoacids from fat metabolism in diabetes mellitus.

H+ concentration is kept **constant by 3 mechanisms**:

[1] Chemical buffers.

[2] Role of lungs.

[3] Role of kidneys.

[1] Chemical buffers

They are chemical compounds which prevent marked change in H^+ concentration of solutions when acids or bases are added.

Most buffers consist of weak acid & its salt with a base.

Handerson-Hasselbachs equation: express the relation between $[H^+]$ and the ratio of buffer members in the solution.

$$pH = pK + \frac{\log HCO_3}{CO_2}$$

*__The effectiveness of a buffer system depends on :__

1- The pH which the buffer has to preserve. A buffer is most effective if its pK is equal to the pH which it preserves. The pK of the buffer will be equal to pH when the ratio of the salt to the acid is equal to 1 (log 1 is zero).

2- The concentration of the buffer members.

(A) Bicarbonate buffer: it consists of H_2CO_3 & HCO_3

- It is not powerful buffer because:
- Its pK = 6.1 i.e. away from pH of blood (7.4)
- Its concentration is not great (24 mmol/L)

- But it is very effective buffer because its two components can be regulated: H_2CO_3 by lungs & HCO_3 by kidneys.

(B) <u>Phosphate buffer</u> : it consists of H_2PO_4 & HPO_4

- Its pK is 6.8 which is near to pH of plasma.
- Its concentration is low.
- The net result is that phosphate buffer is not a strong buffer.
- But it is **very important** at two sites in the body:

    1) Intracellular fluid because of its high concentration than in extracellular fluid and pH of intracellular fluid is 7.
    2) Kidney tubules ,it is greatly concentrated & renal tubular fluid is more acidic.

(C) <u>Protein buffer</u>:

- In pH of blood (7.4), the blood proteins act as weak acids.
- Plasma proteins (its conc. = 7 gm %) are stronger buffers than bicarbonate system because of its large amount, they buffer 1/6 of the blood.
- Hemoglobin is the strongest blood buffer system. Its power is six times that of plasma proteins & more than all the rest of the blood buffers together.
- It plays the most important role in buffering CO_2 (Chloride shift phenomenon).
- Tissue proteins are the strongest chemical buffers in the body due to their huge amount.

<u>The principal buffers in body fluids</u> are:

- In blood: bicarbonate , protein & hemoglobin.
- In interstitial fluid: bicarbonate.
- In intracellular fluid : protein & phosphate.

[2] Role of respiration:

The respiratory system controls pH of body fluids by controlling the CO_2 tension (PCO_2) of the blood.

- From Handerson Hasselbach equation: $pH = pK + \log \frac{HCO_3}{CO_2}$

It is observed that, increased PCO_2 will decrease the pH (it becomes acidic) & vice versa.

- In case of acidosis, the peripheral chemoreceptors are stimulated to send impulses to stimulate the respiratory center in the medulla, so hyperventilation occurs, CO_2 is washed and the pH will increase to normal.
- In case of alkalosis, the peripheral chemoreceptors stop sending impulses, the respiratory center is depressed (hypoventilation), PCO_2 is increased and the pH of blood is decreased to normal.
- The ability of respiration to regulate the pH is limited because the resulting changes in CO_2 tension have the opposite effect on respiration.
- Thus, the respiratory system acts as a feedback regulation system control of pH. It responds to pH changes within minutes (15 minutes). It is 2 times as powerful as all chemical buffers combined. It is a moderate regulator with moderate efficiency because its ability is limited.

[3] Role of kidney:

It takes hours or days (slow) to correct pH.

In general, the kidneys can excrete variable amounts of H^+ in urine. According to blood pH, acidic or alkaline urine is excreted.

In acidosis: increased H^+ excretion & urine is acidic. Minimum pH =4.5

In alkalosis: less H^+ excreted & urine is alkaline. Maximum pH= 8.

Normally, the pH of urine is 6 (acidic).

The principal mechanisms are:

[A] H^+ secretion against bicarbonate Reabsorption.

[B] Production of titeratable acid & bicarbonate regeneration.

[C]Excretion of Ammonia.

[A]H^+ secretion:

1-Secondary active secretion in proximal convoluted tubules (85%) & thick ascending loop of Henle (10%).

2-Primary active secretion in late tubules (distal tubules & cortical collecting tubules) (5%).

1-Secondary active secretion:

-In tubular cells, CO_2 reacts with water (in presence of carbonic anhydrase) to form carbonic acid.

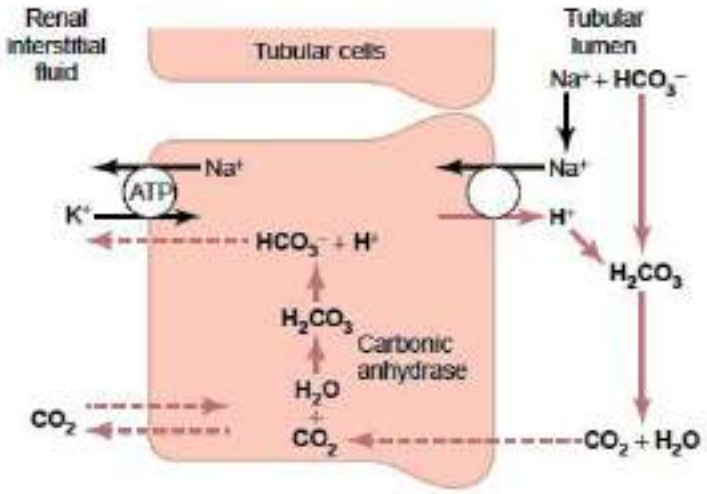
-Carbonic acid dissociates to H^+ & HCO_3

-HCO_3 is passively reabsorbed to blood (85 % in proximal convoluted tubules & 10 % in ascending loop of Henle)

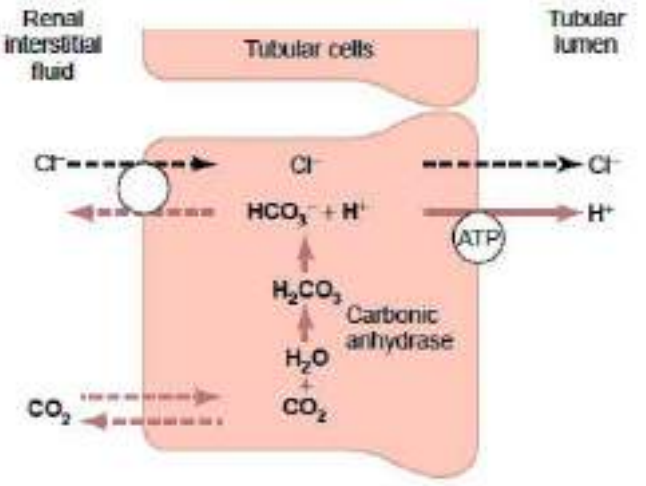
-H^+ is actively secreted in exchange with Na^+ (Na^+-H^+ counter transport)

-It uses energy provided by gradient for Na^+ movement across luminal border.

-In lumen of tubules: H^+ reacts with filtered bicarbonate to form carbonic acid which dissociates to CO_2 & H_2O. CO_2 diffuses into the cell.



2-**Primary active secretion**:



-In tubular cells, CO_2 reacts with water (in presence of carbonic anhydrase) to form carbonic acid.

-Carbonic acid dissociates to H^+ & HCO_3

-HCO_3 is passively reabsorbed to blood.

-H^+ is actively secreted by specific transport protein (H^+-ATP ase).

- In the lumen of the tubules: H^+ is buffered by phosphate buffer & NH_3

- It is stimulated by aldosterone.

Factors affecting acid secretion:

1/ aldosterone: stimulates H^+ & K^+ secretion

2/ intracellular CO_2

3/K^+ concentration intracellular: low K^+→increase H^+ secretion

[B] **Production of titeratable acids & bicarbonate regeneration**:

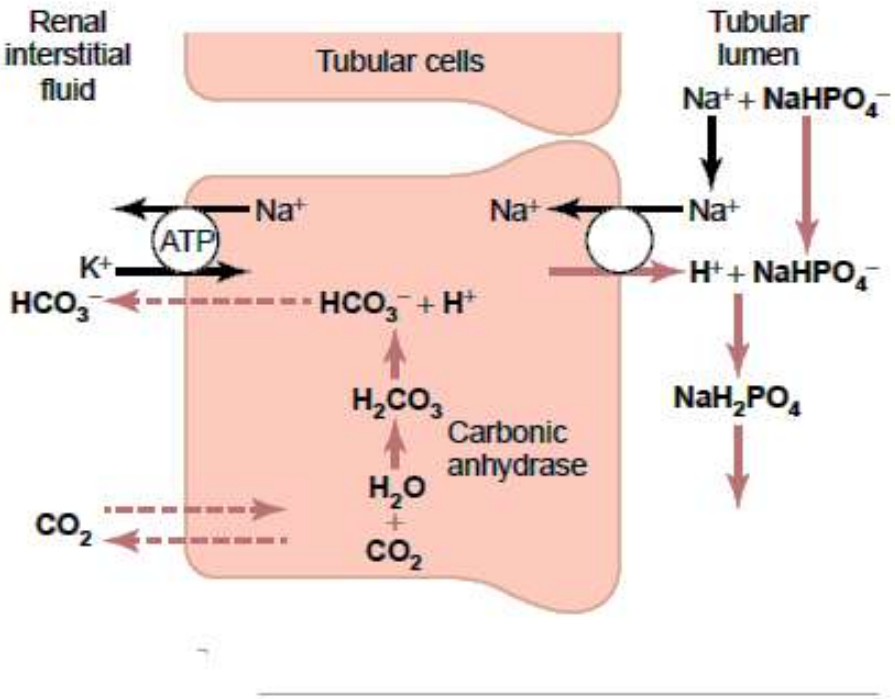
-It occurs in distal tubules & collecting ducts.

-The tubular cells continue to secret H^+ as explained above.

-In the tubular lumen: H^+ reacts with filtered sodium monohydrogen phosphate (Na_2HPO_4) to form sodium dihydrogen phosphate (NaH_2PO_4) which is termed titeratable acid.

-Thus for each molecule of titeratable acid formed in urine, one HCO_3 is generated and added to blood.

-20 meq/day titeratable acid are excreted in urine.



Buffering of secreted hydrogen ions by filtered phosphate ($NaHPO_4^-$). Note that a new bicarbonate ion is returned to the blood for each $NaHPO_4^-$ that reacts with a secreted hydrogen ion.

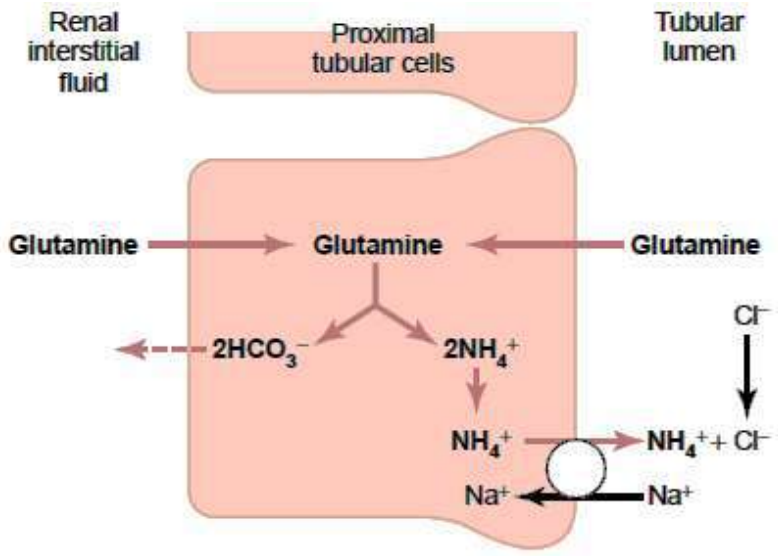
[C]Excretion of Ammonium in proximal convoluted tubules, loop of Henle & distal convoluted tubules and excretion of ammonia in collecting duct:

{1} Excretion of ammonium (NH_4) in PCT, loop of Henle & DCT: -

Ammonium is synthesized in these tubules form glutamine.

-2 NH_4 + 2 HCO_3 are formed from each glutamine molecule.

-NH_4 is transported into tubular fluid by counter transport in exchange with Na_+.



{2}Excretion of ammonia (NH_3) in collecting duct:

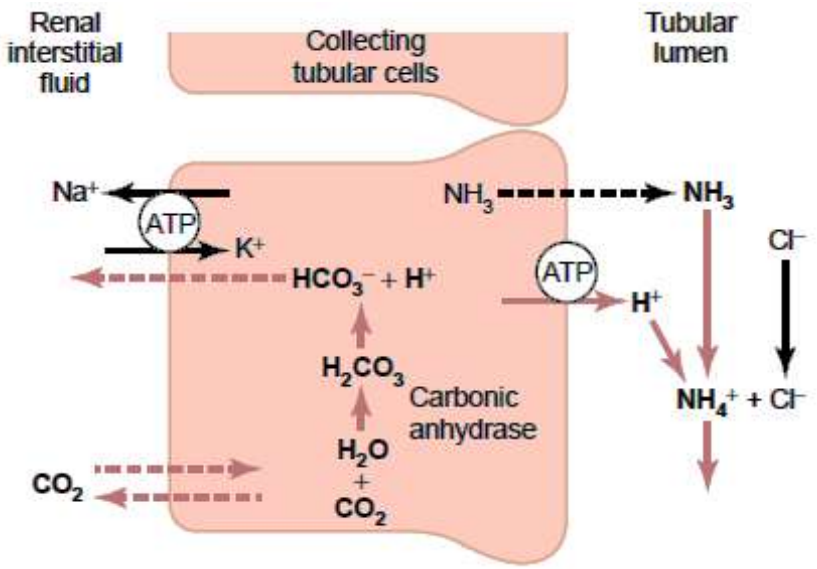
-NH_3 is produced by tubular cells from glutamine, glutamic acid, glycine & alanine.

-NH_3 diffuses rapidly to the lumen (fat soluble)

-In the lumen, it acts as a H^+ acceptor and combines with extra H^+ forming NH_4 (ammonium ions). This mechanism is called **diffusing trapping**.

-NH_4 combines with cl^- to form NH_4cl which is slightly acidic allowing excretion of huge amount of H+ without much change in pH of urine (So, NH_4 is the best mechanism in treatment of chronic acidosis).

-For each H^+ excreted, one $NaHCO_3$ is added to blood.



Clinical abnormalities of acid base homeostasis:

$$H^+ \propto \frac{CO_2}{HCO_3}$$

Life is only possible within a pH range of 7-7.8

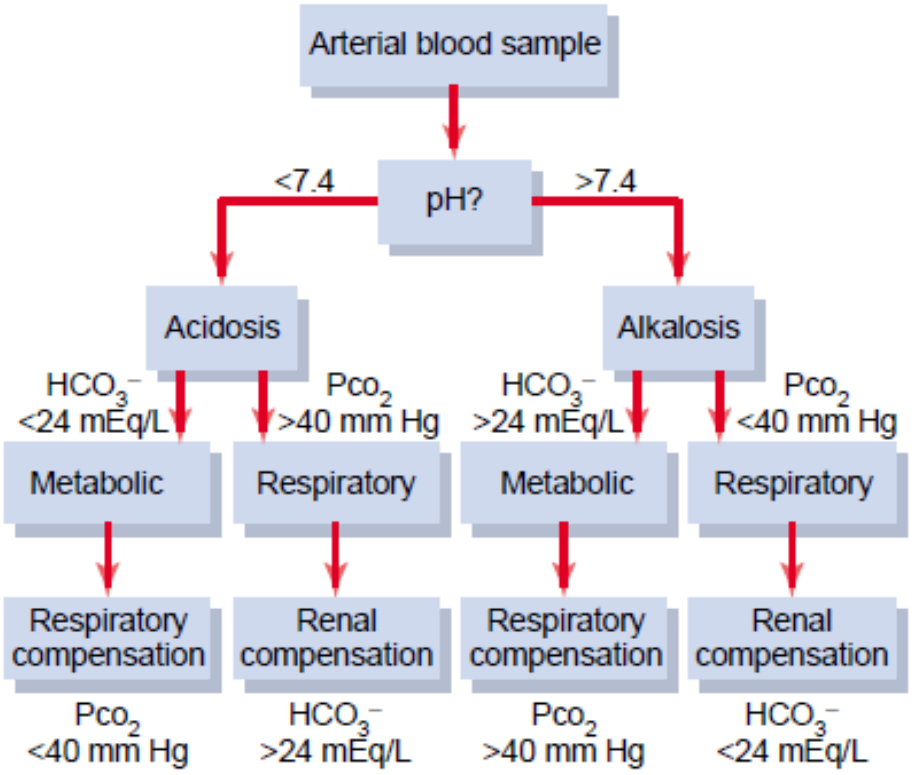
-Acidosis (decrease pH): it may be due to:

1-increased CO_2 (respiratory acidosis)

2-decreased HCO_3 (metabolic acidosis)

-**Alkalosis (increase pH)**: it may be due to :

1- decreased CO_2 (respiratory alkalosis)
2- Increased HCO_3 (metabolic alkalosis).



Analysis of simple acid-base disorders. If the compensatory responses are markedly different from those shown at the bottom of the figure, one should suspect a mixed acid-base disorder.

	Acidosis		**Alkalosis**	
Cause	<u>Respiratory</u> - Retention of CO_2 e.g. hypoventilation - Respiratory center depression - Obstructive lung diseases	<u>Metabolic</u> Decreased HCO_3 e.g. diarrhea - Renal failure: kidney cannot excrete normal amount of acids formed by metabolism	<u>Respiratory</u> Excessive loss of CO_2 due to hyperventilation: (voluntary,hysterical)high altitudes-chemical poisoning	<u>Metabolic</u> Increased HCO_3 due to excess fixed base or loss of acids as in: vomiting(loss of gastric Hcl)- excess intake of

	- Restrictive lung diseases	- Diabetes: increase ketone body formation due to fat oxidation. - Muscle exercise: increase lactic acid		alkali to treat peptic ulcer-diuretics which increase H^+ secretion
Compensation	1-Chemical buffers 2-Respiration : no role 3-Kidney:Increase HCO_3 reabsorption - Increase titeratable acids - Increase NH4 formation	1-Chemical buffers 2-Respiration: stimulated to wash CO_2 3-Kidney: increase HCO_3 reabsorption.	1-Chemical buffers 2-Respiration: drop of PCO_2 limits hyperventilation 3-Kidney: excretion of HCO_3 Decrease H^+ secretion	1-Chemical buffers 2-Respiration depression of respiration 3-Kidney: excretion of excess HCO_3
Signs & symptoms	Cyanosis, dyspnea & coma	Deep & rapid respiration & coma	Stimulated respiration(cause) Tetany due to over excitability	Shallow respiration (compensation) Tetany, apathy & confusion

Sodium (Na+) Balance

- **Functions of sodium:**

(1) Na+ is the main cation in ECF. It regulates volume , osmolarity of ECF.
(2) Maintenance of blood volume and arterial blood pressure
(3) Tissue excitability
(4) Helps glucose transport in the intestine and kidney.
(5) Formation of ECF buffers.
(6) Concentration of urine (Na+ is main solute in renal medullary interstitium).

- **Disturbance of sodium in the body**:

- **Hyponatremia (Na+ depletion)**: $Na^+ < 135$ mEq/L

Causes: decrease Na^+ intake – excess Na^+ loss – decrease water excretion.

- **Manifestations**:

(1) Hypotension leads to -→tachycardia, fainting, shock

(2) Loss of skin elasticity.

(3) Muscle cramps

(4) Weakness, apathy, lassitude.

(5) Anorexia, nausea, vomiting.

(6) Confusion, coma & convulsions.

- **Treatment**:

1-if due to Na^+ loss →Na administration oral with glucose or intravenous isotonic solution.

2-if due to excess water -→restrict water intake & treat the cause.

- **Hypernatremia (Na $^{+}$ retention)**:

- **Causes**: decrease water intake & increase water loss & failure to excrete Na^{+}

- **Manifestations**:

(1)Generalized oedema: in adult if more than 4 liter accumulation.

(2)Hypertension.

(3)Thirst, weakness & lethargy.

(4)Urine: scanty & concentrated except diabetes insipidus.

(5)Plasma: increase Na^{+} concentration & osmolarity.

- **Treatment:**

1- Replacement of lost water by mouth or i.v.

2- ADH in neurogenic diabetes insipidus.

3-Reduction of Na intake

4-Treat the cause.

Potassium (K^{+}) balance

- **Functions of potassium**:

(1) cell volume regulation (main intercellular cation)
(2) cell growth (protein & DNA synthesis)
(3) Optimal environment for cellular enzymes.
(4) Resting membrane potential.

- **Disturbances of K^{+} concentration**:

- **Hypokalemia:** $K^{+} < 3.5$ mEq/L

- **Causes:**

1-Vomiting – diarrhea- diuretics.

2-Aspiration of gastrointestinal contents.

3-Aldosterone excess

4-Metabolic alkalosis.

- **Symptoms:**

1-Muscle weakness, fatigue, paralysis due to hyperpolarization of nerve & muscle.

2-GIT symptoms : nausea, vomiting, intestinal distension (paralytic ileus).

3-Renal damage.

4-Decrease mentality.

- **Treatment:** K^+ rich diet –K^+ tablets or injection.

➢ **Hyperkalemia** : K^+ >5 mEq/L

- **Causes:** Loss of cellular K^+ and decrease renal function.

1-Shock: K^+ loss from cells due to ischemia & decrease renal flow.

2-Hemolysis of RBCs.

3-Chemotheraby

4-Crush injury: damage cells & decrease renal functions due to myoglobin precipitation.

5-Terminal renal failure.

6-Rise of plasma osmolarity: water diffuses out of cells & intracellular K+

- **Symptoms:**

1-Weakness of muscles & paralysis: permanent depolarization.

2-Cardiac arrhythmia & arrest.

3-ECG changes: Tall peaked T

Prolongation of QRS

Ventricular arrhythmia.

- **Treatment:**

1-Insulin injection

2-Bicarbonate.

Reference:

- First Aid for the basic Sciences: organ systems, Third edition, Page(s) 630-634
- Oxford Hand Book For Medical Sciences Page(s). 502,503,504,505
- Lippincott illustrated reviews: Integrated system p 277-278, Page(s) 282-283

Part 3
Histology and cell biology

Lecture (1)

Histology Of the Kidney (1)

ILOs:

1- Describe the histological structure of the kidney; medullary and cortical organization.

2- Describe the uriniferous tubules (structural units).

3- Discriminate the different parts of the nephron (functional units)

The urinary system consists of the paired **kidneys**; paired **ureters**, which lead from the kidneys to the **urinary bladder**; and the **urethra**, which leads from the bladder to the exterior of the body.

The histological structure of the kidney

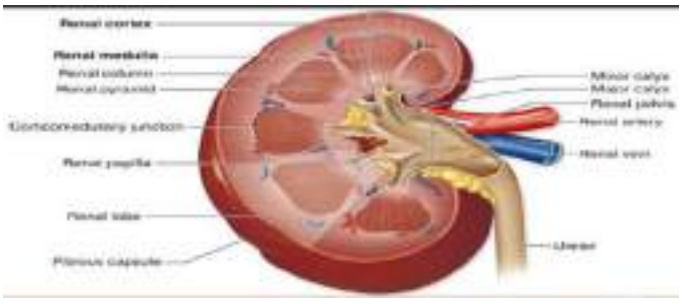
Anatomical structure:

The **kidneys** are large, reddish, bean-shaped organs located on either side of the spinal column in the retroperitoneal space of the posterior abdominal cavity.

They extend from the 12th thoracic to the 3rd lumbar vertebrae, with the right kidney positioned slightly lower.

Examination with the naked eye of a fresh, hemisected kidney reveals that its substance can be divided into two distinct regions:

- Cortex, the outer reddish-brown part
- Medulla, the much lighter colored inner part.



L.M :

Each kidney is surrounded by a thin fibrous connective tissue capsule weakly attached to the surface of the kidney.

The capsule consists of two distinct layers:

1-an outer layer of fibroblasts and collagen fibers

2- an inner layer with a cellular component of myofibroblasts that becomes continuous with the connective tissue forming the walls of the calyces and renal pelvis.

The interstitial connective tissue is scanty.

Each kidney is bean-shaped, with a concave hilum where the ureter and the renal artery and veins enter.

The ureter divides and subdivides into several major and minor calyces, around which is located the renal sinus containing adipose tissue.

The parenchyma:

Formed of an outer renal cortex with many round corpuscles and tubules cross sections, and an inner renal medulla consisting mostly of aligned linear tubules and ducts.

The renal medulla in humans consists of 8–15 conical structures called **renal pyramids,** all with their bases meeting the cortex (at the corticomedullary junction) and separated from each other by extensions of the cortex called **renal columns**.

Each pyramid plus the cortical tissue at its base and extending along its sides constitutes a **renal lobe**.

Parallel ducts and tubules extending from the medulla into the cortex comprise the **medullary rays**; these plus their associated cortical tissue are considered **renal lobules**.

The tip of each pyramid, called the **renal papilla**, projects into **a minor calyx** that collects urine formed by tubules in one renal lobe.

Each kidney contains 1–1.3 million functional units called **nephrons**.

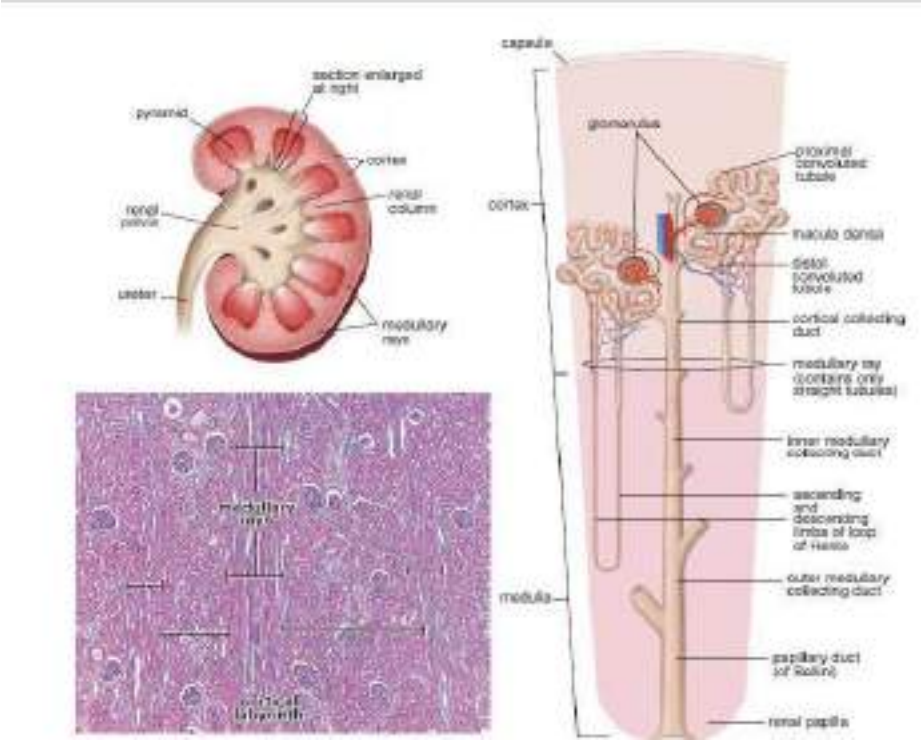
Each nephron consists of : a renal corpuscle and a long, simple epithelial renal tubule with three main parts along its length.

The nephron is a tube about 55 mm in length in the human kidney.

The number of nephrons decreases slightly in older adults, a process accelerated by high blood pressure.

Cortical nephrons are located almost completely in the cortex while juxtamedullary nephrons (about one-seventh of the total nephrons) lie close to the medulla and have long loops of Henle.

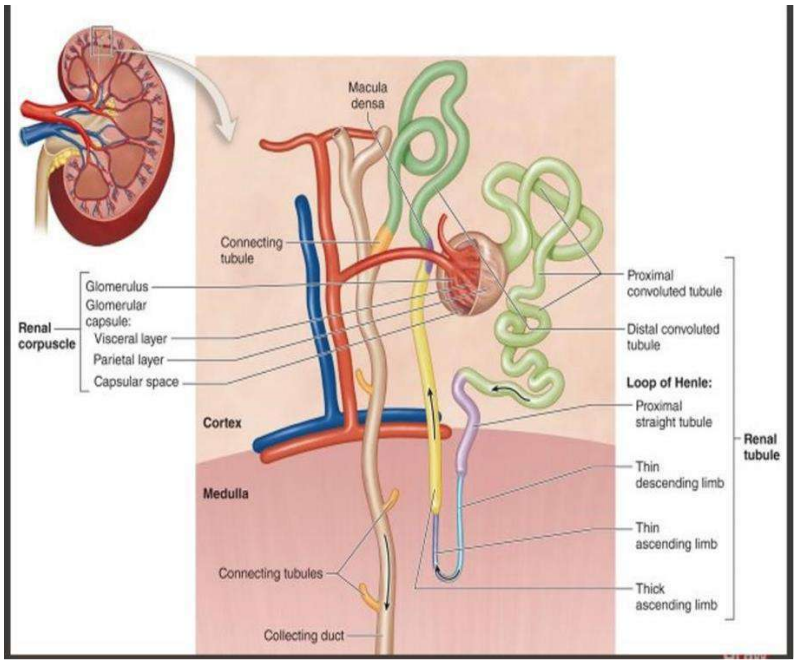
If a kidney is donated for transplant (unilateral nephrectomy), the remaining kidney undergoes compensatory growth with cellular hypertrophy in the proximal parts of the nephron tubules and an increase in the rate of filtration, which allows normal renal function**.**



Nephron:

The major divisions of each nephron are:

Renal corpuscle; Proximal tubule; Loop of Henle; Distal tubule; and Connecting tubule. Connecting tubules from several nephrons merge to form collecting tubules that then merge as larger collecting ducts. These converge in the renal papilla, where they deliver urine to a minor calyx.



Renal Corpuscles:

The renal corpuscle is the initial dilated part of the nephron enclosing a tuft of capillary loops. It is the site of blood filtration, always located in the cortex, about 200 µm in diameter. It consists of a tuft of glomerular capillaries (the glomerulus) surrounded by a double-walled epithelial capsule called the glomerular (Bowman) capsule. It has two poles; a vascular pole & a urinary one.

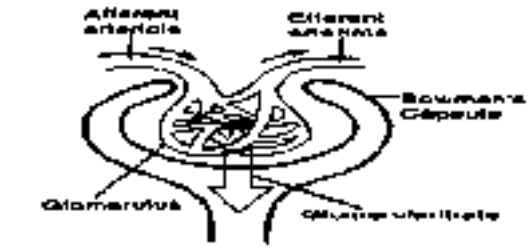


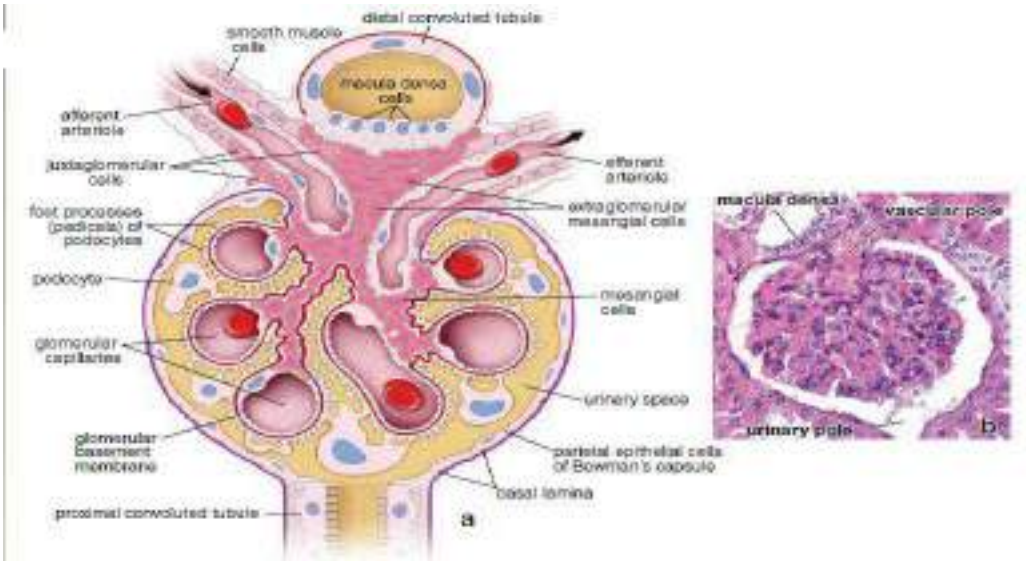
Fig. 4.8 Diagrammatic sketch of a malpighian capsule (Bowman's capsule + glomerulus)

Bowman's Capsule:

*It is a double-walled cup, formed of a parietal and a visceral layer separated by Bowman's space or capsular space, which is continuous with the lumen of the renal tubule.

***The outer parietal layer** of a glomerular capsule consists of a simple squamous epithelium supported externally by a basal lamina.

***The visceral layer** consists of unusual stellate epithelial cells called **podocytes**. From the cell body of each podocyte several primary processes extend and curve around a length of glomerular capillary.



Podocytes:

Each primary process gives rise to many parallel, interdigitating secondary processes or pedicels. Podocyte foot processes are contractile (contain actin and myosin). They are connected to each other by the slit diaphragm and to the basal lamina.

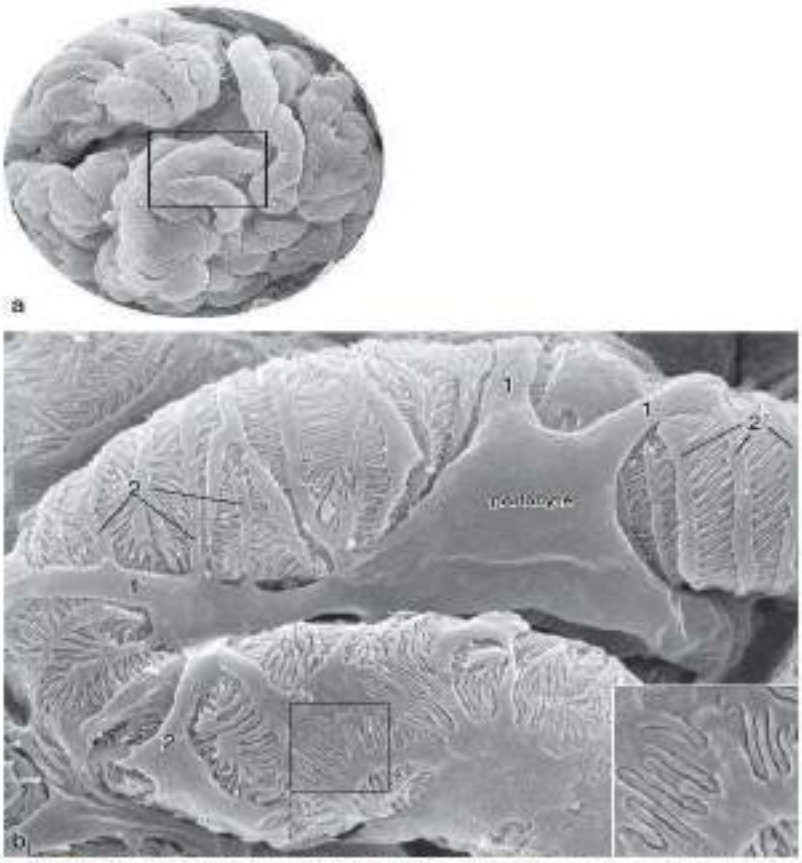


FIGURE 20.12 A Scanning electron micrograph of a glomerulus. a Low-magnification image revealing the tortuous course of the

The slit diaphragm molecular complex is associated with the actin cytoskeleton. Alterations in composition and/or arrangement of these complexes are found in many forms of human and experimental diseases.

*The pedicels cover much of the capillary surface, in direct contact with the basal lamina. Between the interdigitating pedicels are elongated spaces or filtration slit pores (25–30 nm wide) spanned by zipper-like slit diaphragms.

***Slit diaphragms** are specialized occluding junctions composed of proteins, glycoproteins, and proteoglycans important for renal function. These structures carry a negatively charged surface.

Glomerular Capillaries:

*Highly fenestrated endothelial cells located between two arterioles (afferent and efferent), allowing increased hydrostatic pressure favoring plasma movement across the glomerular filter.

*Between endothelial cells and podocytes is a thick (300–360 nm) glomerular basement membrane (GBM), formed by fusion of their basal laminae.

*This membrane is the most substantial part of the filtration barrier (that separates the blood in the capillary lumen from the capsular space) and is formed by fusion of the capillary- and podocyte-basal laminae.
*Laminin and fibronectin in this fused basement membrane bind integrins of both the podocyte and endothelial cell membranes with the meshwork of cross-linked type IV collagen.

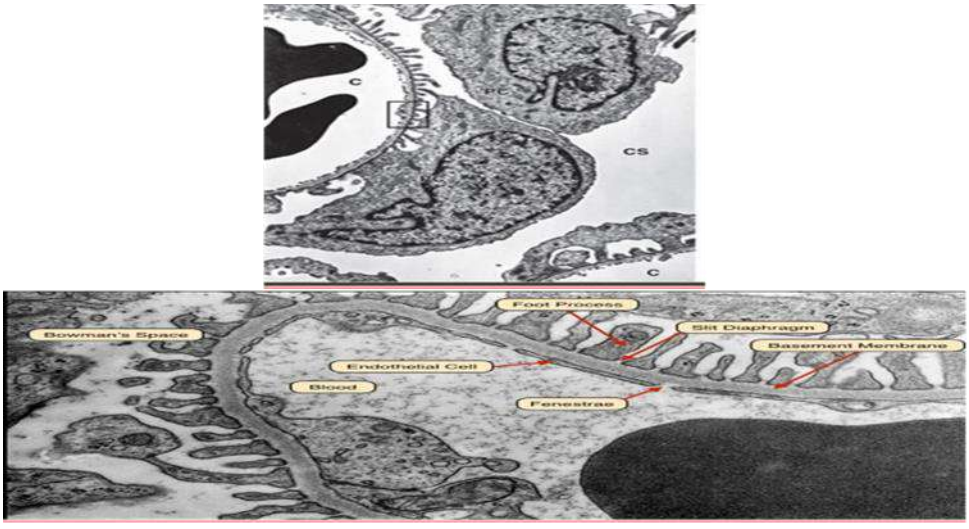
The Glomerular Filtration Barrier consists of:

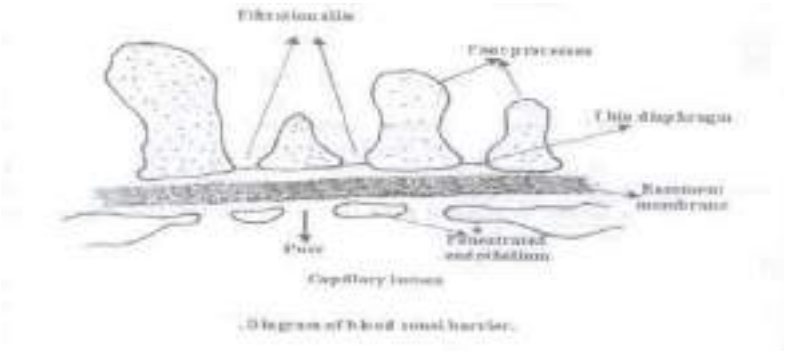
1. Fenestrated capillary endothelium

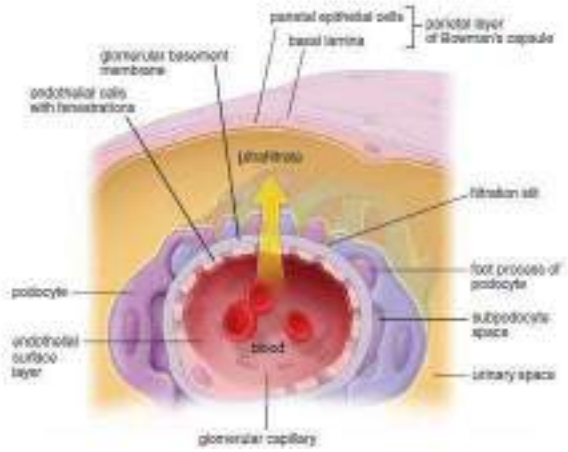
2. Glomerular basement membrane (GBM) the major component of the filter formed by fusion of the basal laminae of a podocyte and a capillary endothelial cell

3. Filtration slit diaphragms between podocytic pedicels.

Fenestrations block the exit of cells, but allow free flow of plasma. The shared basal lamina of podocytes and endothelium constitutes the first, coarser filtration barrier; it blocks the passage of molecules larger than 70 kD. The thin diaphragms covering the slit openings between the podocyte foot processes constitute a more selective filter.







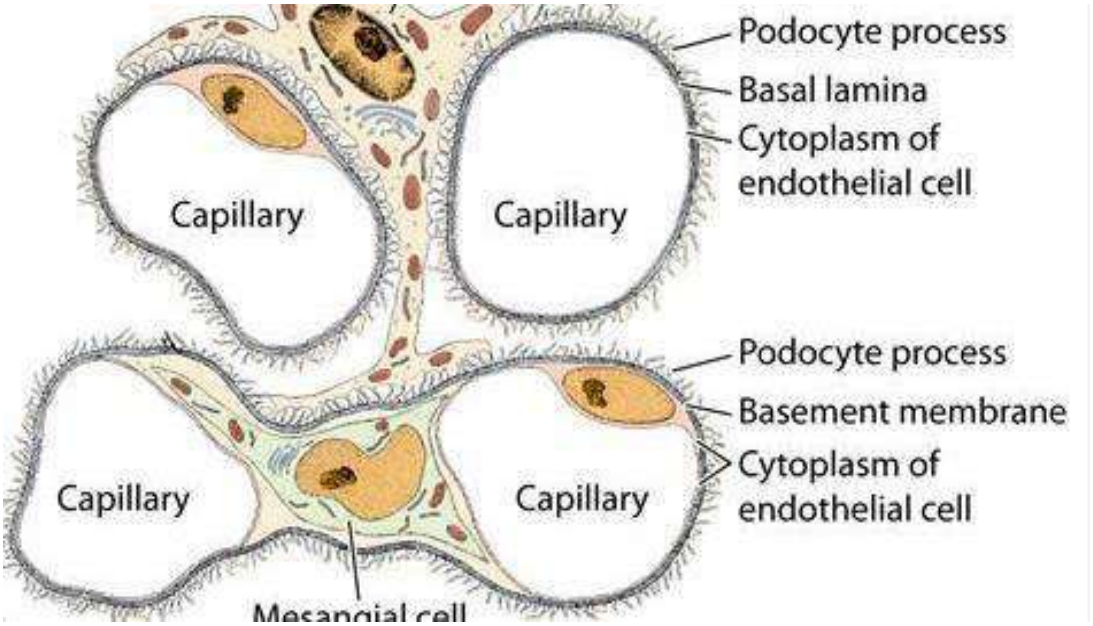
The Mesangium :

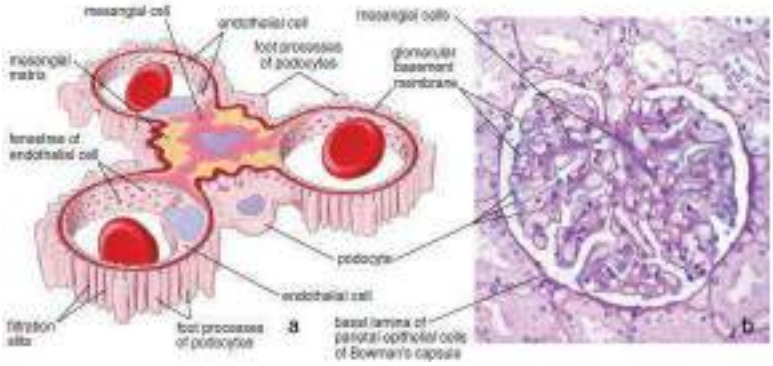
-In addition to capillary endothelial cells and podocytes, renal corpuscles also contain **mesangial cells** , most of which resemble vascular pericytes in having contractile properties and producing components of an external lamina.

-**Mesangial cells** are difficult to distinguish in routine sections from podocytes, but often stain more darkly.

-They and their surrounding matrix comprise the mesangium , which fills interstices between capillaries that lack podocytes.

-Mesangial cells extend contractile processes along capillaries that help regulate blood flow in the glomerulus. Some mesangial processes pass between endothelial cells into the capillary lumen where they may help remove or endocytose adherent protein aggregates





Functions of the Mesangium:

1-Physical support of capillaries within the glomerulus.

2-Adjusted contractions in response to blood pressure changes, which help maintain an optimal filtration rate.

3-Phagocytosis of protein aggregates adhering to the glomerular filter, including antibody-antigen complexes abundant in many pathological conditions.

4-Secretion of several cytokines, prostaglandins, and other factors important for immune defense and repair in the glomerulus

Lecture 2

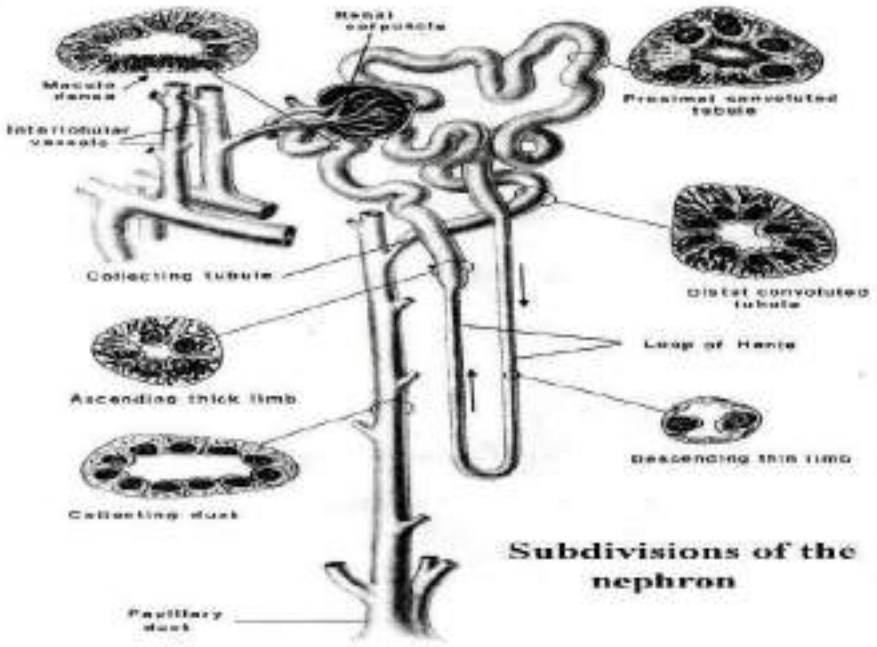
Histology of kidney (2)

ILOs:

- Describe the histological structure of the proximal convoluted tubules. .
- Compare between the histological structure of the proximal convoluted tubules & distal convoluted tubules .
- Discriminate loop of Henle , collecting tubules and collecting ducts (the type of their lining epithelium and identify their functions).
- Describe the histological structure of the Juxtaglomerular apparatus and identify its functions.
- Describe the histological structure of the renal interstitium.
- Describe the blood supply of the kidney .

The renal tubular system is divided into several functional units:

- Proximal convoluted tubule (PCT)
- Loop of Henle
- Distal convoluted tubule (DCT)
- Collecting tubules
- Collecting ducts



Subdivisions of the nephron

Proximal Convoluted Tubule (PCT)

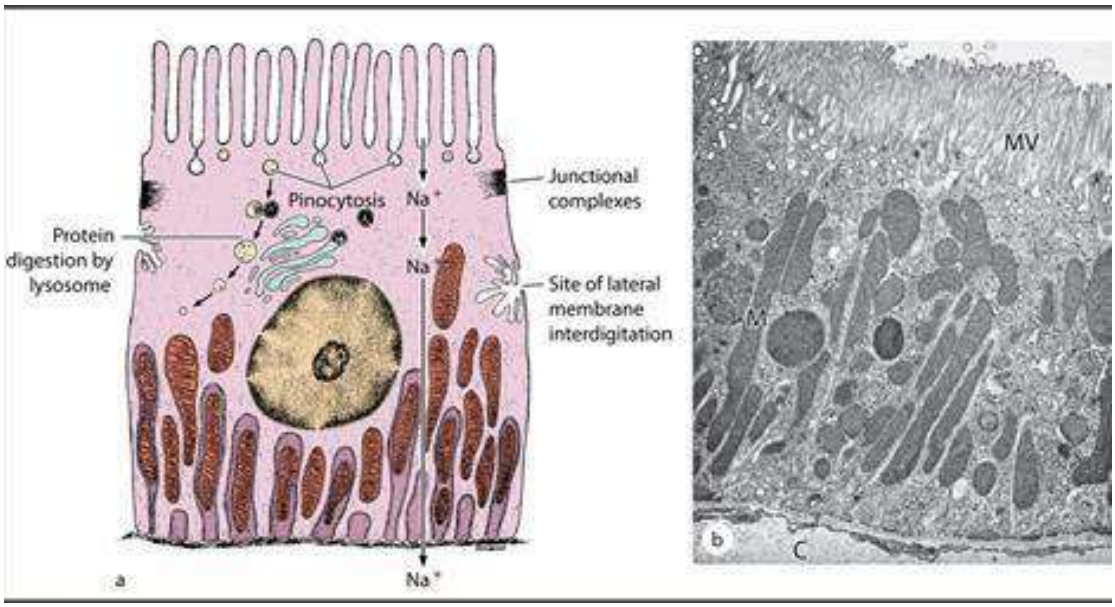
Start at the tubular pole of the renal corpuscle where, the simple squamous epithelium of the capsule's parietal layer is continuous with the simple cuboidal epithelium lining the tubules.

Light Microscopy (L.M):

- Lined with simple cuboidal epithelium.
- Possesses brush borders; in routine histologic preparations, the long brush border may appear disorganized, giving lumens a fuzzy appearance.
- Cytoplasm is granular and deeply acidophilic.
- Basal cytoplasm shows vertical acidophilic striations.
- Nuclei are large and spheroidal, 3–5 visible per cross-section.
- Cell borders are ill-defined, and luminal size varies with cell activity.

Electron Microscopy (E.M):

- Luminal border has countless microvilli.
- Many pinocytotic vesicles below the microvilli indicate active endocytosis and pinocytosis.
- Lateral interdigitations are present between neighboring cells.
- Basal membrane shows long invaginations with mitochondria that provide ATP for active transport.
- Capillaries below the basal lamina remove water absorbed across the epithelium.



Functions:

- Major roles in **reabsorption and secretion** via various pumps, ion channels, and transporters.
- Responsible for **hydroxylation of vitamin D** and releasing it into capillaries.

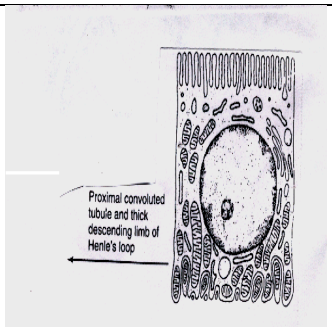
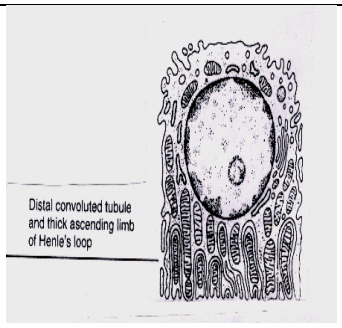
Loop of Henle

- U-shaped structure with **thin descending and ascending limbs**, both lined by simple squamous epithelium.
- Straight part of proximal tubule (60 µm) narrows to 30 µm in thin limbs.
- Thin segments consist of squamous cells with few organelles .
- Lumen is prominent.

Distal Convoluted Tubule (DCT)

- Lined by simple cuboidal epithelium.
- Cells are smaller than those in PCT.
- No brush border; lumen appears more empty.

Feature	**Proximal Convoluted Tubule (PCT)**	**Distal Convoluted Tubule (DCT)**
Lining epithelium	Simple cuboidal epithelium	Simple cuboidal epithelium
Cell size	Large and bulky	Smaller and more compact
Cytoplasm	Eosinophilic (granular and dark due to many mitochondria)	Less eosinophilic, lighter and clearer
Brush border (microvilli)	Well-developed, forming fuzzy lumen the apical cytoplasm of these cells has numerous pits and vesicles near the bases of the microvilli, indicating active endocytosis and pinocytosis .	Absent or sparse, lumen appears clear
Lumen appearance	Narrow and irregular	Wider and more regular
Basal part by LM	The basal part of the cytoplasm show vertical acidophilic striation	Less basal striations.
Nuclei BY LM	Less distinct due to dense cytoplasm	Prominent and centrally placed
Basement membrane	Thin and distinct	Thin and distinct
By EM	1-The luminal border consists of countless microvilli.	1-Few microvilli 2-Less interdigitations

	-2-The cell membranes of the lateral sides of adjacent cells interdigitate with one another. -3-The basal part of the cell membrane gives many infolding. 4-A large number of gaint elongated mitochondria arranged parallel to the long axis of the cells and between the basal infoldings.	-3-Less extensive basal infoldings
Mitochondria	Numerous	Fewer
Functions	Reabsorption of water, glucose, amino acids, Na^+, Cl^-, etc. Responsible for **hydroxylation of vitamin D** and releasing it into capillaries.	Selective secretion and reabsorption of ions (Na^+, K^+, H^+) Much less tubular reabsorption occurs here than in the proximal tubule. The distal tubule is the primary site of urine concentration.
Location	Cortex	Cortex (extends to medullary rays)
		

Collecting Tubules and Ducts

- Composed mainly of **pale staining principal cells** and **intercalated cells**.

Light Microscopy:

- **Principal cells** have few organelles, sparse microvilli, and distinct cell borders.

Electron Microscopy:

- Principal cells show basal membrane infoldings indicating ion transport activity.
- Rich in **aquaporins**, integral proteins acting as water channels.

Juxtaglomerular Apparatus (JGA)

Located where the straight part of the distal tubule contacts the arterioles at the vascular pole of its parent nephron.
Cells become columnar and closely packed, forming the **macula densa**, part of the JGA, which regulates glomerular blood flow and filtration rate.

Components:

1. **Afferent arteriole modification:**
    - Smooth muscle cells become **juxtaglomerular granular (JG) cells** with secretory phenotype.
    - Contain renin granules, rough ER, and Golgi complexes.
2. **Distal convoluted tubule modification:**

Modification in the distal convoluted tubule:

This modification occurs in the portion of the distal convoluted tubule which lies in contact with renal corpuscle.

-The basement membrane is lost.

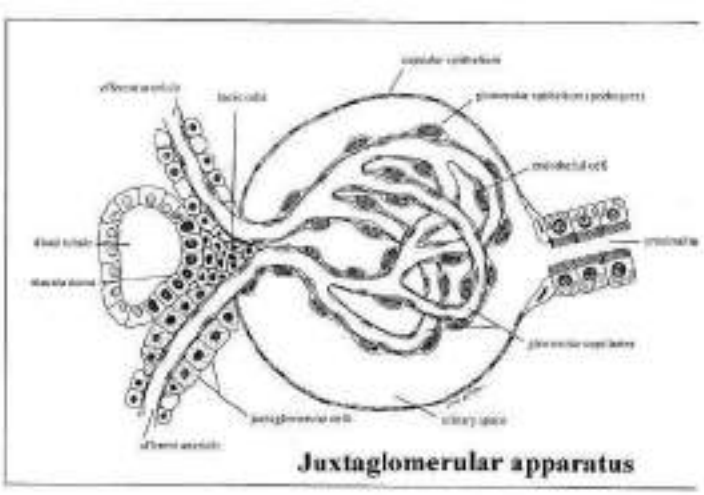
-The cells become taller columnar and crowded.

-The nuclei become deeply stained and close together. These cells are called macula densa cells.

3. **Extraglomerular mesangial cells:**
    - Located between macula densa, glomerulus, and afferent arteriole.

Functions:

- Regulates **GFR** and **blood pressure**.
- Involves:
    1. Local baroreceptors (release of renin).
    2. Monitoring Na^+ and Cl^- concentration in the nephron lumen.



Connecting Tubule and Collecting System

- A ***connecting tubule*** extends from each nephron and several join together in the cortical medullary rays to form collecting ducts of simple cuboidal epithelium and an average diameter of 40 μm.
- -In the medulla these merge further, forming larger and straighter collecting ducts with increasingly columnar cells and overall diameters reaching 200 μm. The medullary collecting ducts are the final site of water reabsorption from the filtrate.
- The last part of each nephron, ***the connecting tubule***, carries the filtrate into a collecting system that transports it to a minor calyx and in which more water is reabsorbed if needed by the body

Renal Interstitial Tissue

- Cortex and medulla contain **interstitial cells** between tubules and vessels.
- More numerous in the medulla; contain lipid droplets involved in **medullipin I** synthesis (converted in the liver to **medullipin II**, a vasodilator).
- Peritubular capillaries abundant in interstitial connective tissue (fills ~10% of cortex).

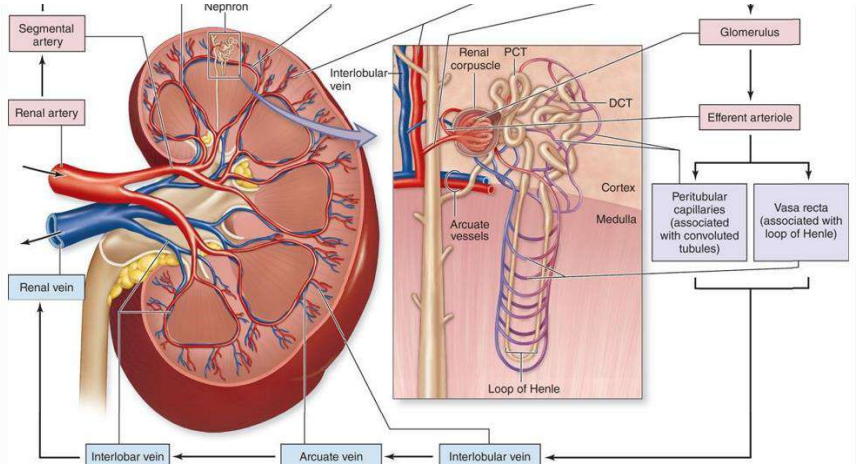
Blood Supply of the Kidney

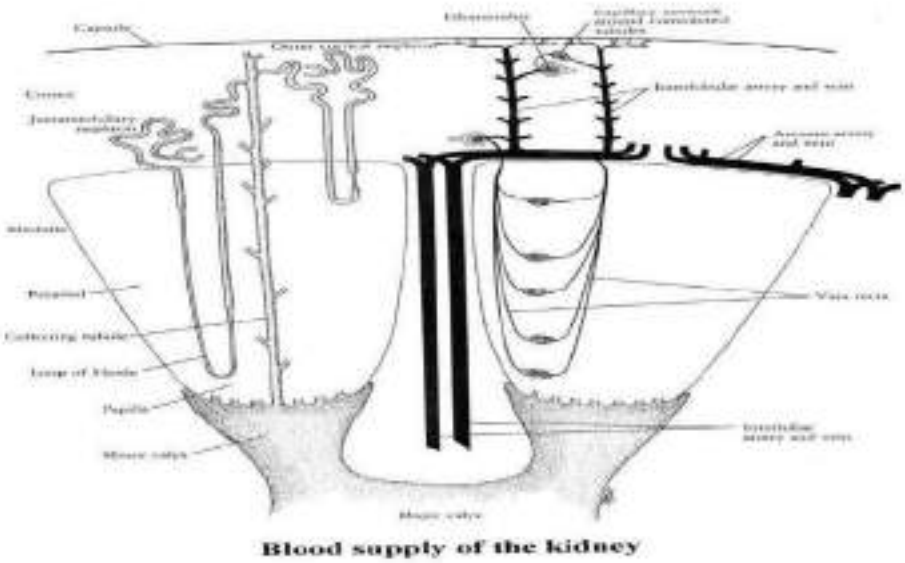
Kidney vasculature is extensive and organized to support blood processing.

- **90–95%** of blood flow in cortex.
- **5–10%** in medulla.

Arterial Supply Sequence:

1. Renal artery →
2. Segmental arteries →
3. Interlobar arteries →
4. Arcuate arteries →
5. Interlobular arteries →
6. Afferent arterioles → **Glomerulus** →
7. Efferent arterioles → **Peritubular capillaries** (in cortex) or **Vasa recta** (in medulla).
8. Collectively, the cortex receives over 10 times more blood than the medulla. Blood leaves the kidney in veins that follow the same courses as arteries and have the same names .





Blood supply of the kidney

Main Kidney Functions

Glomerular Function:

- Excretion of toxic metabolic waste and foreign substances.

Tubular Function:

- Regulation of acid–base, water, and electrolyte balance.

Endocrine Activities:

- **Erythropoietin (EPO):** Produced by endothelial cells of peritubular capillaries → stimulates RBC formation in bone marrow.
- **Renin:** Secreted by juxtaglomerular cells → regulates blood pressure and volume.
- **Vitamin D activation:** Hydroxylation of 25-OH Vitamin D_3 in proximal tubules → forms active 1,25-$(OH)_2$ Vitamin D_3 (Calcitriol).

Lecture 3

Excretory passages

ILOs:

*Describe the histological structure of the minor calyces, major calyces, the renal pelvis

*Describe the histological structure of the ureter, urinary bladder and urethra

Excretory passages

1- Ureter.

2- Urinary bladder

3- Male urethra

4- Female urethra

All excretory passages, except the urethra, have the same general organization.

*On leaving the collecting ducts at the **area cribrosa**, the urine enters a series of structures that do not modify it but are specialized to store and pass the urine to the exterior of the body.

* The urine flows sequentially to a **minor calyx**, a **major calyx**, and the **renal pelvis**, and leaves each kidney through the **ureter** to the **urinary bladder**, where it is stored. The urine is finally voided through the urethra.

*All of these excretory passages, except the urethra, have the same general structures, namely, a mucosa (lined by transitional epithelium), musculosa, and adventitia (or, in

some regions, a serosa).

Transitional epithelium lines the calyces, ureters, bladder, and the initial segment of the urethra.

Transitional epithelium (urothelium)

The cells in the transitional epithelium are composed of at least three layers:

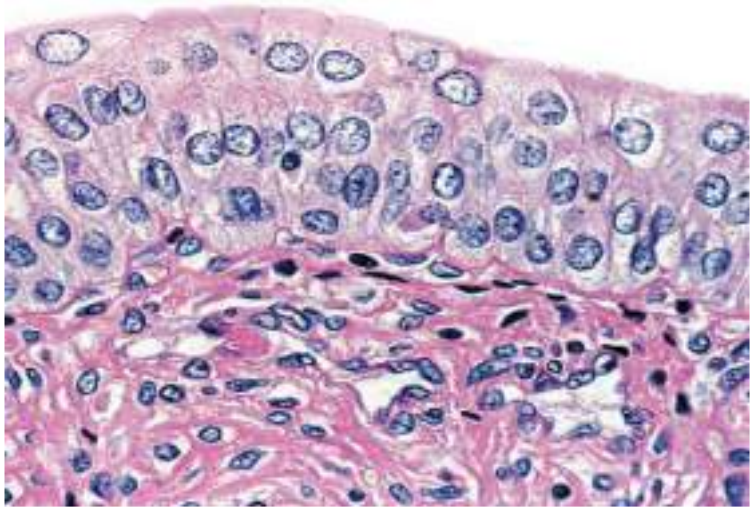
• Th e **superfi cial layer** contains single or multinucleated large, polyhedral cells (25 to 250 µm in diameter) that bulge into the lumen. called **dome-shaped** or **umbrella cells** because of their apical surface curvature. The shape of these epithelial cells depends on the filling state of the excretory passage.

in an empty urinary bladder, dome shaped cells are cuboidal; however, **when the bladder is filled**, they are highly stretched and appear as flat and squamous.

Edges of the cells exhibit ridges, which are formed by the interdigitations of apical surface membranes from adjacent cells. These interdigitations resemble a closed zipper line and contribute to the high- resistance paracellular barrier that reinforces tight junctions.

• Th e **intermediate cell layer** contains pear-shaped cells that are connected to each other and the overlying dome shaped cells by desmosomes. The thickness of this layer varies with the state of the urinary tract expansion, which in humans may reach up to five layers thick. When the overlying dome-shaped cell is lost, the population of intermediate cells rapidly differentiates and replaces the lost surface cell.

• Th e **basal cell layer** consists of small cells containing a single nucleus that rests on the basement membrane. This layer contains stem cells for the urothelium.



Transitional epithelium

How this epithelium accommodate its function?

1-The epithelium begins in the minor calyces as two cell layers and increases to four to five layers in the ureter and as when the bladder is distended, as few as three layers

Th is change reflects the ability of the cells to accommodate distension.

2- The cells in the distended bladder, particularly dome-shaped surface cells, flatten and those in intermediate layers slide past one another to accommodate the increasing surface area.

3-The luminal surface of the transitional epithelium is covered by rigid urothelial plaques containing crystalline protein uroplakins, makes the plaque impermeable

to small molecules (water, urea, and protons). Which In conjunction with tight junctions play an important role in the urothelial permeability barrier.

4-As the bladder or other urine-containing organs distend, the folded surface of the mucosa becomes stretched and expands.

5-Dome-shaped cells also undergo changes of their apical membrane that are associated with the presence of the **fusiform vesicles**.

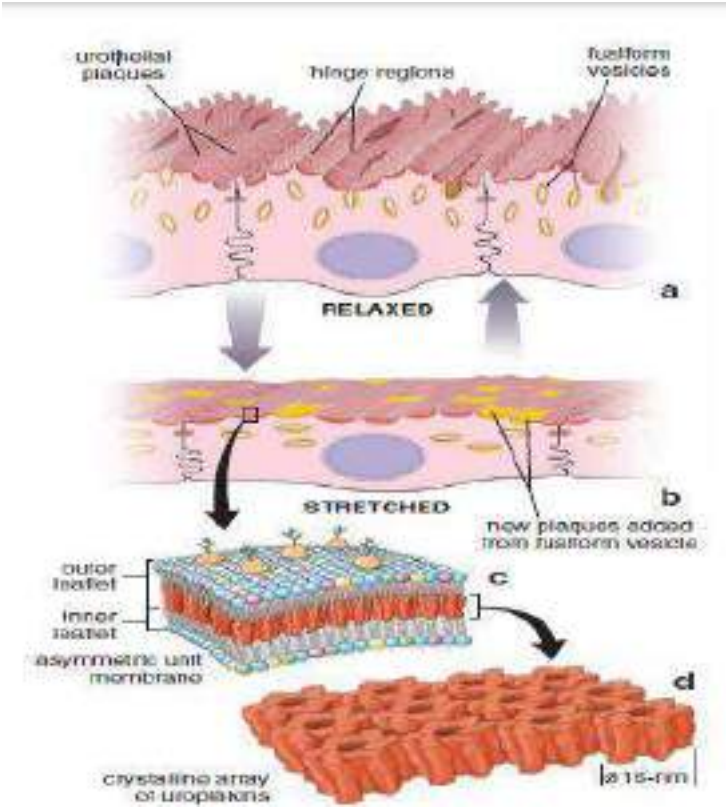
In response to the distention of the bladder, the apical membrane expands as a result of exocytosis of the fusiform vesicles that become part of the cell surface.

During micturition, the process is reversed as added apical membrane is recovered by endocytosis and the apical membrane of the dome-shaped cells shortens.

So in summary:

Th e dome-shaped cells have a modifi ed apical membrane containing **plaques** and **fusiform vesicles** that accommodate the invaginated excess of the plasma membrane,

which is needed for the extension of the apical surface when the organ is stretched.



Ureter

are paired tubular structures that convey urine from the kidneys to the urinary bladder.

The wall of the ureter is formed of:

1- Mucosa:

A- Epithelium:

- transitional epithelium (urothelium).
- The transitional epithelium is 4 to 5 cell thick. The epithelium does not have a distinct basal lamina. It rests on a layer of fibroelastic connective tissue.
- The ability of this epithelium to become thinner and flatter allows all of these passages to accommodate to distension by the urine.
- Mucosa shows prominent longitudinal folds giving the lumen a stellate appearance .

B- Lamina propria: loose connective tissue rich in elastic fibers contains numerous blood vessels, nerves, lymphatics and some fat cells..

2- Musculosa:

- upper 2/3rd of the ureter is made of two layers of smooth muscle cells. Inner longitudinal and outer circular layer
- Lower 1/3rd of the ureter has a third outer longitudinal layer (inner longitudinal, middle circular and outer longitudinal).
- Regular peristaltic contractions of this muscle contribute to the flow of urine from the kidney to the urinary bladder.They conduct urine from renal pelvis to urinary bladder
- The bundles of muscle fibers are separated by abundant elastic connective tissue (to allow distention of the wall when filled by urine).

3- Adventitia:

- Fibro elastic connective tissue.

The ureters pass through the wall of the bladder obliquely, forming a valve that prevents the backflow of urine.

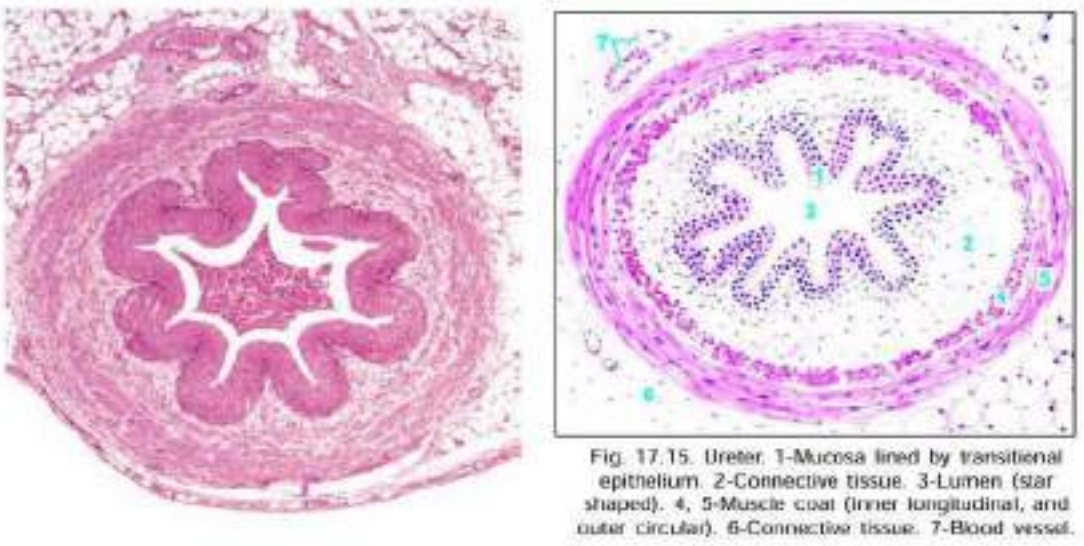


Fig. 17.15. Ureter. 1-Mucosa lined by transitional epithelium. 2-Connective tissue. 3-Lumen (star shaped). 4, 5-Muscle coat (inner longitudinal, and outer circular). 6-Connective tissue. 7-Blood vessel.

Ureter

Urinary bladder

It is formed of 3 layers

1-Mucosa

Shows numerous folds that disappear when the bladder becomes distended except the trigone .

Epithelium :

transitional epithelium resting on folded basement membrane

Lamina propria: loose connective tissue rich in elastic fibers

2-Musculosa

*The muscle layer is thick.

*The smooth muscle in it forms a meshwork.

*Internally and externally the fibres tend to be longitudinal.

*In between them there is a thicker layer of circular (or oblique) fibres.

*Contraction of this muscle coat is responsible for emptying of the bladder.

That is why it is called the **detrusor muscle**.

*Just above the junction of the bladder with the urethra the circular fibres are thickened to form **the sphincter vesicae**.

*The muscle bundles separated by fibroelastic connective tissue to allow bladder distension

*Just above the junction of the bladder with the urethra the circular fibres are thickened to form the sphincter vesicae.

3-Adventitia/ Serosa

The urinary passages are covered externally by an adventitia fibro elastic connective tissue, except for the upper part of the bladder, which is covered by serous peritoneum

Osmotic barrier (urinary bladder barrier)

*The thickened apical membrane of the dome shaped cells by the impermeable plaques

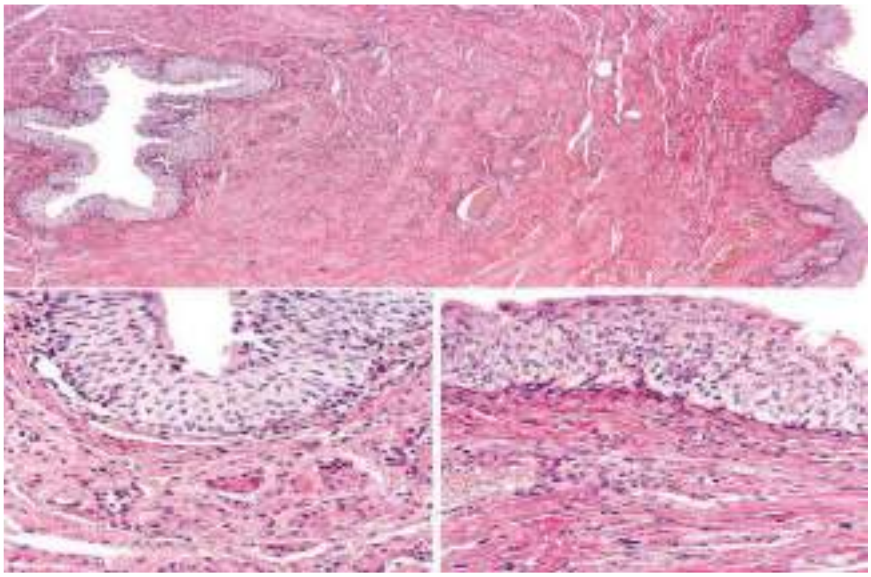
*The occluding junctions between the dome cells

Functions

Protecting the epithelium from the toxic wastes in urine

Preventing dilution of the hyperosmotic urine

Preventing leakage of urine into the extracellular spaces



URETHRA

The urethra is a tube that carries the urine from the bladder to the exterior.

In men, sperm also pass through it during ejaculation.

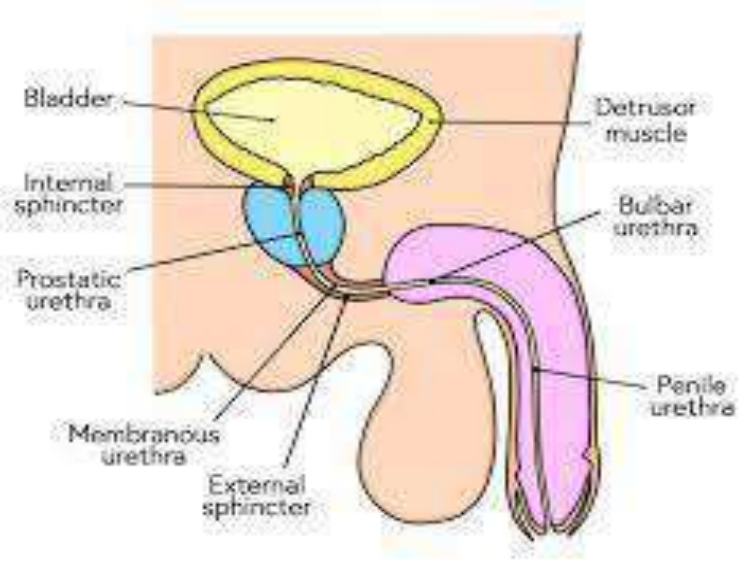
In women, the urethra is exclusively a urinary organ.

Male urethra:

The male urethra consists of :

1. **The prostatic urethra :** the prostatic urethra is surrounded by prostatic tissue. it is lined with transitional epithelium.
2. **The membranous urethra** extends through the perineal membrane and is lined with stratified or pseudostratified columnar epithelium.

3. **The penile urethra** are surrounded by erectile tissue of the corpus spongiosum. The epithelium of this portion of the urethra is mostly stratified columnar. The urethral lumen dilates distally, forming the fossa navicularis which is lined with stratified squamous (non-keratinized) epithelium.



Male urethra

--**The mucosa**: shows invaginations or recesses into which mucous glands open.

--**The submucosa** : consists of loose connective tissue.

--The musculosa : consists of an inner longitudinal layer and an outer circular layer of smooth muscle.

*This muscle coat is better defined in the female urethra. In the male urethra it is well defined only in the membranous and prostatic parts, the penile part being surrounded by occasional fibres only.

*In addition to this smooth muscle the membranous part of the male urethra, and the corresponding part of the female urethra are surrounded by striated muscle that forms the external urethral sphincter

Ducts of the bulbourethral glands (Cowper's glands) and of the mucus-secreting **urethral glands (glands of Littré)** empty into the penile urethra.

Female urethra:

- The female urethra is a tube 4-5 cm long, formed of:

Mucosa : formed of

Epithelium:.

- Transitional epithelium in its initial part.
- Pseudostratified and stratified columnar epithelium in its main part.
- stratified squamous epithelium in its terminal part.
- The mid part of the female urethra is surrounded by an external striated voluntary sphincter.

Submucosa : of highly vascular connective tissue.

Musculosa; very thin and poorly developed smooth muscles

Adventitia.

N.B: Both in the male and female the greater part of the urethra is lined by **pseudostratified columnar epithelium**. A short part adjoining the urinary bladder is lined by **transitional epithelium**, while the part near the external orifice is lined by **stratified squamous epithelium**.

REFERENCES:

JUNQUEIRA'S BASIC HISTOLOGY (TEXT AND ATLAS) (2018) 15 TH EDITION
ELSEVIER'S INTEGRATED HISTOLOGY (2007) 1STEDITION
Oxford Handbook of Medical Sciences 2nd ed (2011)

Part 4
Medical Biochemistry

1- Urinary stones

Objectives:

1-Know the normal urinary pH and describe how its changes can help in diagnosing types of urinary stone

2-List the main chemical types of urinary stones

3-Mention the radiologic appearance of these stones

4-Describe different shapes of urine crystals associated with each type of stone

5-Explain the pathological condition, metabolic disorder that lead to the formation of these stones

Urinary pH

The average value for urine pH is 6.0, but it can range from 4.5 to 8.0. Urine under 5.0 is acidic, and urine higher than 8.0 is alkaline, or basic.

Acidic foods include: grains,fish,sodashigh-protein foods,sugary foods

Alkaline foods include: nuts,vegetables, most fruit.

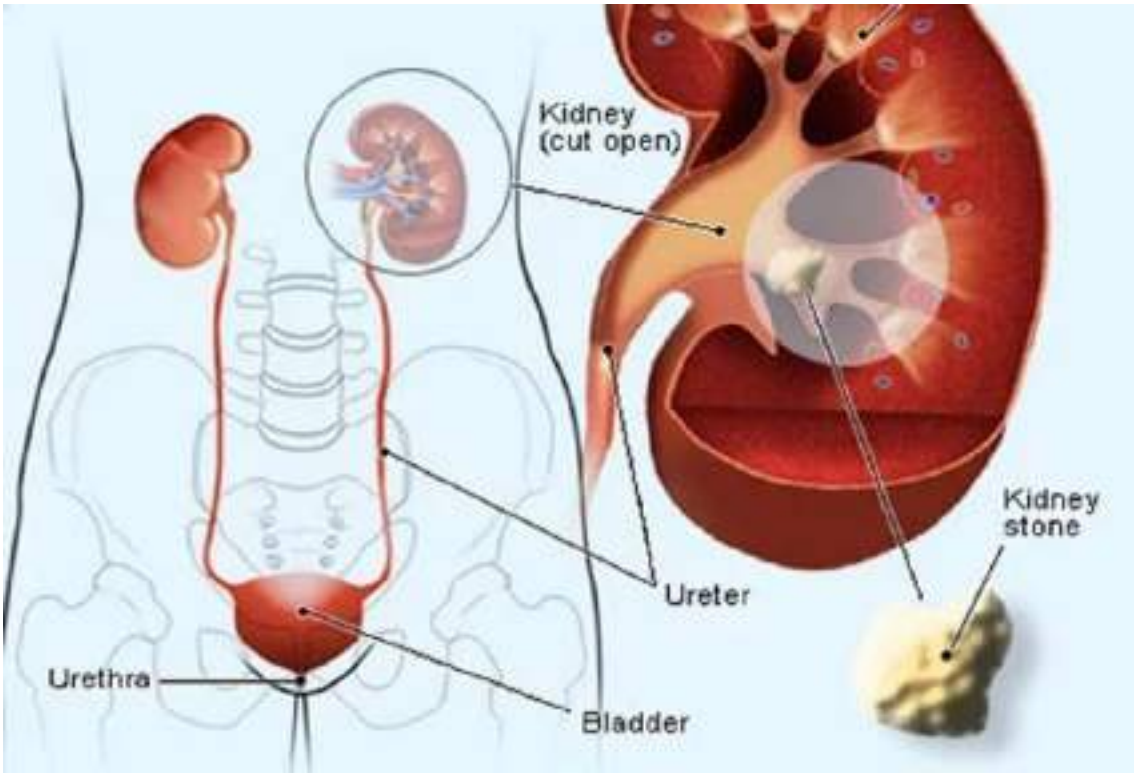
Nephrolithiasis/urolithiasis: The process of forming a kidney stone. Kidney stones are a common cause of blood in the urine and pain in the abdomen, flank, or groin. Kidney stones occur in 1 in 10 people at some time in their life.

The development of the stones is typically related to increased excretion of stone-forming components such as calcium, oxalate, urate or cystine.

In nephrolithiasis/urolithiasis, urine pH has been thought to modulate kidney stone formation at various steps, including crystallization, growth, aggregation and retention. In addition, pH is an important factor that can enhance the generation of solid phase and affects solubility of kidney stones. Moreover, several stone types, including calcium oxalate (CaOx), calcium phosphate, uric acid, etc., have been reported to be modifiable by urine pH. The basic urine pH favors formation of phosphate-containing stones, whereas the acidic urine pH is associated with uric acid and cystine stone

Kidney stones are small masses of salts and minerals that form inside the kidneys and may travel down the urinary tract. Kidney stones range in size from just a speck to as large as a ping pong ball.

The kidneys regulate levels of fluid, minerals, salts, and other substances in the body. When the balance of these compounds changes, kidney stones may form. The type of kidney stone is based on its chemical composition.



Mechanisms of Stone Formation

- **Supersaturation**: When substances like calcium, oxalate, or uric acid become too concentrated in the urine, they can crystallize and form stones.
- **Crystal Aggregation:** These crystals can aggregate, or clump together, leading to the formation of larger stones.
- **Inflammatory Response:** The formation of crystals can also trigger an inflammatory response within the kidney, further contributing to the pathological process of stone formation.

Types of kidney stones:

May be pure or mixed

1-pure: include;

Calcium oxalate, Calcium phosphate, Uric acid, Cystine and Nonspecific organic material

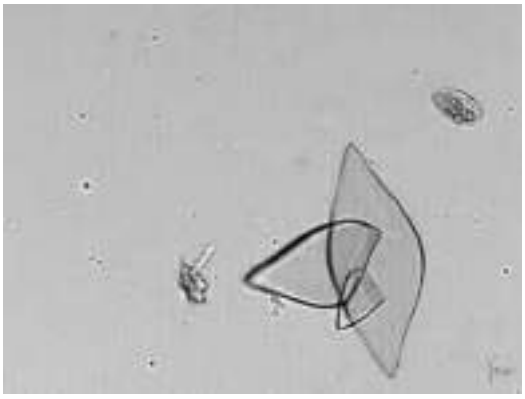
2-mixed: a combination of two or more of the substances mentioned above.

Types of Crystals in Urine

You can classify the urine crystals into diverse types based on the different chemical composition of the crystals. So, each urine crystals has a different treatment plan based on its type

1-Uric Acid Crystals

The crystals appear yellow or orange-yellow in color. The crystals have different shapes. So, the technician can observe diamond, plate-like or barrel shape under the microscope. The crystals appear even in healthy urine due to high protein. So, healthy people who consume protein-rich diet can have uric acid crystals. But, the high uric acid crystals indicate health problems.



Conditions associated with uric acid crystals

1- Kidney stones

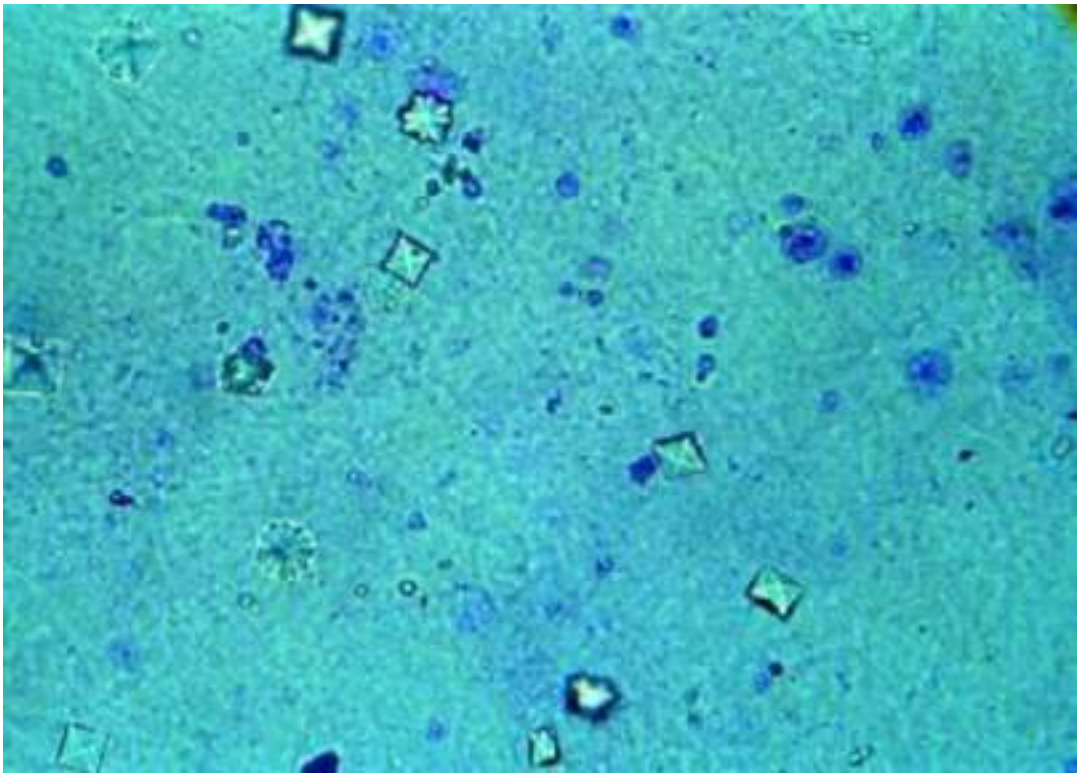
2-Chemotherapy

3-Gout

Drinking a good amount of water is useful irrespective of the underlying health problem.

2-Calcium Oxalate Crystals

The calcium oxalate crystals look like envelopes or dumbbells. You can find the crystals in healthy urine. It appears colorless. In most cases, the calcium oxalate crystals indicate kidney stones. Consuming oxalate-rich food like spinach predisposes to developing the crystals



Treatment For Calcium Oxalate Crystals

The oxalate causing kidney stones have the following treatment option to relieve the distress:

Increase water intake

Consume less salt

Avoid processed foods

Make dietary changes to reduce oxalate accumulation

3-Calcium Phosphate Crystals

The calcium phosphate crystals have a needle-like, star-like, or plate-like appearance under the microscope. The colorless crystals may appear alone or in clusters. You can observe it in normal as well as alkaline urine. In some rare cases, the calcium phosphate crystals in your urine appear due to hypoparathyroidism. When you have the crystals in your urine, you can suffer from several signs like: Muscle cramping and tingling in your hands

Treatment for Calcium Phosphate Crystals

The treatment option for alleviating the problem due to calcium phosphate crystals may include:

Drinking water to stay hydrated

Consuming calcium-rich food or supplements

Taking Vitamin D supplements

Cysteine Crystals

Cysteine crystals are developed in the urine due to the presence of cysteine acid, an amino acid that binds together to form crystals. The condition referred to cystinuria occurs rarely in people. So, the cysteine acid can result in kidney stones that have a larger size compared to other stones. In most cases, genetics play a significant role in developing the condition. When the urine is observed under the microscope, the cysteine crystals have a hexagonal shape. It is usually colorless.

Metabolic Conditions Leading to Stone Formation

- **Metabolic Syndrome:** This group of conditions, including obesity, high blood pressure, and elevated blood sugar, is a major risk factor for kidney stones. It can lead to a low urinary pH, which promotes the formation of uric acid stones.
- **Hypercalciuria**: High levels of calcium in the urine can lead to calcium oxalate and calcium phosphate stones.
- **Hyperoxalururia:** Elevated levels of oxalate, a natural substance found in certain foods, can increase the risk of calcium oxalate stones.
- **Hyperuricosuria**: High levels of uric acid in the urine, often associated with low urine pH, can result in uric acid stones.
- **Primary Hyperoxaluria:** A rare genetic disorder that causes the body to produce too much oxalate, leading to calcium oxalate stones.
- **Cystinuria:** An inherited metabolic disorder where the kidneys fail to reabsorb cystine and other amino acids, leading to an excess of cystine in the urine and the formation of cystine stones.

Radiographic features of kidney stones

Imaging tests may show kidney stones in the urinary tract. Options range from simple abdominal X-rays, which can miss small kidney stones, to high-speed or dual energy computerized tomography (CT) that may reveal even tiny stones.

Other imaging options include an ultrasound, a noninvasive test, and intravenous urography, which involves injecting dye into an arm vein and taking X-rays (intravenous pyelogram) or obtaining CT images (CT urogram) as the dye travels through your kidneys and bladder

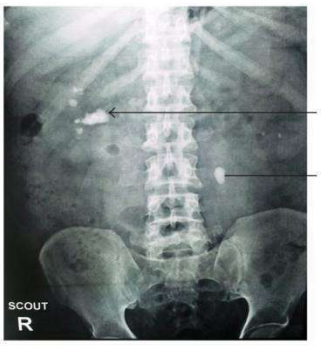
Plain radiograph

Calcium-containing stones are radiopaque:

calcium oxalate +/- calcium phosphate

struvite (triple phosphate) - usually opaque but variable

pure calcium phosphate



Lucent stones include:

uric acid

Cystine

Part 5
Pathology

1- CONGENITAL KIDNEY DISEASES AND INTRODUCTION TO GLOMERULAR DISEASES

Objectives:

- list congenital anomalies of the kidney and discuss polycystic kidney.
- Define glomerulonephritis and the pathogenetic mechanisms underlying glomerular injury and the tissue reaction of glomerular injury.
- Define the terms nephritic and nephrotic syndromes and enumerate its causes.

CONGENITAL KIDNEY DISEASES

- **Agenesis of the Kidney:** Complete absence of one kidney, with the other one showing compensatory hypertrophy.
- **Hypoplasia:** Failure of one kidney to develop to the normal size, so it remains small; the other kidney shows compensatory hypertrophy.
- **Ectopic Kidney:** The kidney fails to migrate up to the normal position and remains in the pelvis or at the pelvic brim.
- **Horse-shoe Kidney:** Both kidneys are fused together, usually along the lower poles by renal or fibrous tissue.

CONGENITAL POLYCYSTIC KIDNEY

Polycystic disease of the kidney (PKD) is a disorder where a major portion of the renal parenchyma is converted into cysts of varying size. The disease occurs in two forms:

- A. An adult type inherited as an autosomal dominant disease.
- B. An infantile type inherited as an autosomal recessive disorder.

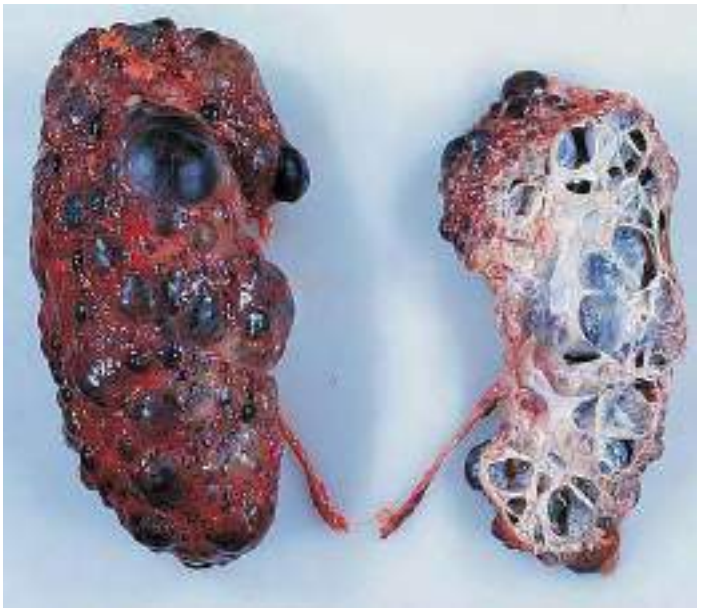
AUTOSOMAL DOMINANT ADULT POLYCYSTIC KIDNEY (ADPKD)

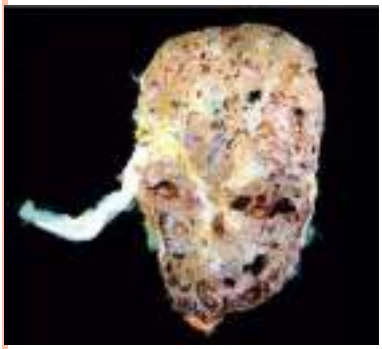
Presentation:

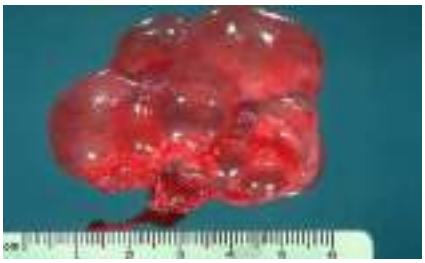
- Inherited as an **autosomal dominant trait**.
- Patients usually present in their **40s** with flank pain, intermittent hematuria, a palpable abdominal/flank mass, hypertension, and a positive family history of kidney disease.
- It may be associated with **congenital cystic liver and congenital cerebral aneurysms**.

Grossly:

- Kidneys in ADPKD are **always bilaterally enlarged, usually symmetrically, heavy** (weighing up to 4 kg).
- They give a **lobulated appearance** on the external surface due to underlying cysts.
- The cut surface shows cysts varying in size from tiny cysts to 4-5 cm in diameter.
- The contents of the cysts vary from clear straw-yellow fluid to reddish-brown material.
- The cysts, however, **do not communicate with the pelvis** of the kidney.







Histologically:

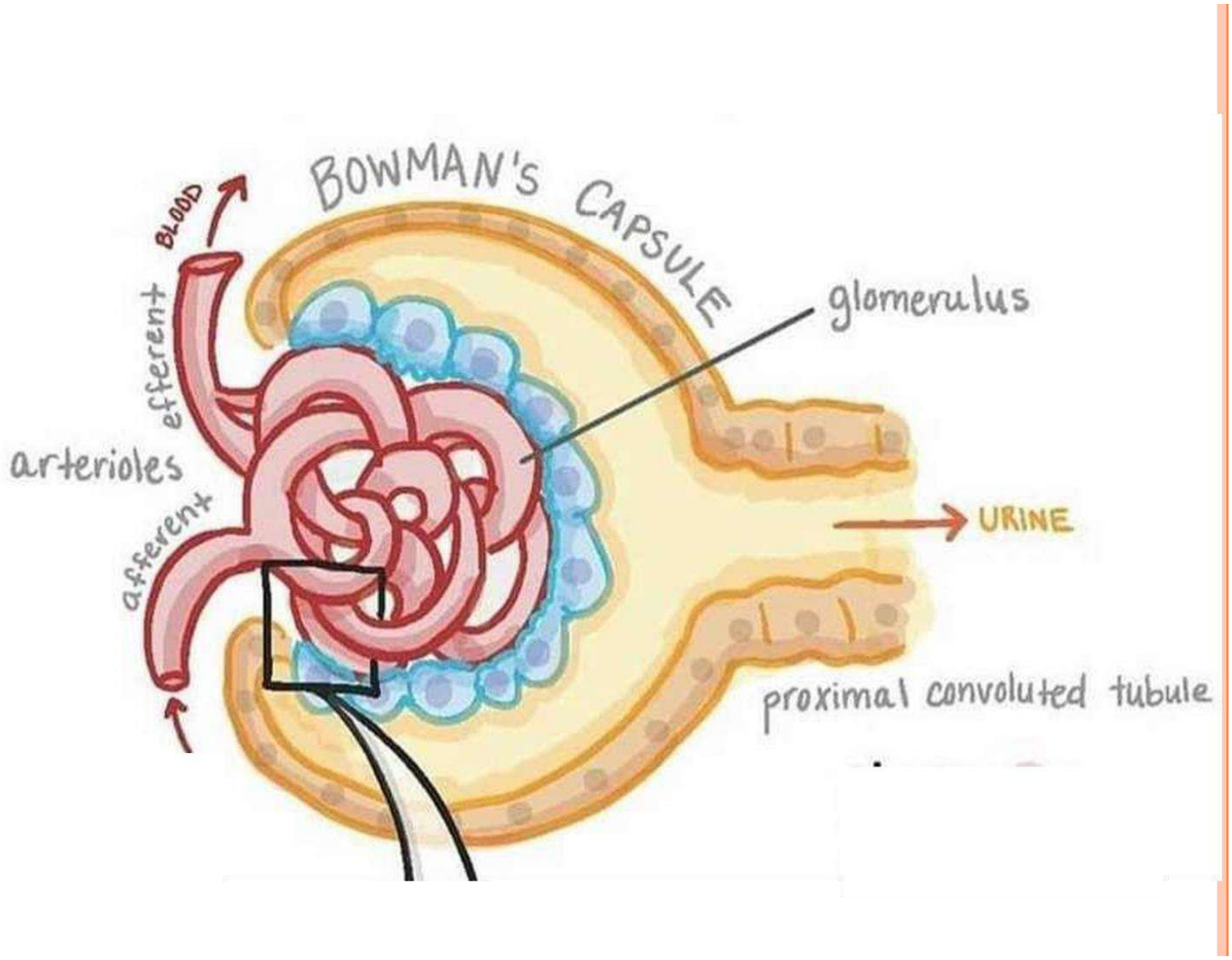
- The cysts arise from **all parts of the nephron**.
- Some cysts may contain recognizable glomerular tufts, reflecting their origin from Bowman's capsule, while others have epithelial lining like that of distal or proximal tubules or collecting ducts.
- The intervening tissue between the cysts shows some **normal renal parenchyma**.
- With advancement of age, **acquired lesions** such as pyelonephritis, nephrosclerosis, and fibrosis are seen.

Diagnosis:

- A **positive family history** and **bilateral kidney cysts** detected by ultrasound.
- **Liver cysts** may also be present.

Prognosis:

- **Chronic renal failure** begins at age **40-60** and is the most common cause of death.



Normal glomerulus

GLOMERULAR DISEASES

- **Definition:** Glomerular disease is the term used for diseases that primarily involve the renal glomeruli.
- **Classification:** Glomerular diseases are conveniently classified into 2 broad groups:
    - I. Primary glomerulonephritis (GN) in which the glomeruli are the predominant site of involvement.
    - II. Secondary glomerular diseases which include certain systemic and hereditary diseases that secondarily affect the glomeruli.

CLINICAL MANIFESTATIONS

The clinical presentation is quite variable, but in general, four features are present: **proteinuria, hematuria, hypertension, and disturbed excretory function**.

Six major glomerular syndromes are recognized:

- I. **Nephritic and nephrotic syndromes**.
- II. **Acute and chronic renal failure**.
- III. **Asymptomatic proteinuria and hematuria**.

ACUTE NEPHRITIC SYNDROME

It is a glomerular syndrome characterized by the **acute onset** of:

- **Microscopic hematuria**.
    - Hematuria is generally slight, giving the urine a smoky appearance.
    - Appearance of **red cell casts** is another classical feature.
- **Mild proteinuria** (less than 3 gm per 24 hrs).
- **Hypertension** (generally mild, depending on the severity of the disease).
- **Oedema** (usually mild, resulting from sodium and water retention).
- **Oliguria** (variable).

It is the classic presentation of **acute post-streptococcal glomerulonephritis**.

CONDITIONS THAT MANIFEST WITH NEPHRITIC SYNDROME (INFLAMMATORY DAMAGE TO THE GLOMERULI)

I. PRIMARY GLOMERULONEPHRITIS

1. Acute GN (Post-streptococcal, Non-streptococcal)
2. Rapidly progressive GN
3. Membrano-proliferative GN
4. Focal and diffuse proliferative GN
5. IgA nephropathy

II. SYSTEMIC DISEASES

1. SLE
2. Polyarteritis nodosa
3. Wegener's granulomatosis
4. Henoch-Schonlein purpura

NEPHROTIC SYNDROME

Nephrotic syndrome is characterized by a constellation of features, which include:

1. **Massive proteinuria** (Heavy protein loss of more than **3 gm per 24 hrs**) is the chief characteristic.
2. **Hypoalbuminaemia** (produced primarily due to urinary loss of albumin, and partly due to increased renal catabolism and inadequate hepatic synthesis)[8].
3. **Edema** (appears due to a fall in colloid osmotic pressure consequent to hypoalbuminaemia).
4. **Hyperlipidaemia** (increased blood levels of total lipids, cholesterol, triglycerides, VLDL, and LDL, but a decrease in HDL).
5. **Lipiduria** (occurs following hyperlipidaemia due to excessive leakiness of the glomerular filtration barrier).
6. **Hypercoagulability** (patients may develop spontaneous arterial or venous thrombosis, renal vein thrombosis, and pulmonary embolism).

Conditions That Manifest with Nephrotic Syndrome (Increased Filtration Barrier Permeability)

- In **children**, **primary glomerulonephritis** is the cause in the majority of cases.
- In **adults**, **systemic diseases** (diabetes, amyloidosis, and SLE) are more frequent causes.

- The most common primary glomerular disease in adults is **membranous glomerulonephritis** (40%).

COMPARISON OF ACUTE NEPHRITIC AND NEPHROTIC SYNDROMES

FEATURE	ACUTE NEPHRITIC SYNDROME	NEPHROTIC SYNDROME
1. Proteinuria	Mild (gm per 24 hrs)	Heavy (gm per 24 hrs)
2. Hypoalbuminemia	Uncommon	Present
3. Oedema	Mild, in loose tissues	Marked, generalised peripheral
4. Mechanism of oedema	and water retention	plasma osmotic pressure, Na+ and water retention
5. Hematuria	Present, microscopic	Absent
6. Hypertension	Present	Present in advanced disease
7. Hyperlipidemia	Absent	Present
8. Lipiduria	Absent	Present
9. Oliguria	Present	Present in advanced disease
10. Hypercoagulability	Absent	Present

PATHOGENESIS OF GLOMERULAR INJURY

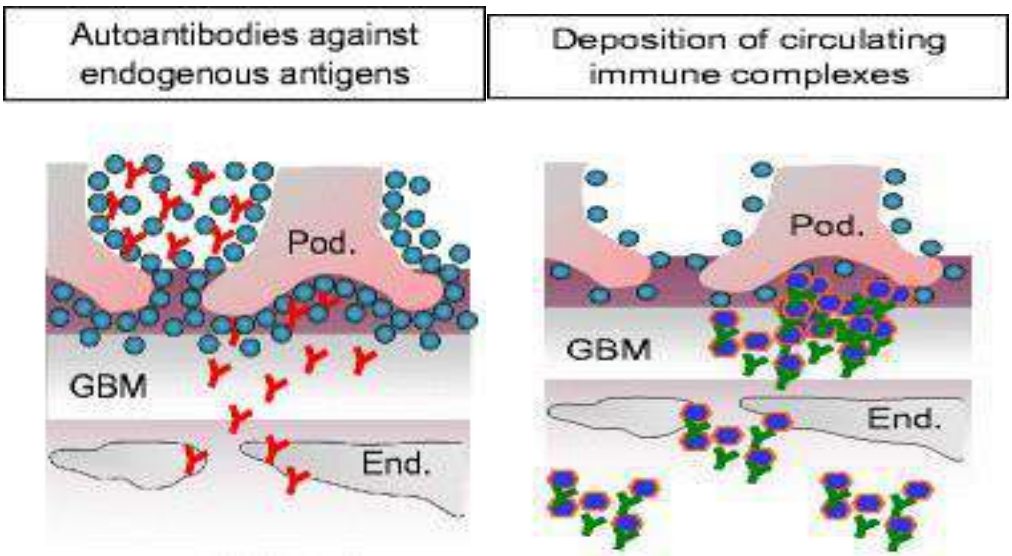
Most forms of primary GN and many of the secondary glomerular diseases have **immunologic pathogenesis**.

The mechanisms include:

1. **Antibody-Mediated Injury**
    - In Situ Immune Complex Deposition
    - Circulating Immune Complex Deposition
2. **Cell-Mediated Immune Injury**

I. Antibody-mediated Injury

- **In-situ immune complex deposition:** Injury by antibodies reacting *in situ* within the glomerulus. Circulating antibodies react directly with antigens placed in the glomeruli. The antibody and antigen form an immune complex that initiates inflammation and glomerular injury.
- **Deposition of circulating immune-complexes within the glomeruli:** Injury resulting from deposition of circulating antigen-antibody (Ag/Ab) complexes trapped within the glomeruli.



II. Cell-mediated immunity

Although antibody-mediated mechanisms may initiate many forms of glomerulonephritis, evidence suggests that **sensitized T cells** cause glomerular injury and are involved in the progression of some glomerulonephritides.

Histological Alteration of G.N.

Various types of GN are characterized by one or more of four basic tissue reactions:

1. **Hypercellularity:** An increase in the number of cells in the glomerular capillary tufts due to proliferation of **Mesangial cells, endothelial cells, or parietal epithelial cells**, in addition to **leucocytic infiltration** (neutrophils, monocytes, and lymphocytes in some cases).
2. **Thickening of the glomerular basement membrane**[76].
3. **Crescent formation:** A crescent-shaped mass of cells that may result from the proliferation of parietal cells.
4. **Hyalinization and sclerosis**.

Other alterations:

- Intra-capillary thrombosis.
- Fibrin deposition.
- Accumulation of lipids.

Terminology for Extent of Changes:

- **Diffuse:** Involving of glomeruli.
- **Global:** Involving **all** of the glomerular tuft.
- **Focal:** Involving of glomeruli.
- **Segmental:** Involving **part** of the glomerular tuft.

References

KAPLAN, medical USMLE step 1 lecture notes

First aid for USMLE step 1

2- Glomerular Diseases

objectives

- Outline the clinicopathological features of the common types of glomerulonephritis

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Clinico-Pathologic Classification of Glomerular Diseases

I. Primary Glomerulonephritis

1. Acute diffuse proliferative G.N.
2. Membranous G.N.
3. Minimal change G.N.

II. Secondary Systemic Glomerular Diseases

1. Diabetic nephropathy

Acute Diffuse Proliferative Glomerulonephritis (ADPGN)

Post Streptococcal Glomerulonephritis

Incidence:

- Mostly in children.
- Males > females.
- Usually develops 1-4 wks. following infection of upper respiratory tract by group A, B-haemolytic Strept.

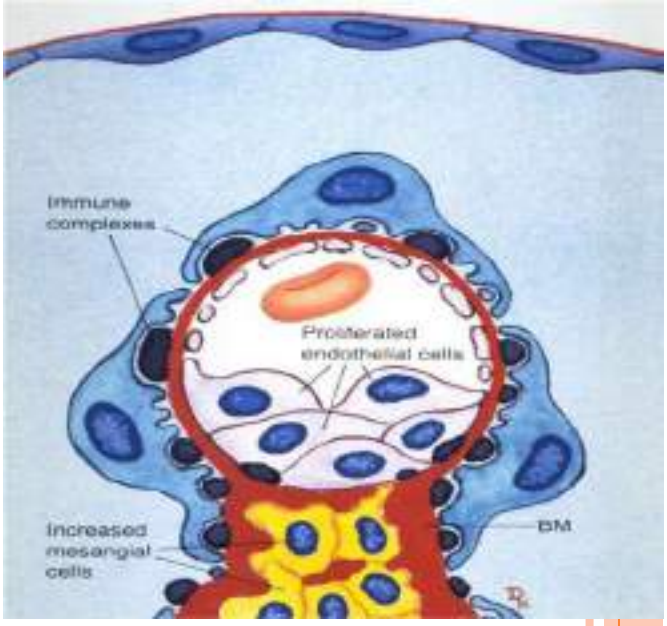
Pathogenesis:

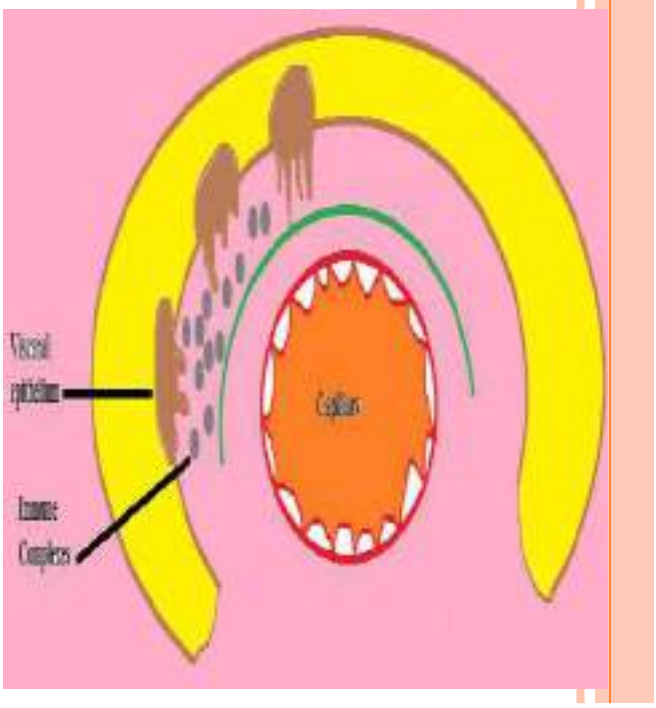
- **Immune complex disease**
- During the latent period; antibodies mainly IgG are formed against streptococcal antigens.
- An immune-complex reaction occurs between streptococcal antigens and the antibodies in patient's serum.

- The immune-complexes deposit between the visceral epithelial cells and glomerular basement membrane followed by complement activation and inflammatory injury to the glomerular capillaries.
- Visceral epithelium
- Immune complexes
- Increased mesangial cells
- Proliferated endothelial cells
- Capillary
- BM

Clinically:

- Sudden onset of fever & malaise





Nephritic syndrome:

- Mild oedema especially periorbital.
- Mild to moderate hypertension.
- Urine: Haematuria (**smoky urine**), oliguria & mild Proteinuria.
- **Azotaemia**: blood urea nitrogen and creatinine

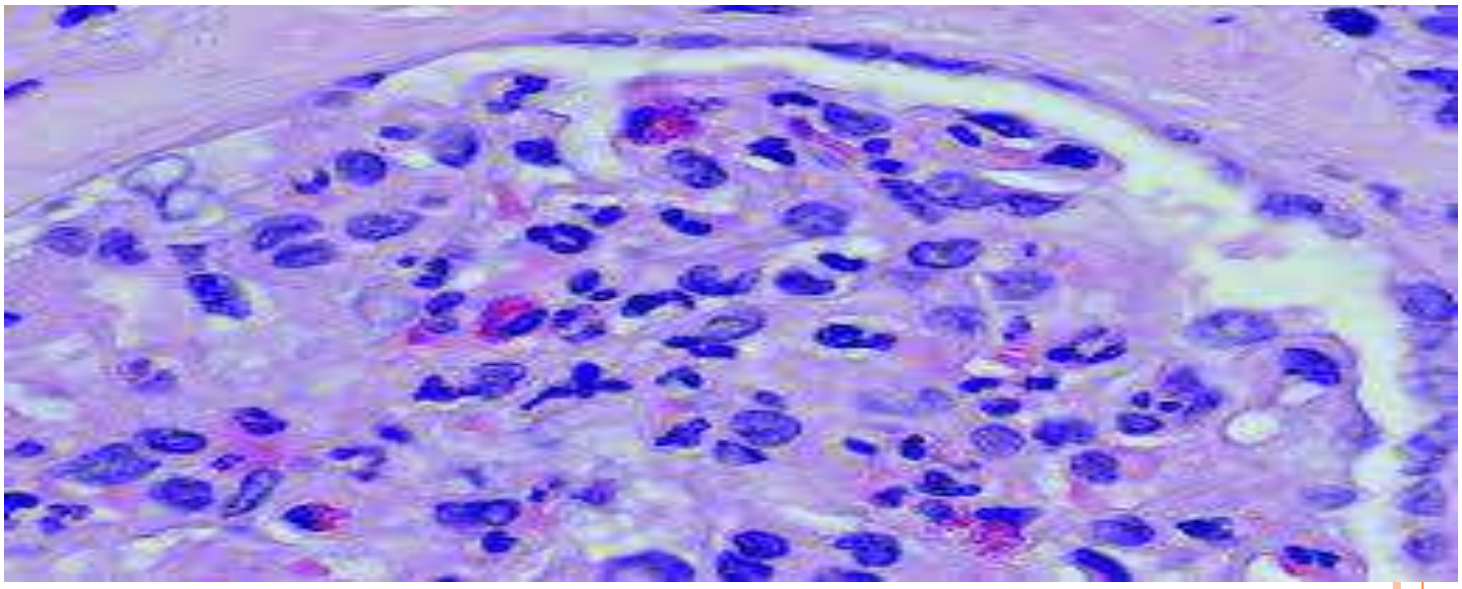
Pathology

■ Grossly:

- Size: both kidneys are slightly **enlarged** .
- Outer surface: smooth, **pale grey** in color with **red spots** due to capsular haemorrhage.
- Capsule: strips easily.
- Cut section: **Cortex is pale**, slightly thickened & easily demarcated from medulla.

Microscopically:

- All glomeruli show **swollen, cellular, bloodless capillary tufts** filling the capsular spaces.
- The increased cellularity is due to **proliferation** of capillary endothelium, glomerular epithelium, mesangial cells and **infiltration by neutrophils and monocytes**.
- The capsular space is narrowed and contains coagulated albumin, fibrin threads, neutrophils, RBCs and desquamated epithelial cells.
- The collecting tubules contain **casts** especially **blood casts**.
- The interstitial tissue is hyperaemic, oedematous and shows neutrophilic infiltrate.



Coarse and fate of disease:

- **Complete recovery** in over **95% of children** and **65% of adults**.
- The disease may progress to rapidly progressive or chronic glomerulonephritis.
- **Death** from acute uraemia or acute heart failure caused by sever hypertension.

Rapidly Progressive GN (RPGN or Crescentic GN)

- It is a **primary glomerulonephritis** characterized clinically by progressive deterioration in renal function that progress to **renal failure** within weeks to few months.

Clinical picture:

- Hematuria, sever oliguria or anuria, hypertension.
- Both edema and proteinuria are variable.

Etiology

I. It may complicate acute post-streptococcal proliferative glomerulonephritis, this complication is common in adults rather than children.

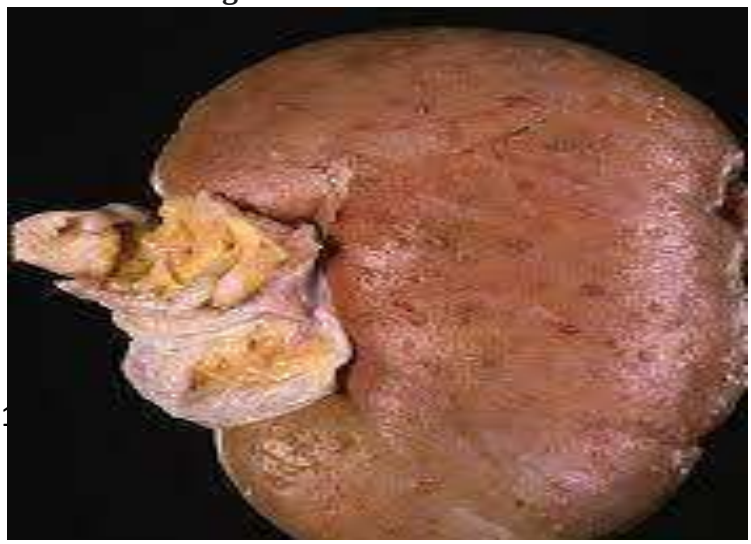
II. It may occur in association with systemic (immunologically based) diseases as systemic lupus erythematosis.

III. It may be idiopathic.

Pathological feature:

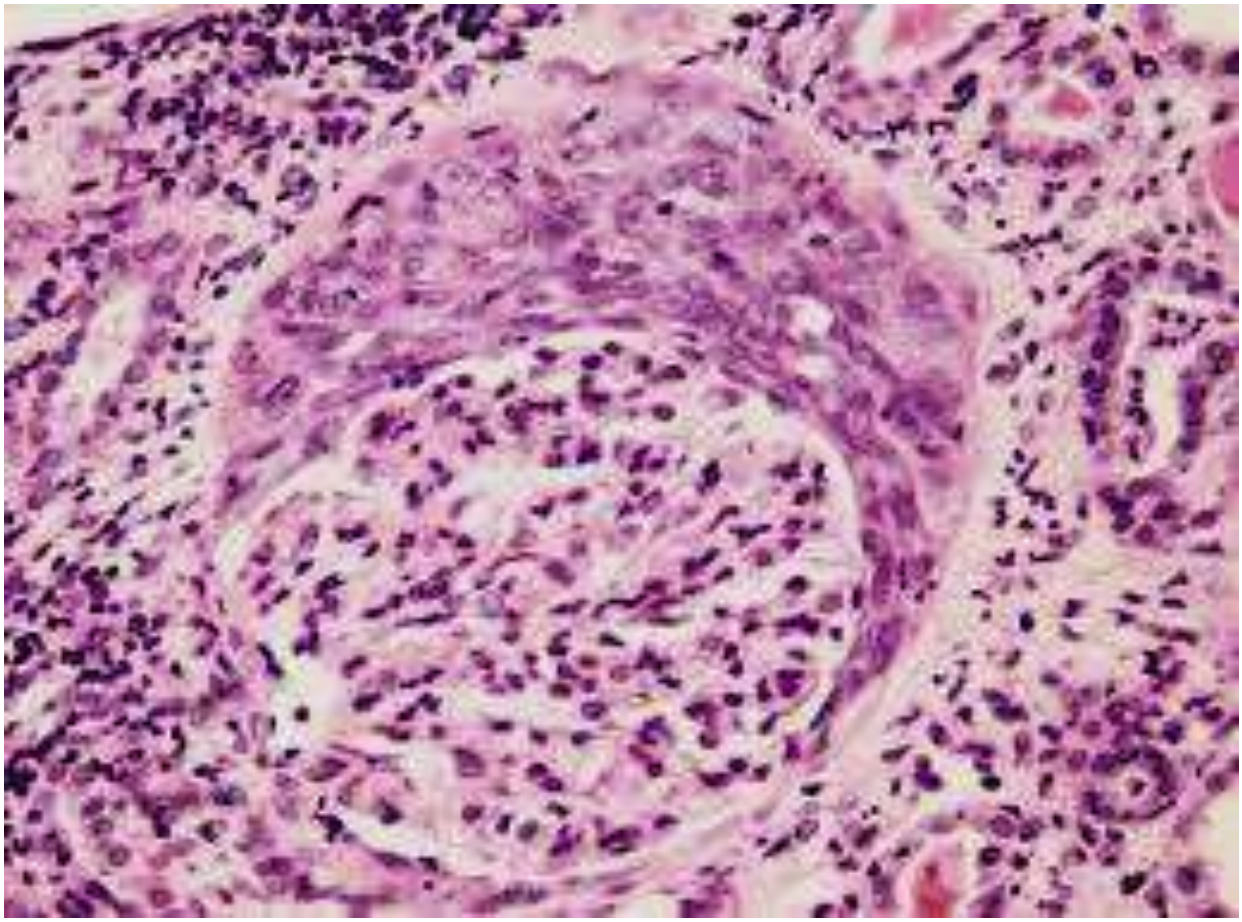
Gross picture:

- Both kidneys are **normal in size or slightly enlarged** due to edema.
- Outer surface is smooth.
- Cut section reveals **pale cortex** and **interstitial hemorrhage**.



Microscopic feature

- Glomeruli are enlarged and show **proliferation of endothelial cells and mesangial cells**.
- **Proliferation of the parietal cells of Bowman's capsule with formation of epithelial crescents** in the capsular spaces.
- Leucocytic infiltration.
- Glomerular capillaries show **thrombosis, necrosis and hemorrhage**.
- Tubular epithelial cells may show **necrosis**, renal tubules contain hyaline casts, RBC casts and cellular casts.



Fate of RPGN

- The disease is **rapidly progressive**.
- Acute renal failure.
- Hypertention.

Membranous Glomerulonephritis

- Is a common cause of **nephrotic syndrome in adults** that is mediated by immune complexes.

Etiology

- **Idiopathic** in **85%** of cases.
- May occur in association with:
    - Systemic lupus erythematosis.
    - Infections as hepatitis B, bilharziasi, malaria, syphilis.
    - Metabolic diseases as diabetes mellitus.
    - Malignant epithelial tumors as carcinoma of lung, carcinoma of colon.

Gross feature

- The kidneys are **enlarged and pale**.

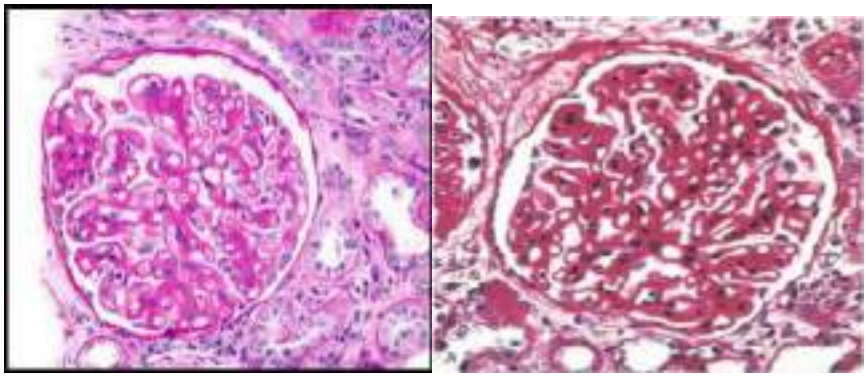
Microscopic feature

- **Diffuse thickening of the glomerular basement membrane** easily demonstrated by PAS stain.
- **No cellular proliferation** of the glomeruli.
- In advanced cases, glomerular sclerosis and hyalinosis occur, atrophy of tubules and interstitial fibrosis.

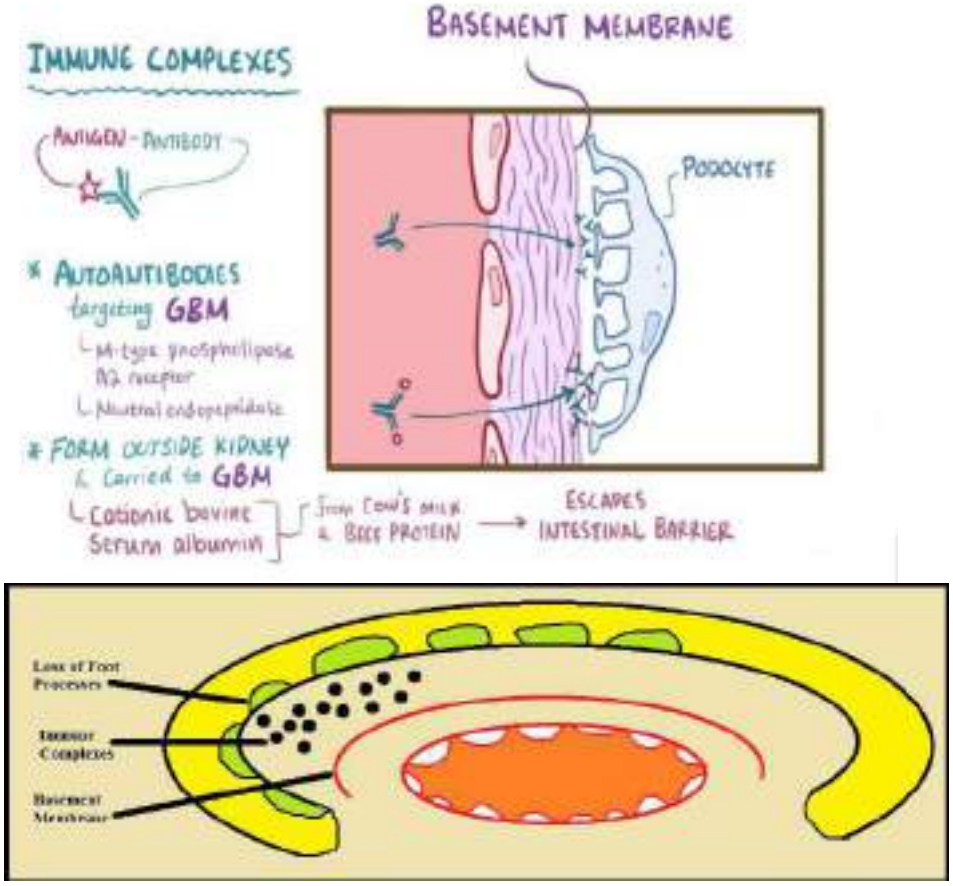
Clinical presentation

- Patients suffer from **nephrotic syndrome**.
- In advanced cases, renal insufficiency and hypertension develop.

Histologic image of membranous glomerulopathy. Note capillary and glomerular basement membrane



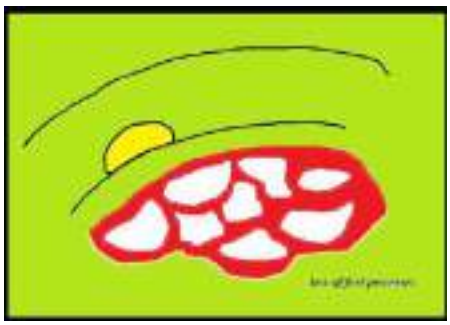
- **By Electron microscopy:**
  - The epithelial cells are swollen and **loss their foot processes**.
  - **dense IgG deposited between basement membrane and overlying epithelial cells**.



Minimal Change Disease

Lipoid Disease/ Light Negative GN/ Foot Process Disease

- Is the **most common cause of nephrotic syndrome in children**. Peak incidence is age 2–6.
- **Light microscopy** shows **normal glomeruli** with **lipid accumulation in proximal tubule cells (lipoid nephrosis)**.
- **EM** shows **effacement of epithelial (podocyte) foot processes** and **no immune complex deposits**.
- The prognosis is **excellent** because treatment with **corticosteroids** produces a **dramatic response** in children.



The majority have a complete recovery.

Secondary Glomerulonephritis

- Secondary glomerulonephritis is glomerular disease that is **secondary to other disease processes**.
- Diabetes causes **nodular glomerulosclerosis**, **hyaline arteriolosclerosis**, and diabetic microangiopathy.
- Clinically, diabetic patients may develop micro albuminuria that can progress to **nephrotic syndrome**.

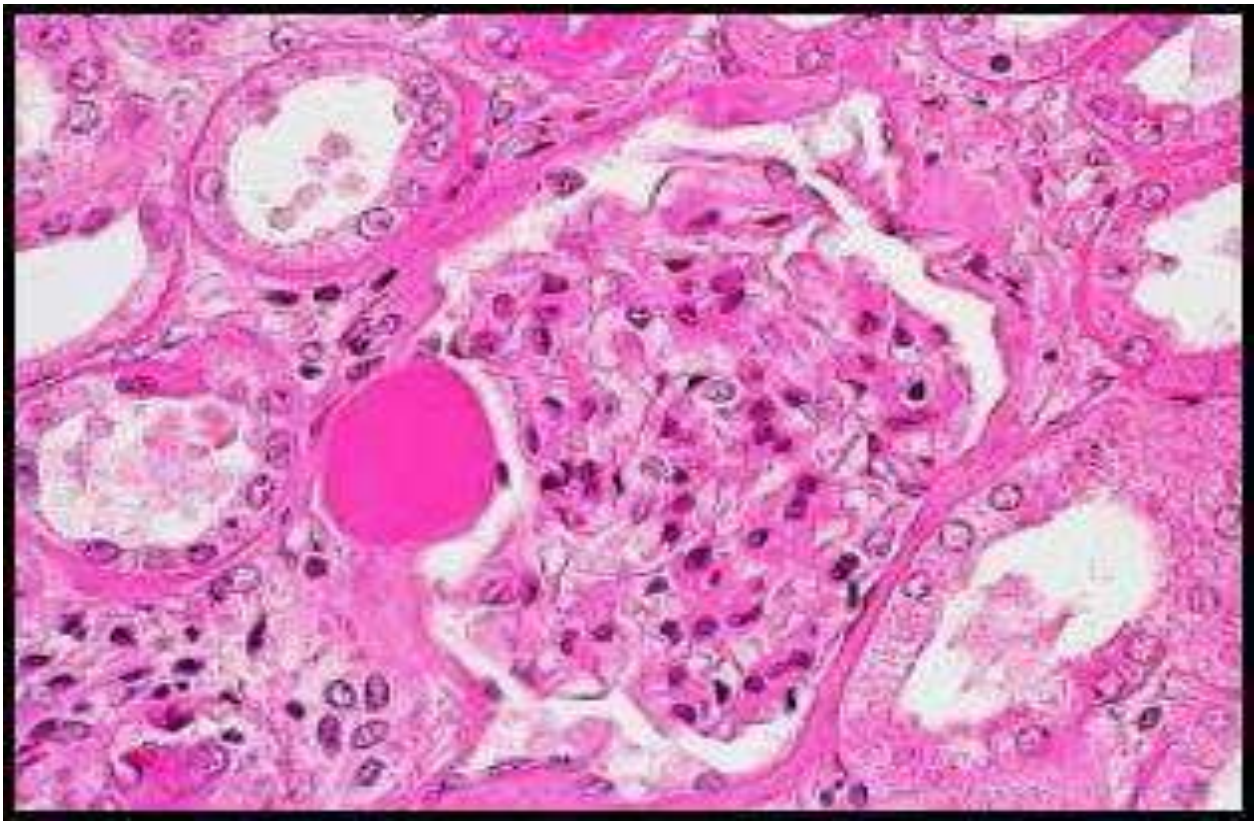
"Diabetic Glomerulosclerosis" / "Diabetic Nephropathy"

- Diabetes mellitus is a major cause of renal morbidity and mortality.
- It occurs in patients with long standing DM for **12 years or more**.

- **Diabetic nephropathy** is the **leading cause of end stage renal disease (ESRD)**, secondary to glomerular hypertension and hyperfiltration. These glomerular changes are caused by arteriolosclerosis.

Pathological features:

- It may take the form of:
    1. **Diffuse glomerulosclerosis**: Increase in mesangial matrix with thickening of GBM.
    2. **Nodular glomerulosclerosis (Kimmel Steil-Wilson lesion)**:
        - This is a localized sclerotic acellular nodule located at one side of the glomerular capillary tuft.
        - It is almost always superimposed on a pre-existing diffuse diabetic glomerulosclerosis.
        - It appears as amorphous, eosinophilic material.



Chronic Glomerulonephritis

- The **end stage** of various forms of GN.

Aetiology:

- In of cases, no history of renal disease.
- It may follow APSGN, MGN, MPGN, or FGN.

Gross Picture:

- The kidneys are **symmetrically contracted & firm**.
- Capsule is **adherent**.
- The outer surface is **pale** in colour, **finely granular** with projecting small bluish cysts.
- In the cut surface, the **cortex is atrophic** and indistinct from the medulla. The blood vessels are thickened.
- The **peri-pelvic fat is apparently increased** due to reduction in the kidney size.
- (The renal pelvis & calyces are not affected).

Microscopic Picture:

- **Glomeruli**: Some show segmental or global fibrosis & hyalinosis and are adherent to BC.
- Some show compensatory hypertrophy and may show features of etiology.
- **Tubules** attached to the fibrosed glomeruli are **atrophic**, while those attached to the functioning glomeruli show hypertrophy, dilatation and cyst formation and contain hyaline and granular casts.
- The **interstitial tissue** is infiltrated by **chronic inflammatory cells**; lymphocytes and plasma cells and shows areas of **fibrosis**.
- The **arteries** show the picture of **end arteritis obliterans**.

Course & prognosis:

- **Fatal disease**.
- Death due to **chronic uraemia** or hypertension, Heart failure. Cerebral haemorrhage.

References
KAPLAN, medical USMLE step 1 lecture notes
First aid for USMLE step 1

3- DISEASES OF RENAL TUBULES AND INTERSTITIUM

objectives

1. Knowledge of the Etiology and pathology of acute tubular necrosis
2. Define pyelonephritis and describe the risk factors.
3. Describe morphology and complication of acute and chronic pyelonephritis

Tubular and Interstitial Diseases

- Most forms of tubular injury involve the interstitium as well; therefore, diseases affecting these two components are discussed together.
- (1) ischemic or toxic tubular injury.
- (2) inflammatory reactions of the tubules and interstitium (tubulointerstitial nephritis).

Acute Tubular Injury/Necrosis (ATI)

Definition: It is a clinico-pathologic entity characterized by **Sudden decline in renal function**, secondary to **ischemic or toxic damage to renal tubular epithelial cells**.

- It is the **most common cause of acute renal failure**.
- Usually associated clinically with **oliguria, high serum creatinine, acute renal failure and hypertension**.

Etiology

ATI can be caused by a variety of conditions, including:

1. Ischemia, due to decreased or interrupted blood flow, such as:

- Malignant hypertension
- Systemic conditions associated with thrombosis (e.g., hemolytic uremic syndrome, and disseminated intravascular coagulation)

- Decreased effective circulating blood volume, as occurs in hypovolemic shock

2. Toxic injury to the tubules by:

- **Endogenous agents** (e.g., myoglobin, hemoglobin, monoclonal light chains, bile/bilirubin)
- **Exogenous agents** (e.g. drugs, radiocontrast dyes, heavy metals, organic solvents)

Postulated sequence in ischemic or toxic acute tubular injury:

Toxic injury or Ischemia (via Vasoconstriction) leads to Tubular injury.

Tubular injury results in:

- **Tubular back leak** Decreased urine output
- **Sloughed cells** Obstruction Decreased urine output and Decreased GFR
- **Interstitial inflammation** Decreased GFR

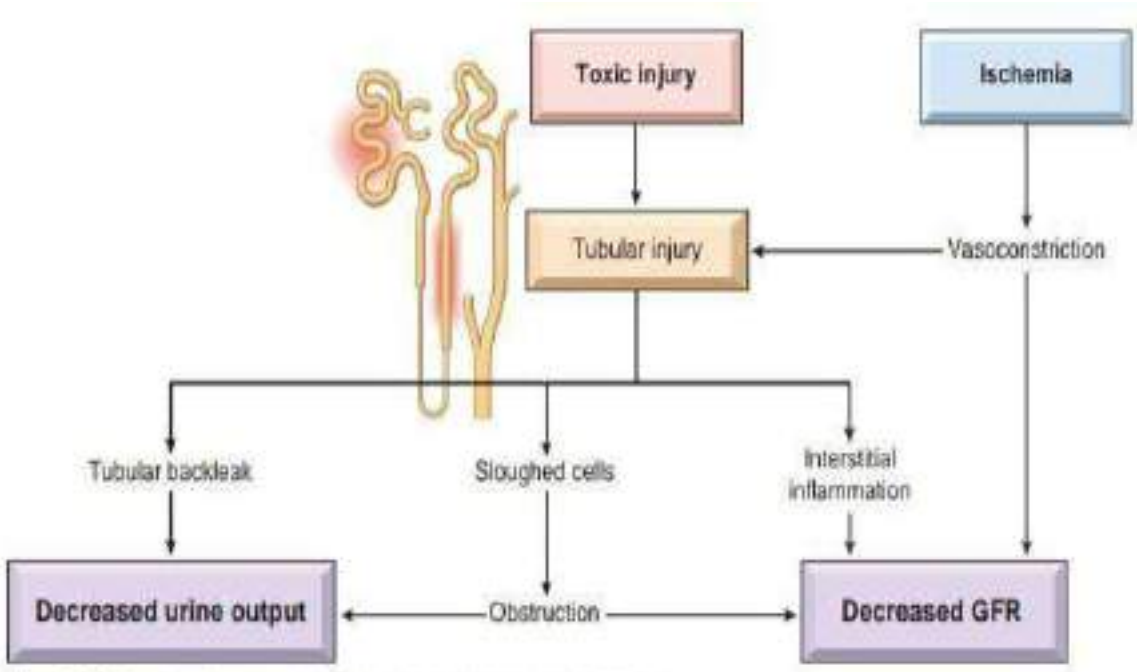
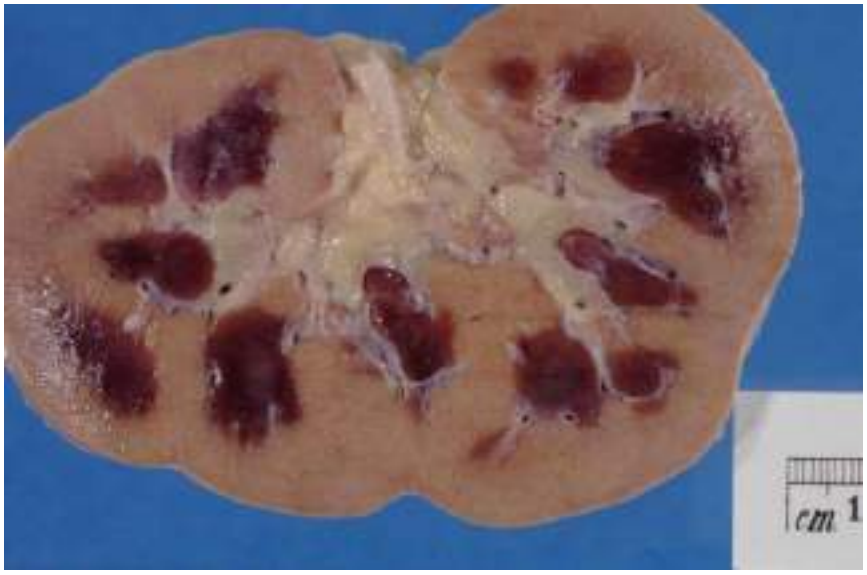


Figure 20-22 Postulated sequence in ischemic or toxic acute tubular injury.

Pathological Features:

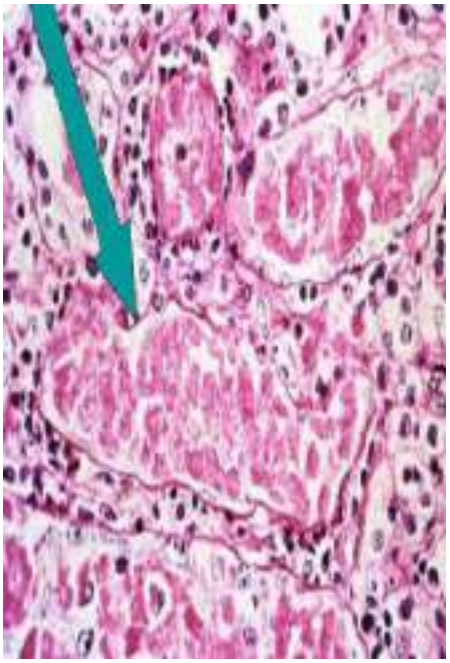
Grossly: * In toxic tubular necrosis, both kidneys are enlarged and soft and the cut surface shows a **pale cortex**.

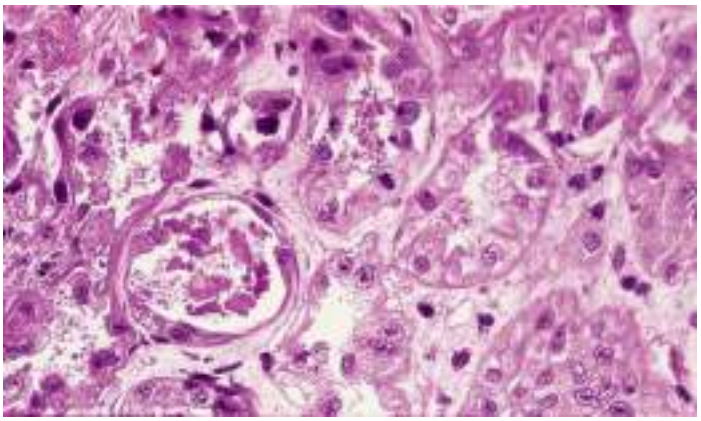
- **Patchy destruction of renal cortex and medullae with multiple foci of necrosis**.

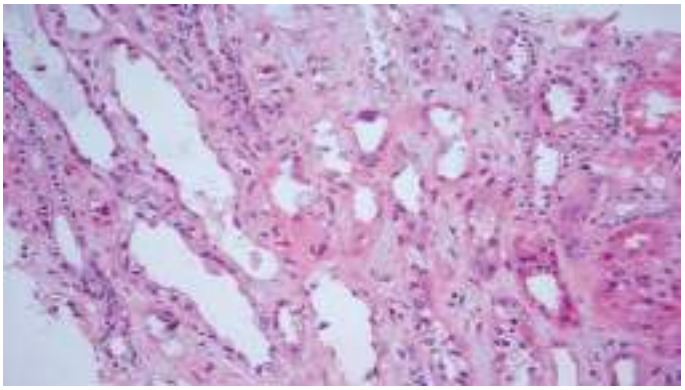


Microscopically:

- The tubular epithelium, specially in the **proximal tubules**, shows **extensive necrosis**. The necrotic tissue blocks the tubular lumen.
- **Shedding of tubular epithelium**, Focal destruction of tubular wall.
- **Hemorrhage within tubular lumen with RBCs casts**.
- **Interstitial tissue edema and infiltration by acute inflammatory cells**.







Effects:

1. **Anuria** due to Blockage of the tubules by the necrotic cells and cast.
2. **Acute uraemia**.
3. **Acute cardiac failure** caused by hyperpotassaemia.
4. Tubular regeneration and **recovery** rarely occurs.

Tubulointerstitial Nephritis Induced by Drugs

- Drug induced tubulointerstitial nephritis is the **second most common cause of acute kidney injury** (after pyelonephritis) due to acute or chronic drug consumption.
- Characterized by inflammation of renal interstitial tissue with progressive destruction of renal tissue.
- **Causes:** Exposure to different drugs induces variable deleterious effect on renal tubules and interstitium. **Interstitial nephritis is commonly induced by antibiotics, analgesics and chemotherapy**.

Clinically:

Drug-induced acute interstitial nephritis

- Begins about **15 days** (range: 2-40) after drug exposure.
- Characterized by: **fever**, **eosinophilia** (which may be transient), and a **rash** in about 25% of patients.
- Renal abnormalities take the form of **hematuria, mild proteinuria, and leukocyturia**.
- A **rising serum creatinine or acute kidney injury with oliguria** develops in about 50% of cases, particularly in older patients.

Drug-induced Chronic interstitial nephritis (Also called: analgesic nephropathy)

- **Pathogenesis:** Induction of progressive degeneration and necrosis of renal papillae associated with interstitial tissue inflammation.

- **Grossly:**
    - **Depressed cortex** due to cortical atrophy overlying necrotic papillae.
    - Papillae show varying stages of **necrosis and sloughing**.
- **Microscopically: Coagulative necrosis of renal papillae**, interstitial infiltration by **lymphocytes** followed by **patchy fibrosis** on long standing cases.

Pyelonephritis

Definition: Bacterial inflammation of the interstitial tissues of the **renal pelvis, medulla and cortex**.

- Pyelonephritis is a very common kidney disease.

Etiology (Organisms)

- ***E. coli*** is the commonest causative organism.
- Other causative bacteria are *streptococcus foecalis, staphylococcus aureus, bacillus proteus aerobacter aerogenes* and *typhoid bacilli*.
- Mixed infection is common.

Risk Factors

1. **Urinary tract obstruction:** Caused by urinary bilharziasis, Strictures, Stones, Tumors, enlarged prostate and congenital malformations.
2. **Diabetes mellitus**.
3. **Instrumentation of the urinary tract**.
4. **More common in females** due to:
    - The short wide urethra.
    - Pressure of the enlarged pregnant uterus on the ureters at the pelvic brim.

Routes of Infection

1. **Haematogenous infection:** Occurs in most cases. Bacteria enters the blood from foci of infection as tonsillitis, sinusitis, otitis media, abscess, bronchiectasis, cervicitis and prostatitis.
2. **Ascending infection:** From the bladder by the following routes:
    - The lumen of the ureter.
    - Through the periureteric lymphatics.
    - Through the subepithelial tissues of the bladder and ureters.
3. **Direct infection:** As from the colon is rare.

Pathological Features (Acute and Chronic)

(1) Acute Pyelonephritis

Gross picture: * Commonly the lesion is **bilateral**.

- The kidney is **enlarged and congested**.
- The capsule **strips easily**.
- The outer surface shows **multiple abscesses**.
- The cut surface shows **tiny abscesses in the cortex and medulla**.
- The abscesses in the medulla are arranged as **radial streaks**.
- The calyces and pelvis are congested and contain **purulent exudate**.

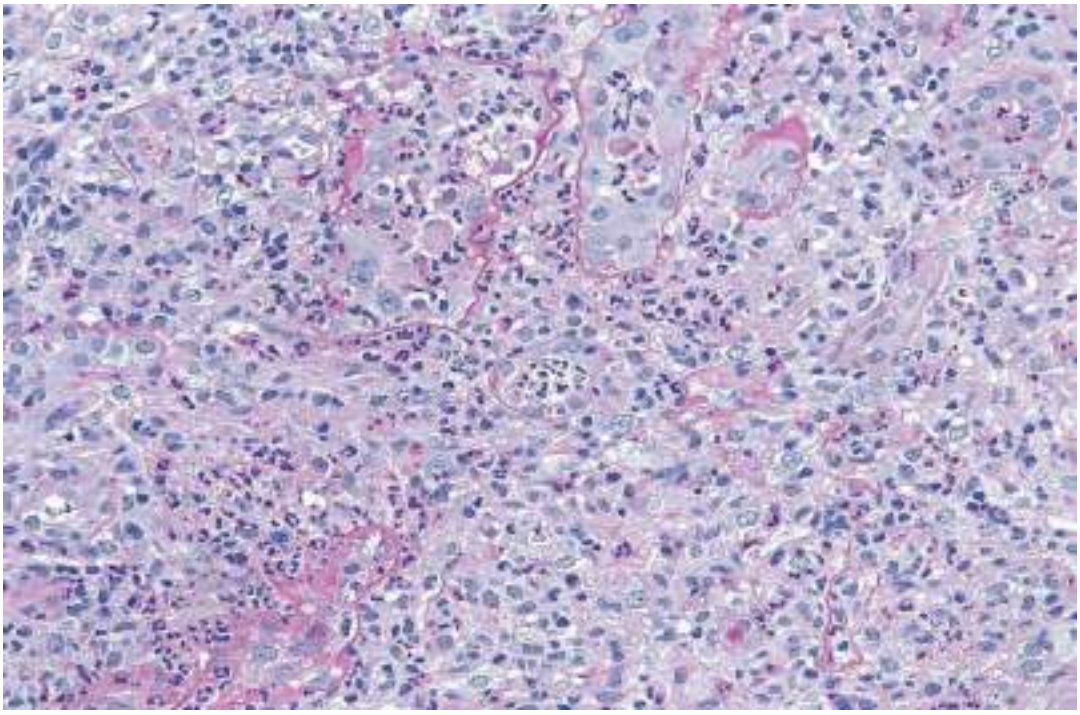
Microscopic picture:

- The interstitial tissue is infiltrated by **polymorphonuclear leucocytes and pus cells**.
- The tubules show **tubular degeneration, necrosis and leucocytic casts**.
- The calyces and pelvis are hyperaemic, oedematous and infiltrated by **acute inflammatory cells**.

Clinical picture: Fever, rigors, renal tenderness, dysuria and pyuria.

Course:

1. Resolution and **recovery** in mild cases.
2. Change to **chronic pyelonephritis**.
3. Death due to **acute uraemia** in severe bilateral cases.



(2) Chronic Pyelonephritis

- May follow acute pyelonephritis, but commonly starts as chronic inflammation.

Gross picture: * The kidney is **reduced in size**.

- The capsule is **thick and adherent**.
- The surface shows **irregular depressions** due to cortical scarring.
- The calyces and pelvis are **thickened, distorted, dilated** and contain purulent exudate and shedded mucosal cells.

Microscopic picture:

1. The interstitial tissue is infiltrated by **lymphocytes with lymphoid follicles formation**, also **plasma cells, macrophages and shows fibrosis**.
2. Some tubules are atrophic, others are **dilated and contain large hyaline casts (colloid casts)**.
3. The blood vessels are **thickened and show endarteritis obliterans**.
4. The calyces and pelvis show **chronic inflammation and fibrosis**.

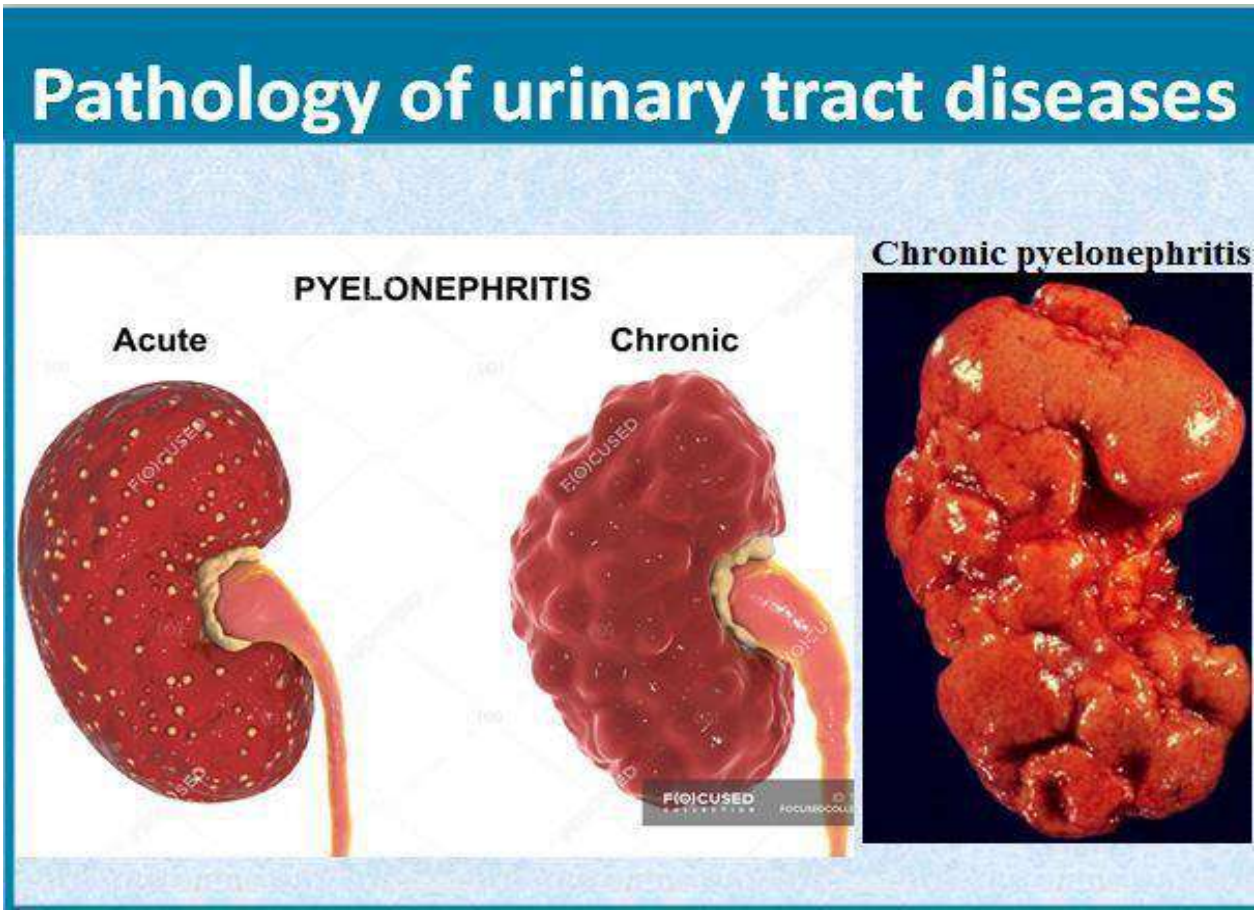
Effects:

1. Secondary **hypertension**.
2. **Chronic renal failure**.

Comparison of Acute and Chronic Pyelonephritis

Feature	Acute	Chronic
Clinically	- Frequency and dysuria - High grade fever & rigors - Acute loin pain	- Chronic mild loin pain - Hypertension - Repeated acute attacks
Renal Function/Urine Analysis	- Numerous pus cells, RBCs, proteins and cell casts + high serum creat.	- Pus cells and microscopic RBCs + high serum creatine.
Grossly		
Size	- Enlarged	- Asymmetrically contracted

Feature	Acute	Chronic
Surface	- Smooth	- Irregular
Capsule	- Strips easily	- Adherent
Cut section	- Cortex is differentiated - Small cortical abscesses	- Cortex is not differentiated - Fibrotic
Microscopic Picture (MP)		
Glomeruli	- No significant changes	- May be fibrotic or atrophic
Tubules (Lining)	- Degenerated or damaged	- Atrophic lining or fibrosis
Tubules (Lumen)	- RBCs cast	- Hyaline cast (**colloid casts**)
Vessels	- Congested capillaries	- End-arteritis obliterans
Interstitium	- Infiltration by PNLs, pus cells, plasma cells and macrophages	- Infiltration by plasma cells, lymphocytes (**lymphoid follicles**) and fibroblasts
Fate and Effects	- If mild: recovery - If severe: acute renal failure - May lead to chronic form	- Hypertension - Renal calculi - End by chronic renal failure



References

KAPLAN, medical USMLE step 1 lecture notes

First aid for USMLE step 1

4- Urinary Outflow Obstruction & Lower Urinary Tract Infection

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Objectives:

- Define hydronephrosis and enumerate its types, causes, and their complications.
- Define Urinary Tract Infections (UTIs) and describe their etiology.
- Define cystitis and describe its etiology, pathology, and enumerate complications.

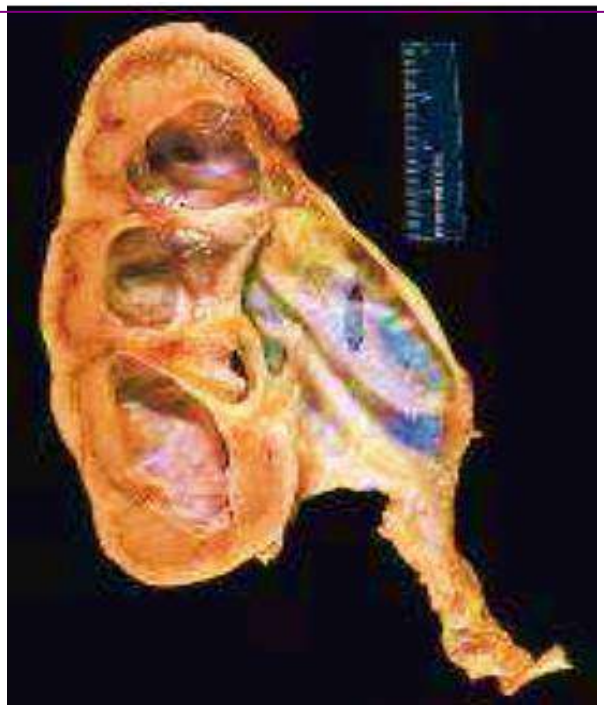
Urinary Outflow Obstruction

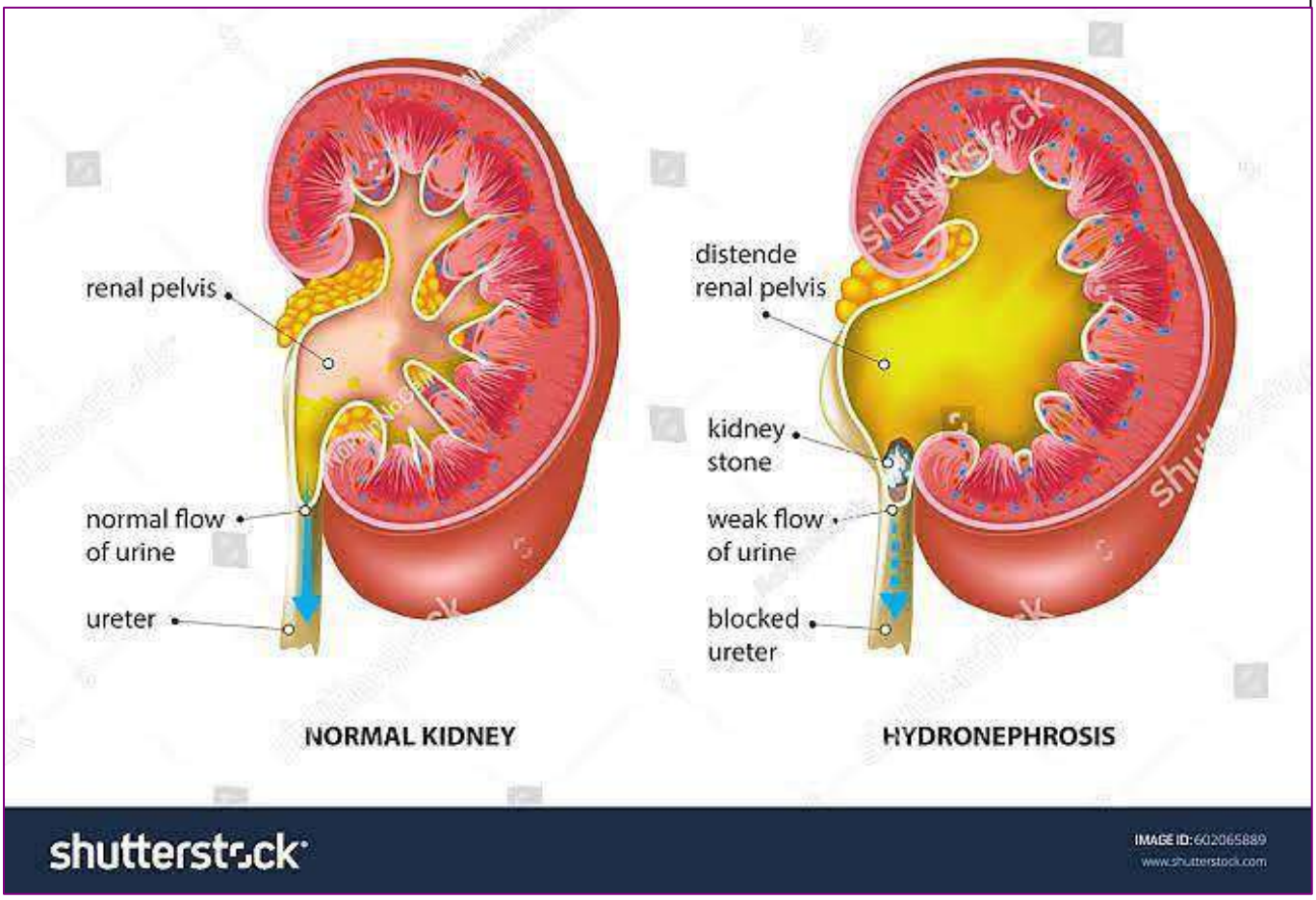
Hydronephrosis

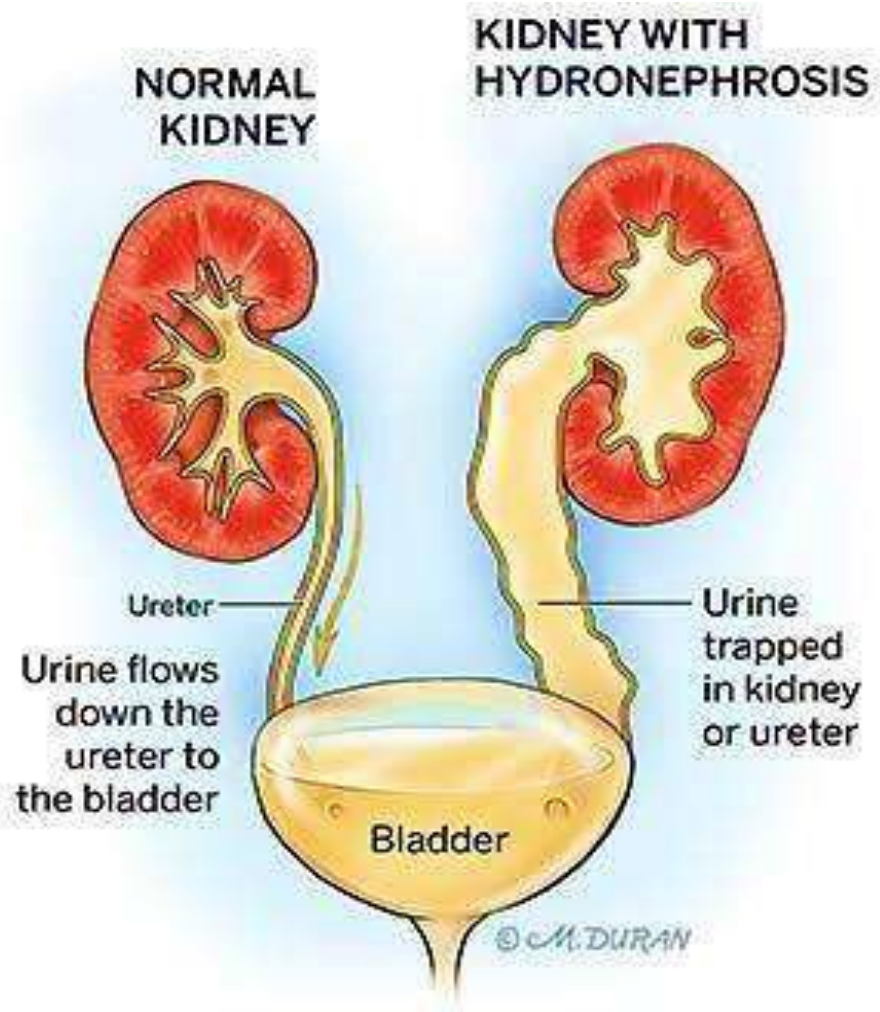
Definition:

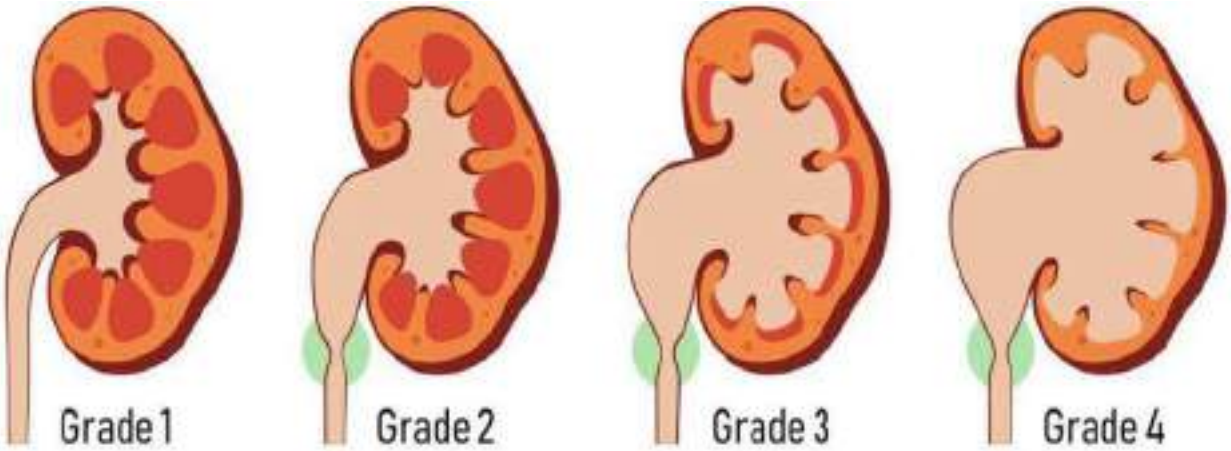
Hydronephrosis refers to the dilation of the renal pelvis and calyces, accompanied by atrophy of the parenchyma, which is caused by an obstruction to the outflow of urine7. This obstruction can be sudden or gradual, and it may occur at any level of the urinary tract, from the urethra to the renal pelvis.

Hydronephrosis






NORMAL KIDNEY
KIDNEY WITH HYDRONEPHROSIS
Ureter
Urine flows down the ureter to the bladder
Urine trapped in kidney or ureter
Bladder
© M. DURAN


Grade 1
Grade 2
Grade 3
Grade 4

Types of Hydronephrosis:

A. According to site of obstruction:

1. **Bilateral:** Occurs only when the obstruction is below the level of the ureters.
2. **Unilateral:** If the blockage is at the ureters or above, the lesion is unilateral.

B. According to type of obstruction:

1. **Complete:** Allows no urine to pass.
2. **Partial:** Allows urine outflow.

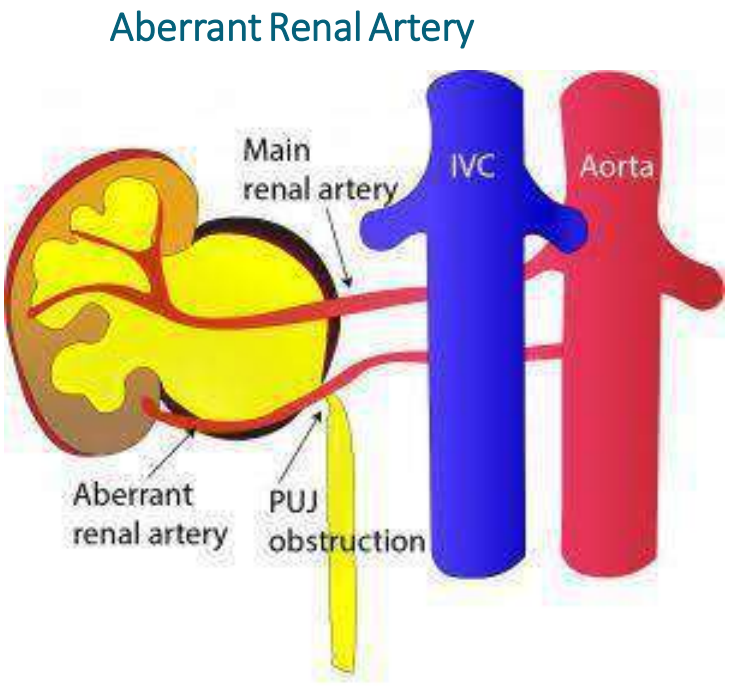
Main Causes of Hydronephrosis: [15]Causes can be categorized into Congenital and Acquired

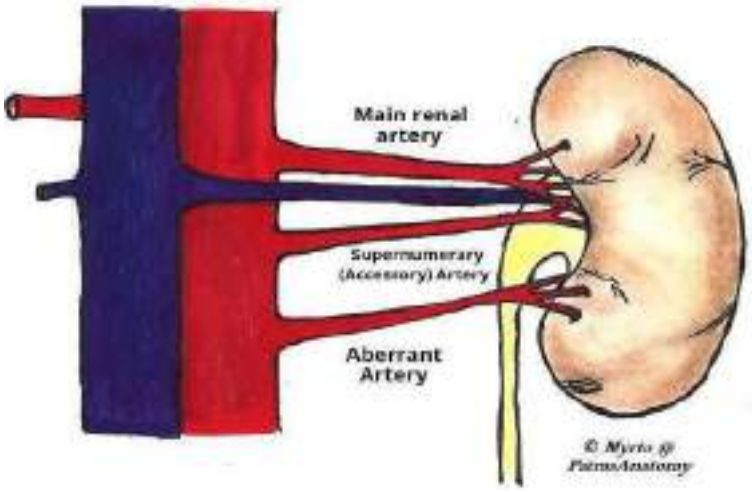
A. Congenital causes:

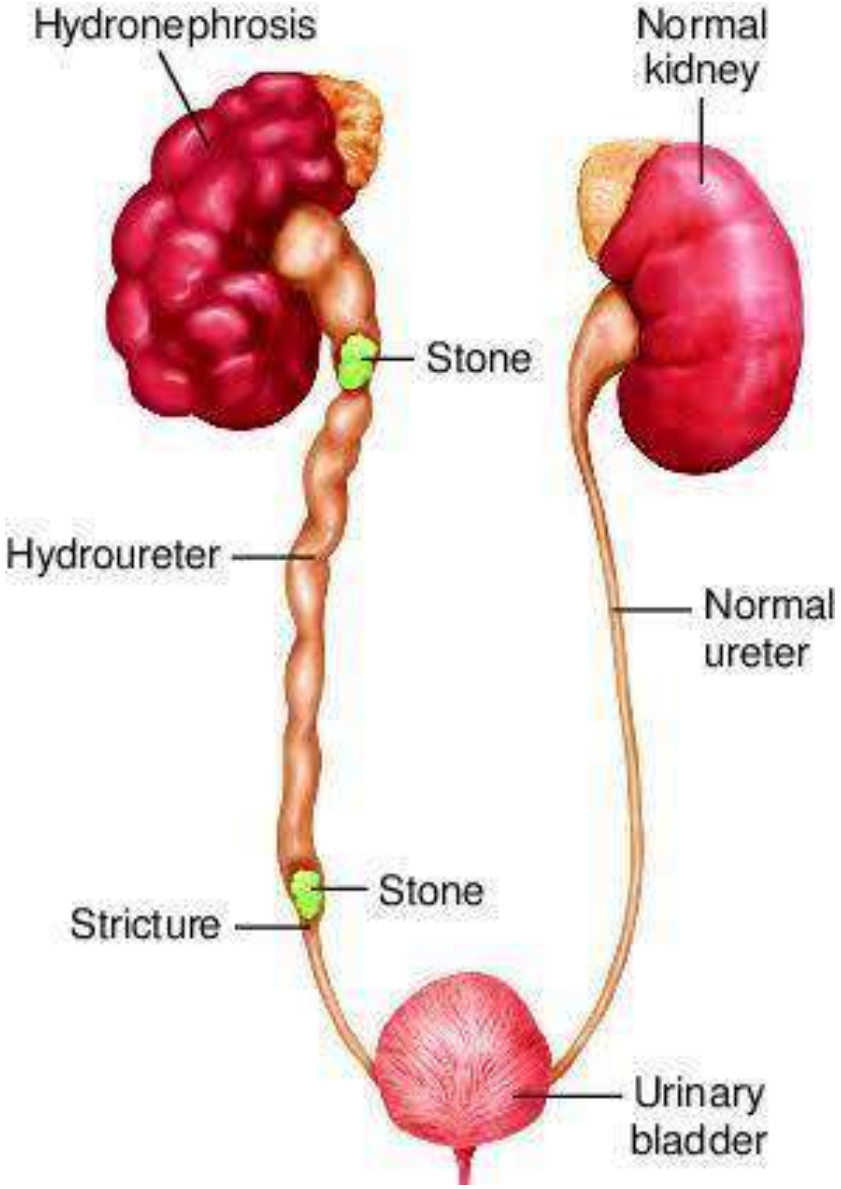
1. **Atresia of the urethra**.
2. **Valve formations** in either the ureter or urethra.
3. An **aberrant renal artery compressing the ureter**.

B. Acquired causes:

1. **Foreign Bodies:** Such as calculi
2. **Proliferative Lesions:** Such as BPH (Benign Prostatic Hyperplasia), carcinoma of the prostate, bladder tumors, or contiguous malignant disease (e.g., carcinoma of the cervix or uterus)
3. **Inflammatory Lesions:** Such as ureteritis and urethritis
4. **Neurogenic:** Such as paralysis of the bladder following spinal cord damage
5. **Normal Pregnancy**




Main renal artery
Supernumerary (Accessory) Artery
Aberrant Artery


Hydronephrosis
Normal kidney
Stone
Hydroureter
Normal ureter
Stone
Stricture
Urinary bladder

Complications of Hydronephrosis:

- In addition to functional changes, obstruction also triggers an interstitial inflammatory reaction, leading eventually to **interstitial fibrosis**.
- Depending on the level of obstruction, one or both ureters may be dilated (**Hydroureter**).
- **Superimposed pyelonephritis**
- **Pyonephrosis** (pelvis and calyces are distended with pus, followed by atrophy of renal tissue)
- Stasis of urine predisposes to **calculi formation**
- **Renal failure** in bilateral cases
- Experimental studies indicate that serious **irreversible damage** occurs in about **3 weeks with complete obstruction**, and in **3 months with incomplete obstruction**

Urinary Tract Infections (UTIs)

Definition: UTIs are infections of the lower urinary tract, usually bacterial34.

Etiology:

- Common bacteria that cause UTIs include **E. coli** and **Staphylococcus saprophyticus**
- UTIs are extremely common in several different populations and conditions.

UTIs are common in populations & settings such as:

1. **Outpatient:** Especially common among **females**, thought to be due to the short female urethra and the small distance between the urethra and the anus
2. **Inpatient:** Very common, especially with **catheter use**
    - **E. coli** is the most common causative organism.
    - *Klebsiella*, *Proteus*, *Enterobacter*, and *Serratia* are also common offenders.
3. **Pregnancy:**
    - **Asymptomatic bacteriuria** is common.
    - There is a higher risk for UTIs to develop into **pyelonephritis** in pregnant women.
    - UTIs also raise the risk for **preterm labor and low birth weight**.
4. **Children:** Children with recurrent UTIs should be evaluated for **vesicoureteral reflux (VUR)**.

Cystitis

Definition:

Cystitis refers to a variety of inflammatory lesions involving the urinary bladder46.

Types:

1. **Acute cystitis**
2. **Chronic cystitis**
    - Chronic specific
    - Chronic non-specific

1. Acute Cystitis

Etiology:

- **Predisposing factors:**
    - Low immunity (e.g., in Diabetes Mellitus)
    - Urine stasis (e.g., in urethral or bladder neck obstruction & functional abnormalities like spinal cord injuries)
    - Medical instruments (e.g., catheter, cystoscope)
- **Causative organisms:** *Staphylococci*, *streptococci*, *gonococci*, **E. coli**, viruses (e.g., herpes simplex), fungal (rare).
- **Routes of infection:**
    - Direct from urethra
    - Descending from kidney
    - Lymphatic spread from pelvic organs
    - Blood spread from bacteremia

Clinical presentation:

- **Dysuria** (burning or painful urination)
- **Frequency**
- **Urgency** (desire of immediate urination)
- **Suprapubic pain**
- **Pyuria** (pus in urine in cases of septic inflammation)
- **Hematuria**

- In an uncomplicated UTI, there is **no fever, nausea, vomiting, or costovertebral angle (CVA) tenderness** (which is seen in pyelonephritis)¨

Pathology:

- Urinary bladder shows:
    1. Predominantly **neutrophilic infiltration** of the lamina propria and urothelium.
    2. **Edema** of lamina propria.
    3. Frequent **urothelial ulceration**.
- Cytological examination of urine reveals the presence of many **neutrophils & pus cells**.

Complications:

1. Spread of infection.
2. Chronicity.

2. Chronic non-specific Cystitis

Etiology:

May follow acute cystitis or start as chronic from the beginning.

Clinical presentation:

Frequency, dysuria, pyuria, and maybe hematuria.

Complications:

1. Spread of infection
2. Calculi formation
3. Contracted bladder
4. Hyperplasia, metaplasia or dysplasia, or carcinoma

3. Chronic specific Cystitis

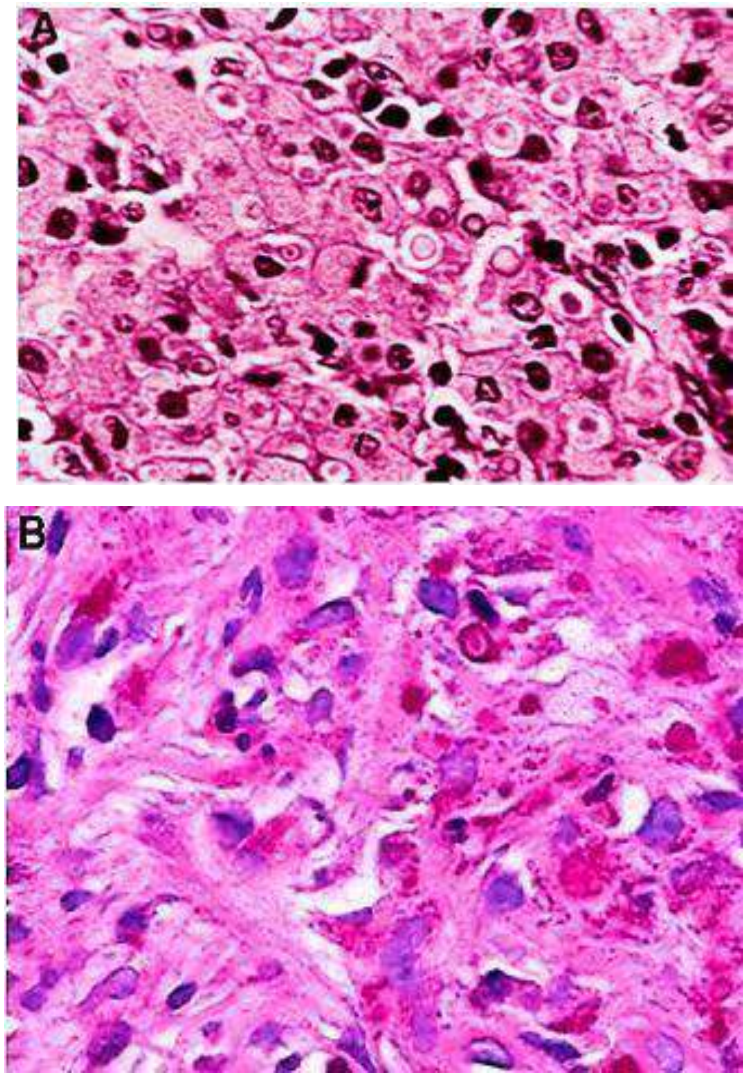
Pathology:

There is chronic inflammatory infiltrate of lamina propria as well as edema and fibrosis66.

Variants include:

- **Granulomatous C:** e.g., bilharziasis, tuberculosis
- **Eosinophilic C**

- **Polypoid C**
- **Chronic interstitial cystitis**
- **Follicular cystitis**
- **Gangrenous**
- **Malakoplakia:**
    - Atypical infection by bacteria (usually Gram negative bacteria).
    - The bladder shows multiple small **yellow mucosal nodules or plaques**, usually in the area of the trigone.
    - Characterized by large numbers of **epithelioid histiocytes (von Hannemann histiocytes)** with abundant granular eosinophilic cytoplasm and **intracytoplasmic inclusions (Michaelis-Gutmann bodies, 3–10 μm)**.



Malakoplakia

References Robbin's Basic pathology, 10th edition.

Renal & Bladder tumors

Objectives:

- Classify renal tumors.
- Outline renal cell carcinoma, the presenting features and morphological appearances.
- Outline nephroblastoma, the presenting features and morphological appearances.
- Classify tumors of the urinary bladder.
- Describe and discuss the epidemiology, risk factors and pathology of transitional cell carcinoma.
- Describe of the urinary bladder; epidemiology, risk factors and pathology of squamous cell carcinoma.

The following table:

Classification of Renal Tumours	**Benign**	**Malignant**
I) Epithelial tumors of renal parenchyma:	- Adenoma. - Oncocytoma.	- Adenocarcinoma (Hypernephroma, Renal cell carcinoma).
II) Epithelial tumors of renal pelvis:	- Transitional cell papilloma.	- Transitional cell carcinoma. - Others (squamous cell carcinoma, adenocarcinoma of renal pelvis).
III) Embryonal tumors:	- Mesoblastic nephroma. - Multicystic nephroma.	- Wilms' Tumor (nephroblastoma).
IV) Non epithelial tumors:	- Angiomyolipoma. - Medullary interstitial tumors (fibroma).	- Sarcomas (rare).
V) Miscellaneous:	- Juxtaglomerular cell tumor.	
IV) Metastatic tumors.		

Renal Cell Carcinoma (Hypernephroma)

Definition & Epidemiology:

Renal cell carcinoma (RCC) is an adenocarcinoma arising from tubular epithelium of the kidney and here they are located in the cortex.

This cancer comprises 80 to 85% of all renal cancers & 2-3% of adult cancers.

It occurs most commonly from 6th to 7th decades.

There is male predominance (2:1).

Etiology:

Risk factors:

- 1. Tobacco.
- 2. Exposure to asbestos & cadmium.
- 3. Hypertension.
- 4. Hereditary and acquired cystic diseases of the kidney. RCC increased 30-fold in acquired cases.
- 5. Obesity and estrogen therapy**.**
- 6. Hereditary: about 5% cases are inherited, but the majority of cases of RCC are sporadic.

Classification of RCC:

Based on cytogenetics of sporadic and familial tumors, RCC has been reclassified recently into: 1) clear cell, 2) papillary, 3) chromophobe, 4) granular cell, 5) sarcomatoid and 6) collecting duct type.

The first 3 types are the commonest.

Clear cell tumours are associated with homozygous loss or inactivation of the VHL tumor suppressor protein.

Gross picture of RCC:

RCC commonly arises from the poles of the kidney as a solitary and unilateral tumor, more often in the upper pole.

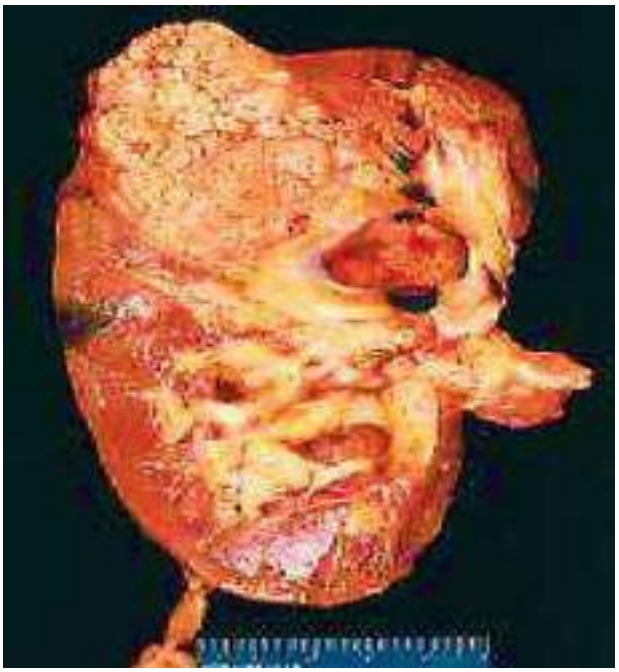
The tumor is generally large, golden yellow and circumscribed.

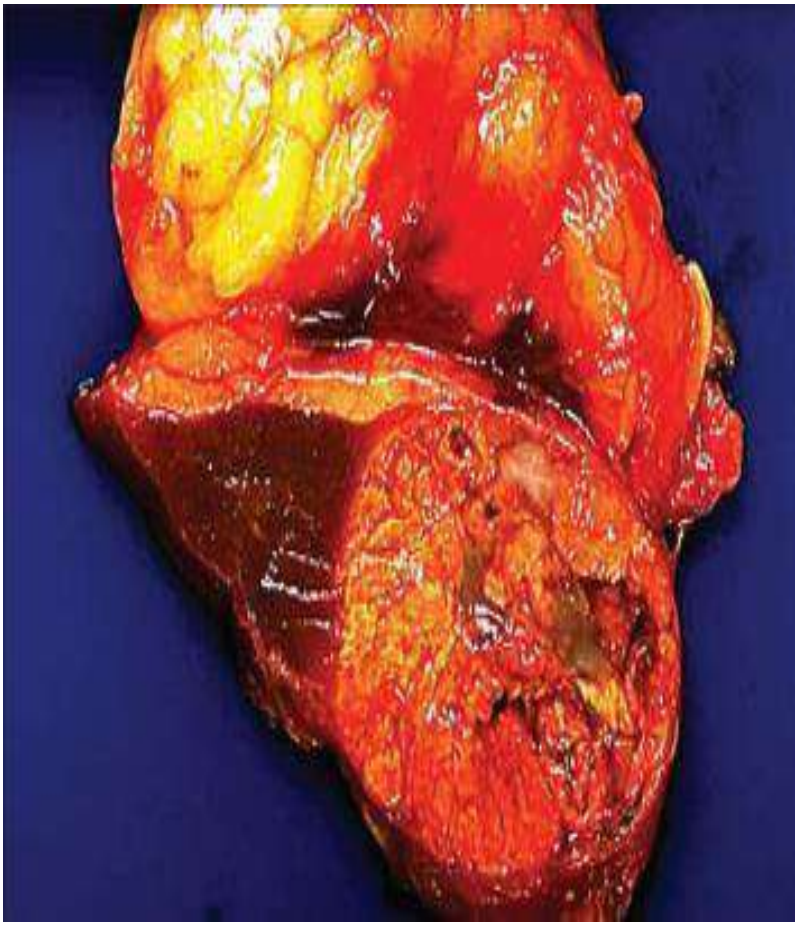
Papillary type may be multifocal and bilateral, grossly visible papillae.

Cut section of the tumor may show areas of ischaemic necrosis, cystic change and foci of haemorrhages.

Another significant characteristic feature is the frequent presence of tumor thrombus in the renal vein which may extend into the vena cava.

RCC

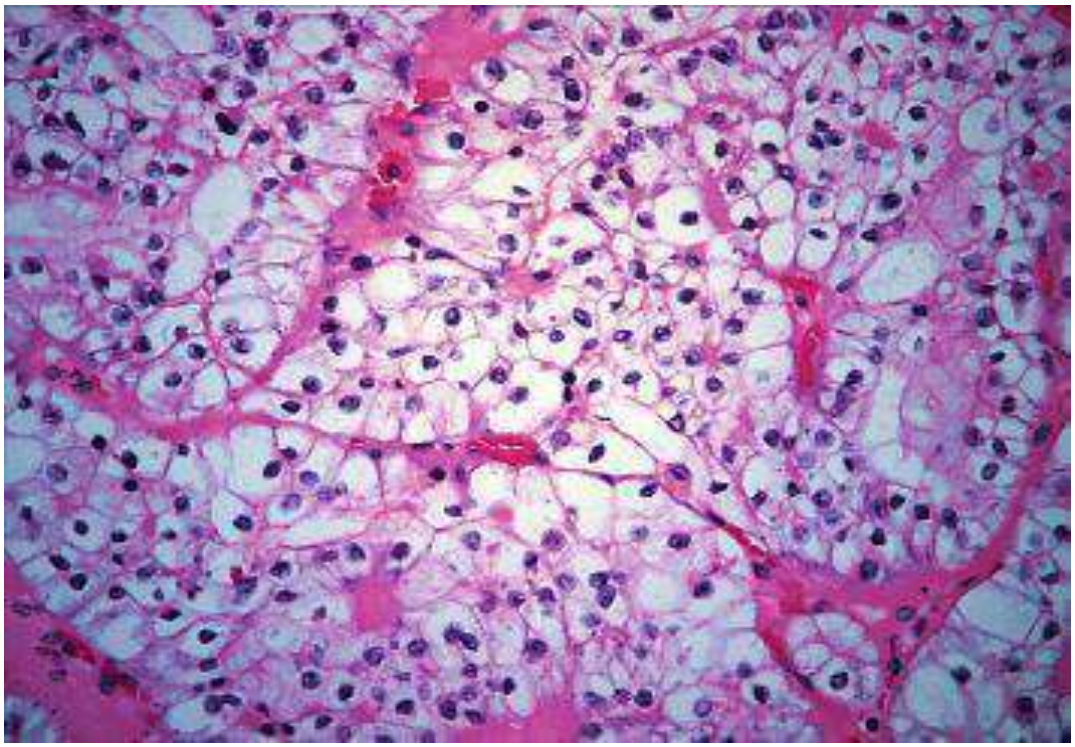


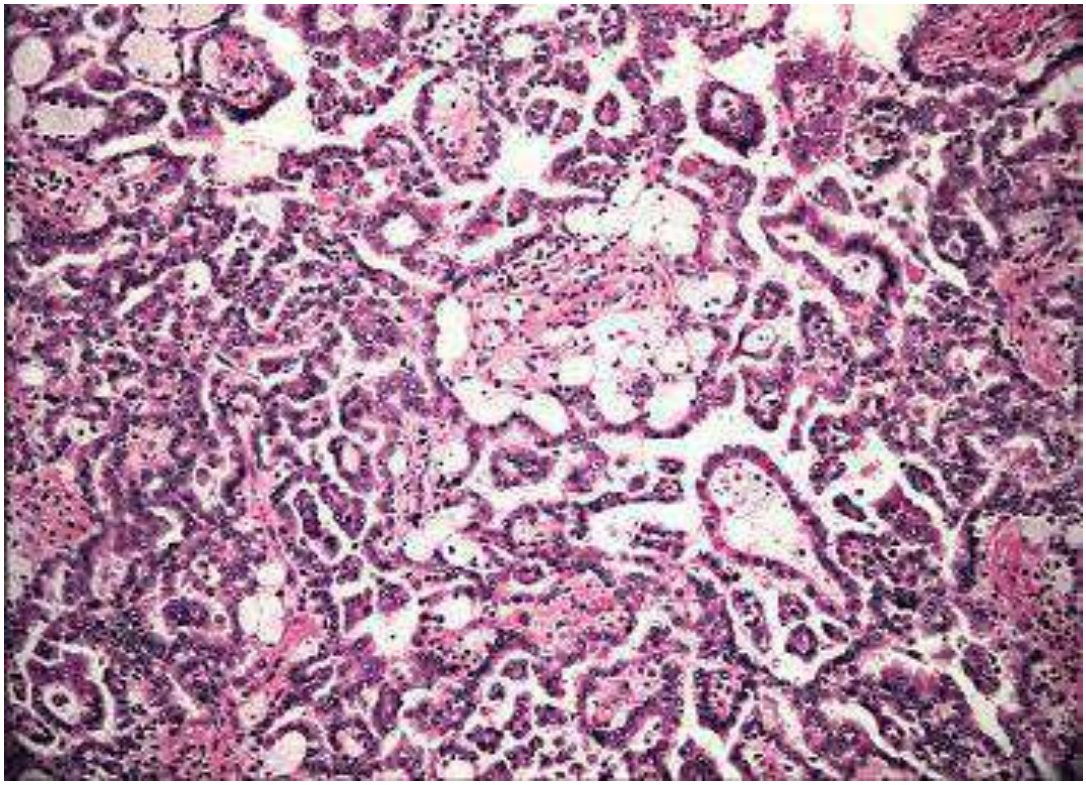


Microscopic picture of RCC:

- **1. Clear cell type RCC (70%): This is the most common pattern, the clear cytoplasm of tumor cells is due to removal of glycogen and lipid from the cytoplasm during processing of tissues. Majority of clear cell tumors are well differentiated.**
- **2. Papillary type RCC (15%): The tumor cells are arranged in papillary pattern over the fibrovascular stalks. Psammoma Bodies may be seen.**
- 3. Chromophobe type RCC (5%): [Source: 61] This type shows admixture of pale clear cells with perinuclear halo and acidophilic granular cells.

Clear cell RC





Papillary RCC

❑ Clinical picture of RCC:

- ➢ **The classical evidence for diagnosis of renal cell carcinoma is the presence of gross haematuria, palpable abdominal mass.**
- ➢ A number of paraneoplastic syndromes have been described, such as: ▪ Polycythaemia, hypercalcaemia (by parathyroid hormone and prostaglandins), hypertension, effects of feminization or masculinization and Cushing syndrome.

Nephroblastoma (Wilms' Tumor)

❑ Definition & Epidemiology:

- ⚫ Nephroblastoma or Wilms' tumor is an embryonic tumor derived from primitive renal epithelial and mesenchymal components.
- ⚫ It is the most common abdominal malignant tumor of young children.

  ⚫ It is seen between 1 to 6 years of age
- ⚫ There is equal sex incidence.

❑ **Gross picture of Wilms' tumor:**

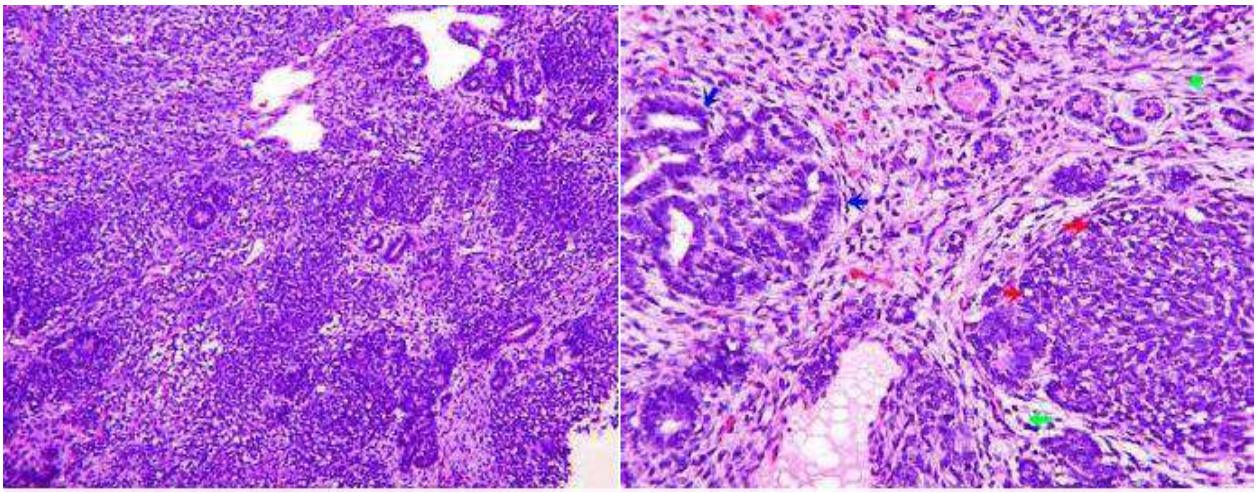
- **➢ The tumor is usually quite large and spheroidal replacing most of the kidney.**
- **➢ It is generally solitary and unilateral but 5-10% cases may have bilateral tumor.**
- ➢ On cut section, the tumor shows characteristic fish flesh-like grey-white to cream-yellow tumor with foci of necrosis and haemorrhages and grossly identifiable myxomatous or cartilaginous elements.

❑ **Microscopic picture:**

- **⚫ Classically the tumor is triphasic & consists of: ➢ Mixture of primitive epithelial and mesenchymal elements.**
- ➢ Most of the tumor consists of small round to spindled anaplastic sarcomatoid tumor cells (blastemal cells). [Source: 80] In these areas, abortive tubules and poorly-formed glomerular structures are present.

Nephroblastoma (Wilms'T)

Wilms' tumor, triphasic, composed of primitive tubules (blue arrows), blastema (red arrows) & stroma (green arrows)



❑**Clinical picture:**

- The most common presenting feature is a palpable abdominal mass in a child.
- Other common presentations are haematuria, pain, fever & hypertension.
- The tumor rapidly spreads via blood especially to the lungs.

- **I- Benign tumors**
  - ➢ A. Epithelial: Villous papilloma and inverted papilloma.
  - ➢ B. Mesenchymal: Fibroma, Neurofibroma, Haemangioma, and leiomyoma.

II- Malignant tumors

A. Primary tumors:

➢ 1- Epithelial: Carcinoma.

- **➢ 2- Mesenchymal: Sarcoma.**
- **➢ 3- Carcino-sarcoma.**
- **➢ 4- Lymphoma.**

B. Secondary tumors.

Classification of epithelial bladder tumors

- ❑ **1- Urothelial transitional cell tumors**
  - **A- Flat lesion: TCC in situ.**
  - **B- Non papillary TCC (infiltrating urothelial carcinoma).**
  - **C- Papillary lesions:**
    - ➢ Inverted papilloma
    - ➢ Villous papilloma
    - ➢ Papillary urothelial neoplasm of low malignant potential (PUNLMP).
    - ➢ Papillary carcinoma, low grade.
    - ➢ Papillary carcinoma, high grade.
- **2-Squamous tumors:**
  - ➢ 1- Squamous papilloma.
  - ➢ 2- Squamous carcinoma in-situ.
  - ➢ 3- Squamous cell carcinoma.
  - ➢ 4- Verrucous squamous carcinoma.
- **3-Glandular tumors:**
  - ➢ 1- Villous or tubular adenoma

- ➢ 2- Adenocarcinoma

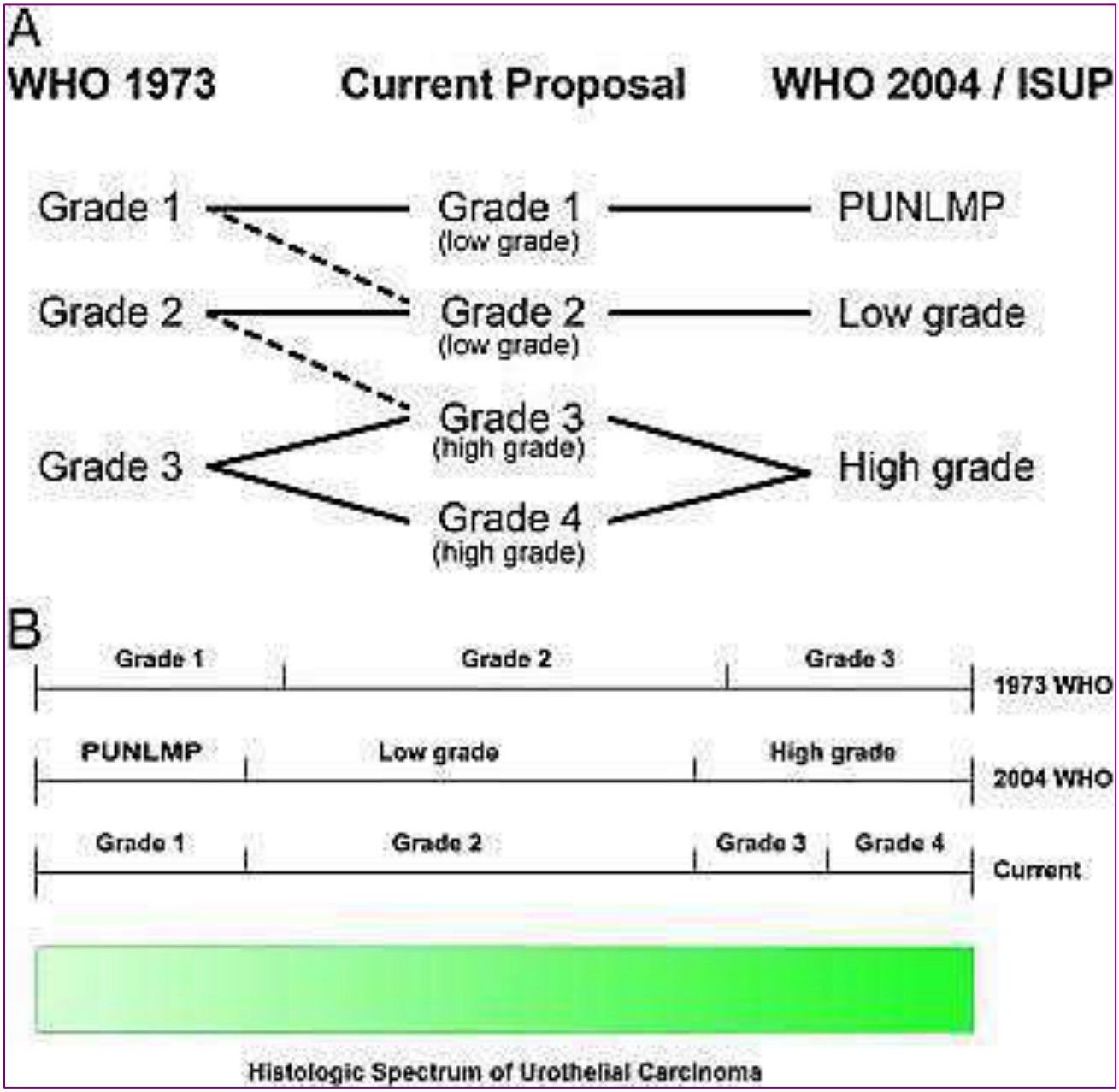


Table 2: WHO Grading of Urinary Tumors in 1973 and 2004

WHO 1973	WHO 2004
* Urothelial papilloma	* Urothelial papilloma
* Grade I well differentiated	* PUNLMP
* Grade II moderately differentiated	* Low-grade papillary urothelial carcinoma
* Grade III poorly differentiated	* High-grade papillary urothelial carcinoma

PUNLMP: papillary urothelial neoplasm of low malignant potential. WHO: World Health Organization. Source: Reference (1)

Urinary Bladder Carcinoma

❑ **Incidence**

- ➢ UTIs are infections, usually bacterial, of the lower urinary tract.

❑ **Site:**

- ➢ Common locations are the trigone, posterior and lateral walls.

Urinary Bladder Carcinoma

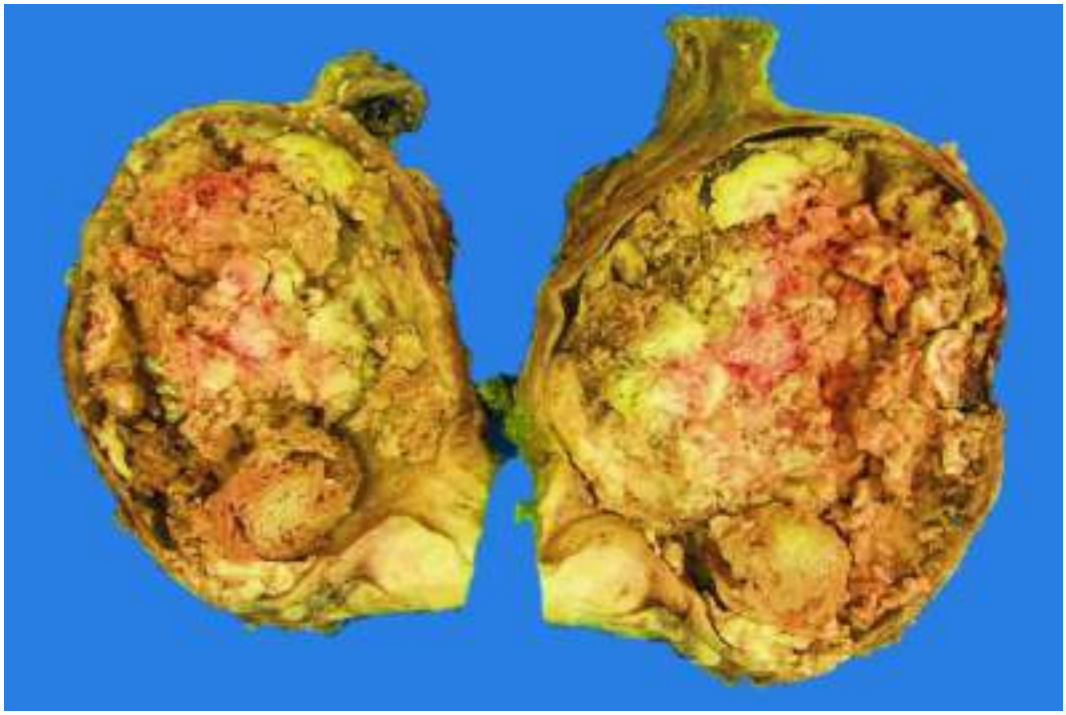
❑ **Risk Factors:**

- ➢ 1.Schistosomiasis: There is increased risk of bladder cancer in patients having bilharzial infestation (Schistosoma haematobium) of the bladder. ▪ Schistosomiasis is common in Egypt and accounts for high incidence of bladder cancer in that country. ▪ It is thought to induce local irritant effect and initiate Bilharzial urothelial precancerous lesions followed by carcinoma. ▪ Tryptophan metabolites from the worm released in blood and excreted in urine are carcinogenic▪ Secondary infection by E-coli changes nitrites and nitrates into nitrosamine (carcinogenic particularly to metaplastic urothelium).
- ➢ 2. Industrial occupations: Workers in industries that produce aniline dyes, rubber, plastic, textiles, and cable have high incidence of bladder cancer. Bladder cancer may occur in workers in these factories after a prolonged exposure of about 20 years. The carcinogenic substances responsible for bladder cancer in these cases are the metabolites of B naphthylamine and benzene.

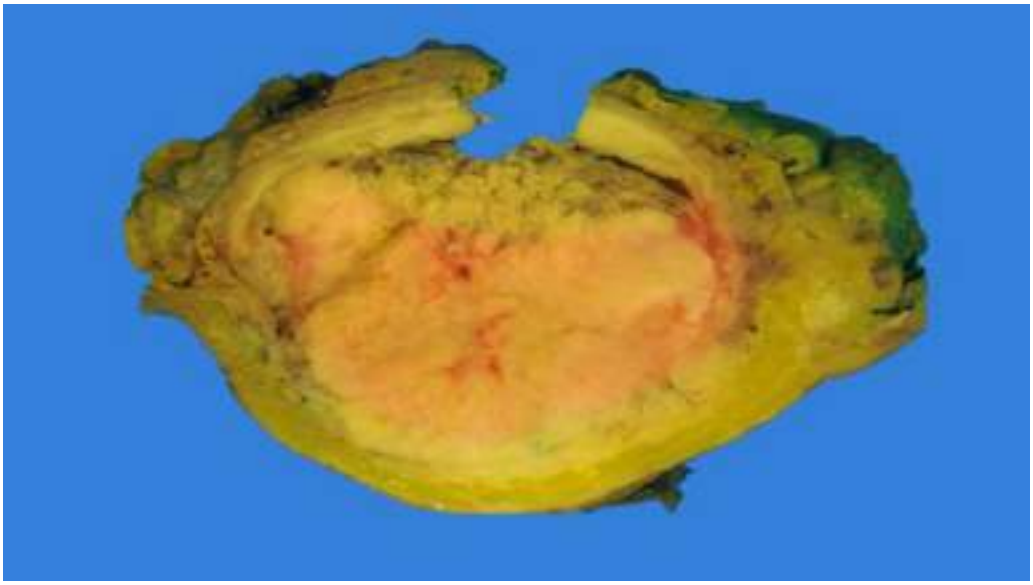
- ➢ **3. Local lesions.** A number of local lesions in the bladder predispose to the development of bladder cancer. [Source: 109] These include: vesical diverticulum, leukoplakia of the bladder mucosa, chronic cystitis and stones.
- ➢ 4. Smoking. [Source: 110] Tobacco smoking is associated with 2 to 3 fold increased risk of developing bladder cancer, probably due to increased urinary excretion of carcinogenic substances.

❑ **Gross Picture:**

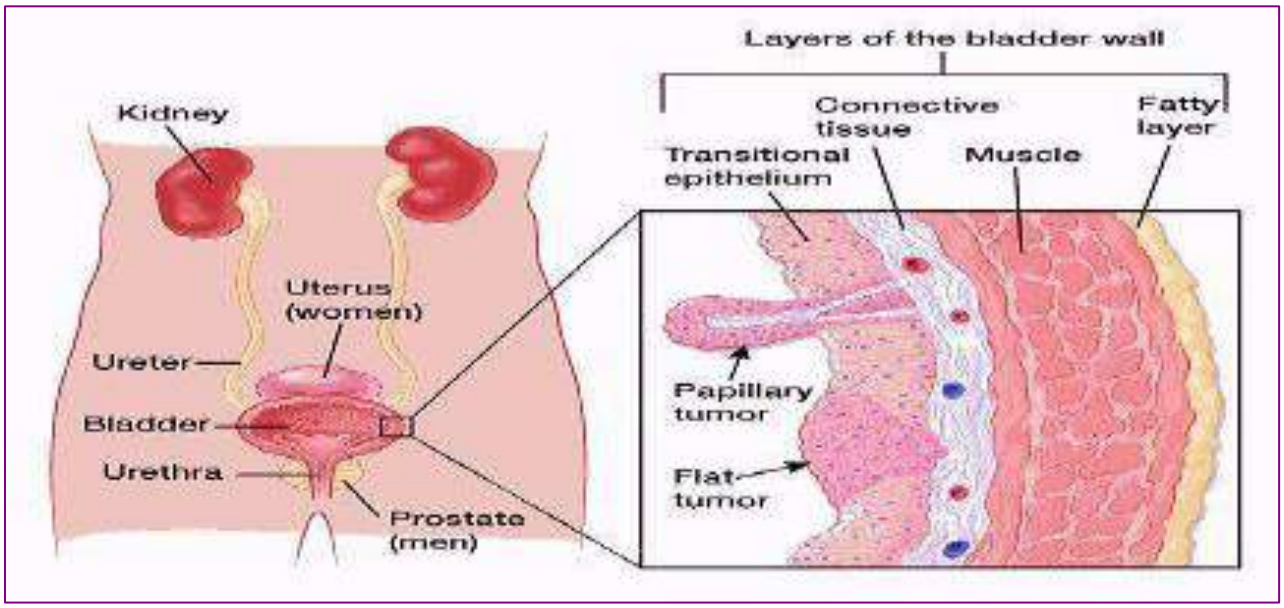
- **1. Papillary (common**): more commonly seen in non bilharzial bladder cancer**.**
- **2. Non papillary.**➢ a. Polypoid fungating. ➢ b. Ulcerative pattern. ➢ c. Infiltrative pattern. ➢ d. Combined.



Bladder Carcinoma

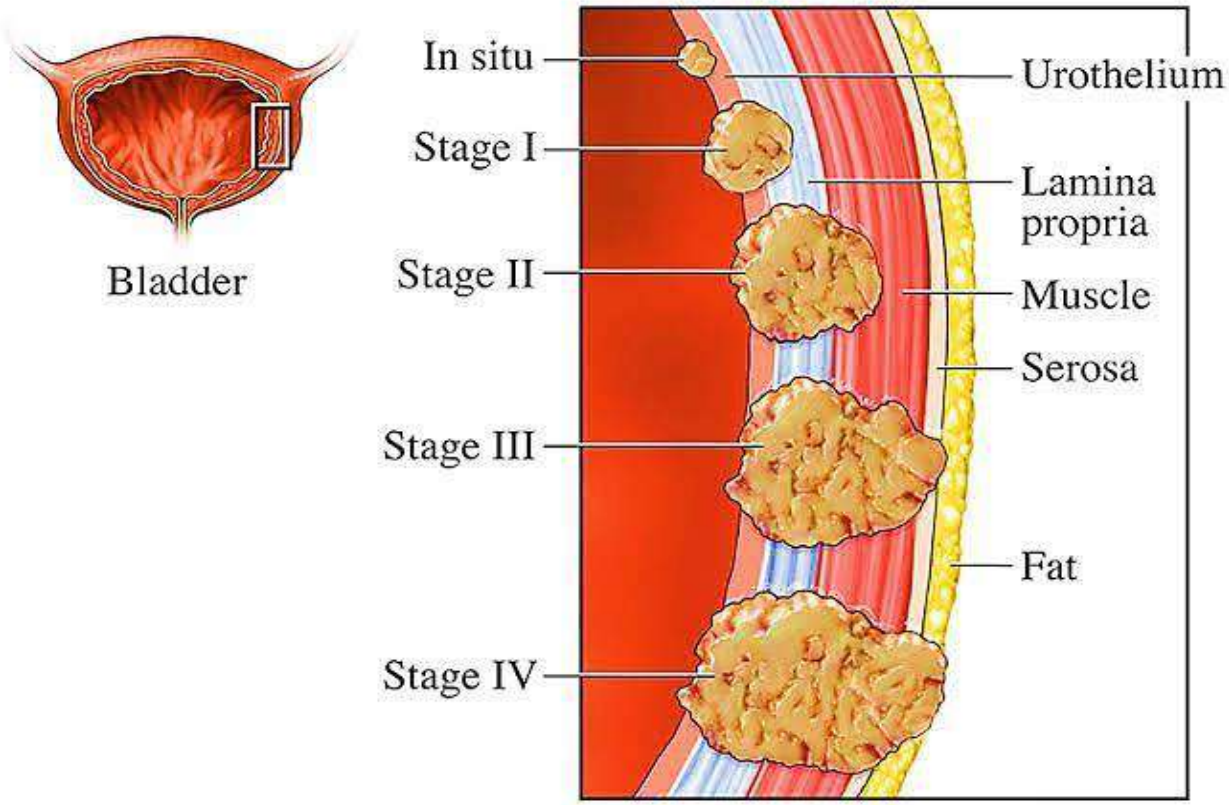


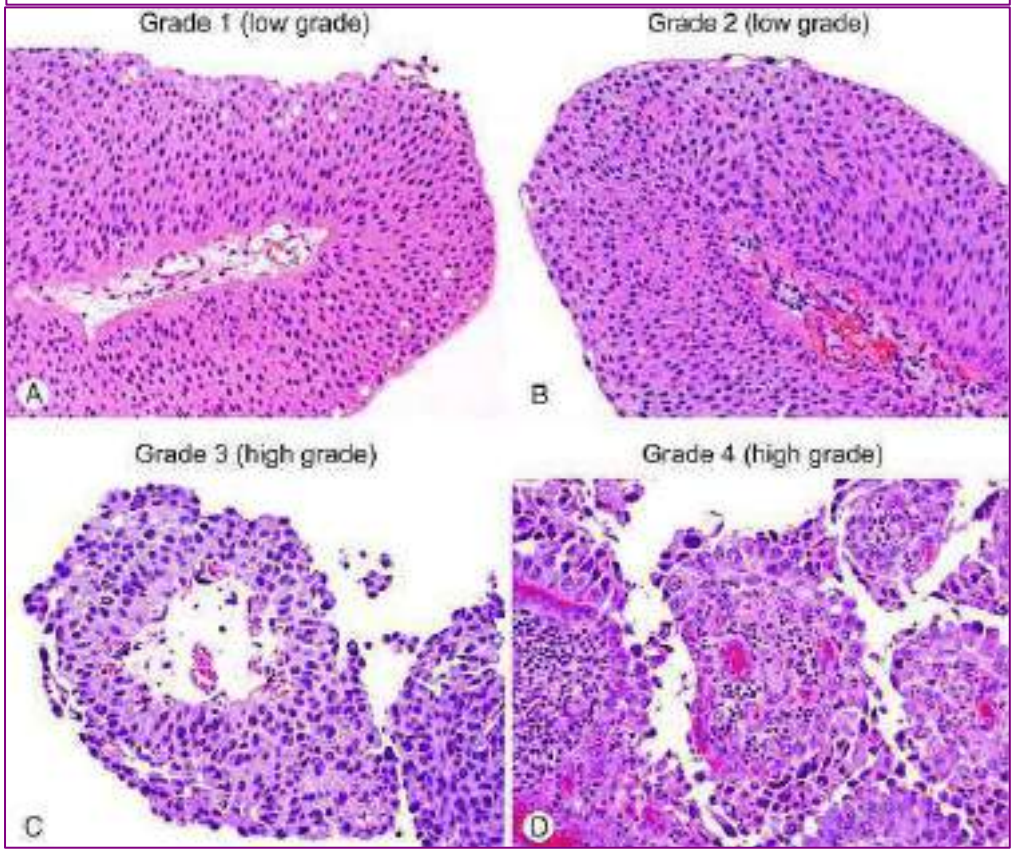
Bladder Carcinoma



❑ **Microscopic Picture:**

- **A. Transitional Cell Carcinoma:**
  - 1. Papillary pattern consists of exophytic villous papillae composed of connective tissue core covered by several layers of malignant urothelial cells with low and high grades of cellular anaplasia.
  - 2. Non papillary pattern consists solid groups of malignant urothelial cells that invade lamina propria or deeper. [Source: 122] It is usually high grade.


Bladder
In situ
Stage I
Stage II
Stage III
Stage IV
Urothelium
Lamina propria
Muscle
Serosa
Fat


Grade 1 (low grade)
Grade 2 (low grade)
A
B
Grade 3 (high grade)
Grade 4 (high grade)
C
D

A :Grade 1 (low grade)

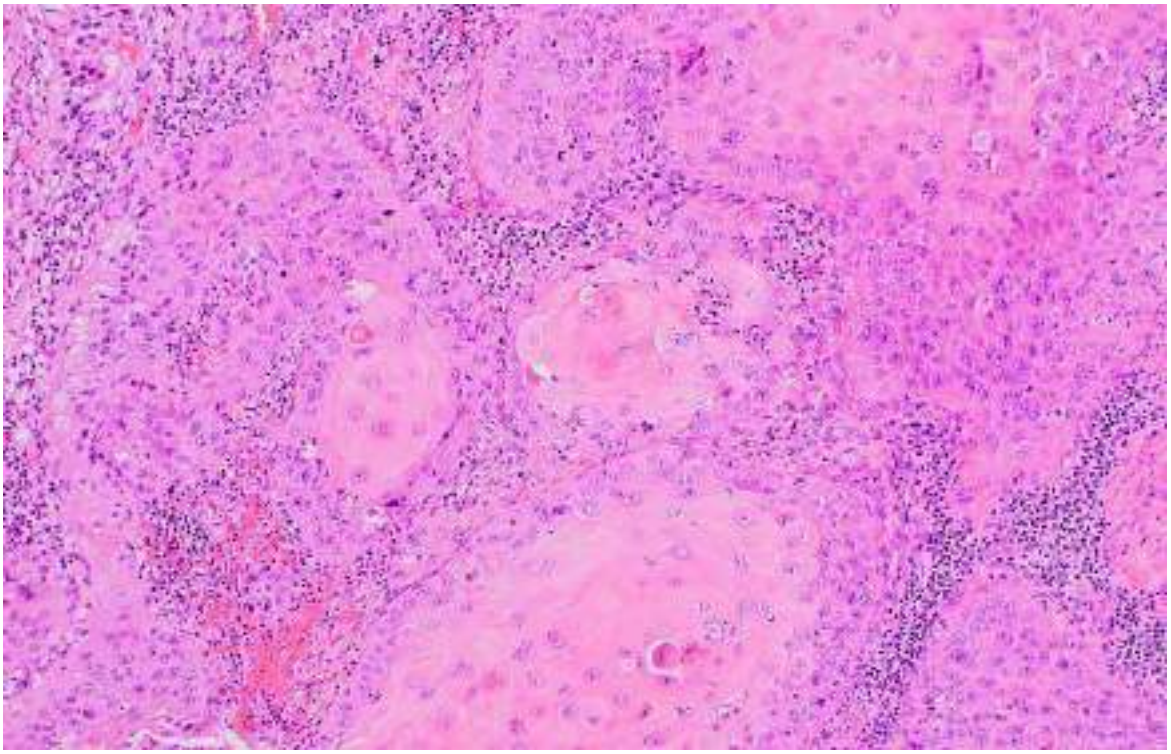
B: Grade 2 (low grade)

C:Grade 3 (high grade)

D:Grade 4 (high grade)

- ❖ **B. Squamous Cell Carcinoma:**
    - Squamous carcinomas of the bladder are infiltrative squamous carcinoma and most commonly develop on top of Bilharzial cystitis.
    - The carcinoma may be well, moderately, poorly or un-differentiated, according to the percentage of keratin pearl formation.

SCC



❑ **Effects & Complications:**

- **Spread: ➢ 1**. Direct to Prostate, seminal vesicles, ureters, rectum and vagina. ➢ 2. Lymphatic to iliac and para-aortic LNs. [Source: 128] ➢ 3. Blood to Lung, liver and bone.
- Urinary obstruction: Hydroureter, hydronephrosis, urine retention and renal failure.
- Infection: Cystitis, pyelonephritis, etc.
- Haematuria.
- Fistula: with rectum or vagina due to direct spread.

References

- Robbin's Basic pathology.

Part 6
Pharmacology

Intended Learning Outcomes (ILOs)

 # By the end of the course, students should be able to:

- List common types of diuretics (e.g., loop diuretics, thiazides, potassium-sparing diuretics).

- Recall the primary sites of action for each class.

- Explain how diuretics increase urine output by affecting different segments of the nephron.

- Describe the physiological effects of diuretics on electrolyte balance and blood pressure.

- Prescribe appropriate diuretics for conditions like hypertension, edema, or heart failure.

- Differentiate between the mechanisms and indications of various diuretics.

- Analyze potential side effects and contraindications for each class.

- Identify drugs known to cause kidney injury (e.g., aminoglycosides, NSAIDs, contrast agents).

- Recall signs and symptoms of nephrotoxicity.

- Explain the mechanisms by which nephrotoxic drugs damage renal tissue.

- Describe factors that increase susceptibility to nephrotoxicity.

- Differentiate between types of renal injury caused by various nephrotoxic agents.

I-DIURETICS

 # Terminology & overview:

- *"Diuretics" are agents that increase urine volume by promoting excretion of salt & water from kidneys.*
- *They are used in variety of conditions such as high blood pressure, glaucoma & edema.*

RENAL TUBULE TRANSPORT MECHANISMS

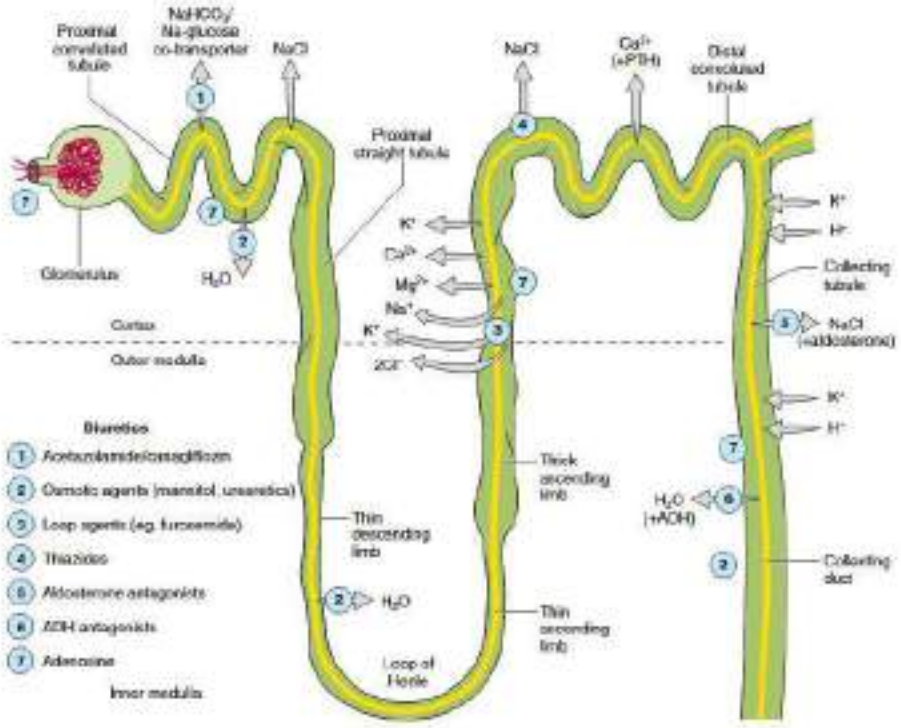


Figure (1-1): Tubule transport systems and sites of action of diuretics (Basic and Clinical Pharmacology 16th Edition).

Segment of Nephron	Major Transport Processes
Proximal Convoluted Tubule (PCT)	- Reabsorption of ~65-70% of filtered Na+, Cl-, water, glucose, amino acids, bicarbonate, Secretion of organic acids, bases, drugs
Loop of Henle (Thick Descending & Ascending limbs)	- Descending limb: Water reabsorption via aquaporins. - Thick ascending limb: Active reabsorption of Na^+, K^+, Cl^- via NKCC2 transporter; impermeable to water.
Distal Convoluted Tubule (DCT)	- Reabsorption of Na+, Cl^- (via NaCl symporter). - Reabsorption of calcium (regulated by PTH). - Secretion of K^+ and H^+.
Collecting Duct (CD)	- Reabsorption of water (via aquaporins regulated by ADH). - Reabsorption of Na^+ (via ENaC channels, aldosterone-dependent). - Secretion of K^+ and H+.

 # Classification of diuretics: according to their natriuretic capacity:

a) ***High efficacy:*** excretes 15-25 % of the filtrated sodium as ***loop diuretics***.

b) ***Moderate efficacy:*** excretes 5-10 % of the filtrated sodium as ***thiazides.***

c) ***Low efficacy:*** excretes less than 5 % of the filtrated sodium as ***K-sparing diuretics and osmotic*** diuretics.

I- LOOP DIURETICS (HIGH CEILING DIURETICS)

 # Members & chemistry:

- ***Furosemide (Lasix)*** is a prototype of this group. *Other members* include:
- ***Bumetanide, torsemide.***
- ***Ethacrynic acid*** (Edecrine) which is old drug belongs to this group.

 # Mechanism of action

- Site of action: thick part of the ascending limb of loop of Henle.
- They act by inhibition of **Na^+ / K^+ / $2Cl^-$ co-transport** mechanism in thick part of the ascending limb of loop of Henle. They also increase the excretion of Ca^{++} and Mg^{++}.
- Rapid onset of action within 1 hour of oral use, peak effect within 30 min. after I.V. use with Short duration (3-6 h.) **so suitable in emergency situations.**

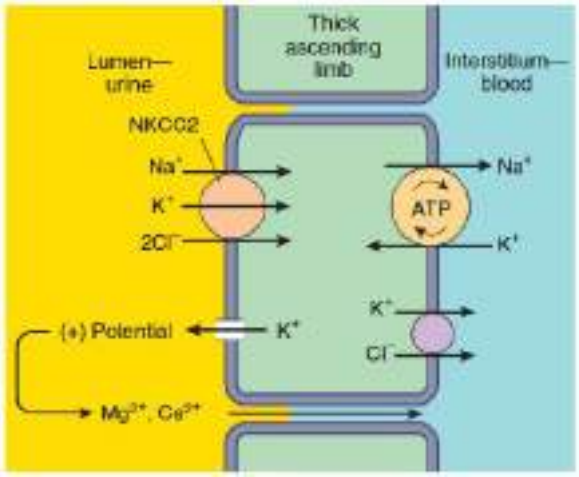


Figure (1-2): Ion transport across the luminal and basolateral membranes of the thick ascending limb cell (Basic and Clinical Pharmacology 16th Edition).

 # Therapeutic uses:

1- **Acute pulmonary edema:** they improve pulmonary edema and left ventricular pressure before the diuresis.

2- **Generalized Edema:** due to renal, hepatic and heart failure. They are useful in patients with renal dysfunction.

3- **Hyperkalemia & hypercalcemia**.

4- **Acute Renal Failure:** they increase the rate of urine flow and enhance K+ excretion in acute renal failure.

5- **Hypertension:** they are indicated in hypertensive crisis as a short term treatment (due to their rapid onset of action) and in presence of renal dysfunction. They are not suitable for chronic use due to their short duration and they causes severe electrolytes disturbance.

6- **Anion Overdose:** Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide.

 # Side effects:

1. **Hypokalemia:** may cause cardiac arrhythmias, particularly in patients taking cardiac glycosides.
2. **Hyponatremia and extracellular fluid volume depletion**.
3. **Metabolic Alkalosis**.
4. **Hypocalcemia and calciuric renal stones**.
5. **Hypomagnesemia**

6. **Hyperglycemia:** due to decreased insulin release or tissue utilization of glucose.
7. **Hyperlipidemia** as they can increase plasma levels of low-density lipoprotein (LDL) cholesterol and triglycerides while decreasing plasma levels of high-density lipoprotein (HDL) cholesterol.
8. **Hyperuricemia and precipitate attacks of gout** in susceptible patients.
9. **Ototoxicity:** can cause dose-related hearing loss that is usually due to changes in the electrolyte composition in the endolymph of the ear.
10. **Nephrotoxicity:** they potentiate nephrotoxicity of cephalosporin and aminoglycosides.
11. **Teratogenicity:** if used during pregnancy.
12. **Allergic Reactions:** Interstitial nephritis, hepatitis fever and rash as they contain sulfonamide moiety (with all except ethacrynic acid).

II- THIAZIDE & THIAZIDE-LIKE DIURETICS

 # Members:

- ***Thiazides***: e.g., chlorothiazide and hydrochlorothiazide.
- ***Thiazide-like diuretics:*** e.g., chlorthalidone, metolazone and indapamide.

 # Mechanism of action:

- They act by inhibition of Na+ / Cl- co-transport mechanism in early segment of distal tubules, so they increase the excretion of Na+ Cl-and water. They also increase the excretion of K+.
- They stimulate reabsorption of Ca^{++} in the distal tubules which is under control of parathyroid hormone (parathormone).
- They increase the excretion of Mg++.

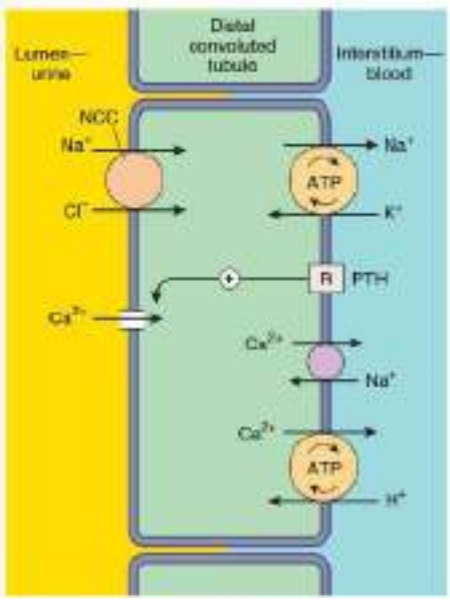


Figure (1-3): Ion transport across the the luminal and basolateral membranes of the distal convoluted tubule cell (Basic and Clinical Pharmacology 16th Edition).

N.B. *Thiazides are ineffective if GFR is less than 30-40 ml / min (except metolazone and indapamide which are effective even the GFR is less than 30 ml / min.), so they are ineffective in severe heart and renal failure.*

 # Therapeutic uses of thiazides:

1- Hypertension:

- The first choice for treatment of mild to moderate hypertension, and they give good response in 50 % of patients when used alone.
- Can be combined with other antihypertensive drugs in moderate to severe hypertension to potentiate the effect and reduce the side effects.
- In comparison to beta-blockers and ACEIs, thiazides are more potent in elder, black, obese patients and in patients with low renin activity and increase in plasma volume.
- Not useful in hypertensive patients with renal dysfunction.

Advantages of thiazide in hypertension:

- Safe, inexpensive, effective, well tolerated, once daily dosage, do not require dose titration and have additive or synergistic effects when combined with other antihypertensive agents.

Mechanism of lowering of blood pressure:

i) Early, they act by decreasing blood volume (by diuresis), so decrease COP (BP = COP x PR). Prolonged treatment may be associated with a decrease in PVR. The decrease in PVR may be due to opening of calcium-dependent potassium channel (Ca^{++}-dependent k^{+}-channel).

ii) Indapamide has a direct vasodilator effect (due to blocking of Ca^{+} channels) in addition to its diuretic effect.

2- ***Generalized edema*** caused by mild to moderate CHF (not severe CHF):

3- **Idiopathic hypercalciuria** (as they decrease Ca^{++} excretion and decrease the incidence of Ca^{++} renal stones).

*4- **Treatment of osteoporosis***

5- ***Nephrogenic diabetes insipidus***: It is a paradoxical effect; unknown mechanism

 # Side effects:

1) **Hypokalemia** (may precipitate cardiac arrhythmias in patients using digoxin), need K^{+} supplements or K-sparing diuretics.
2) **Hyponatremia**
3) **Hypomagnesemia**.
4) **Impotence:** is marked with thiazides diuretics.
5) **Metabolic alkalosis**
6) **Hypercalcemia** (due to increase in reabsorption of Ca^{++} in distal tubules).
7) **Hyperglycemia**: diabetogenic agents.
8) **Hyperuricemia** (due to decrease in the excretion of uric acid) and may cause gout in susceptible people.
9) **Hyperlipidemia** due to increase in plasma cholesterol and triglycerides which may increase the risk of atherosclerosis with chronic use.
10) **Allergic reactions:** rash, fever, hepatitis and pancreatitis. Thiazide diuretics are contraindicated in individuals who are hypersensitive to sulfonamides.

III- K-SPARING (HYPERKALEMIC) DURETICS

- These drugs act on collecting tubules and ducts causing increase in Na^+ excretion and a decrease in K^+ loss in urine. Therefore, they are called K^+-sparing or retaining diuretics.
- These drugs are weak diuretics since the amount of Na^+-reabsorbed at this site of nephron is only 2-5 % of the filtered Na load.
- They are classified according to mechanism of action into two groups:
    - Aldosterone antagonist
    - Inhibitors of renal epithelial Na^+ - channel.

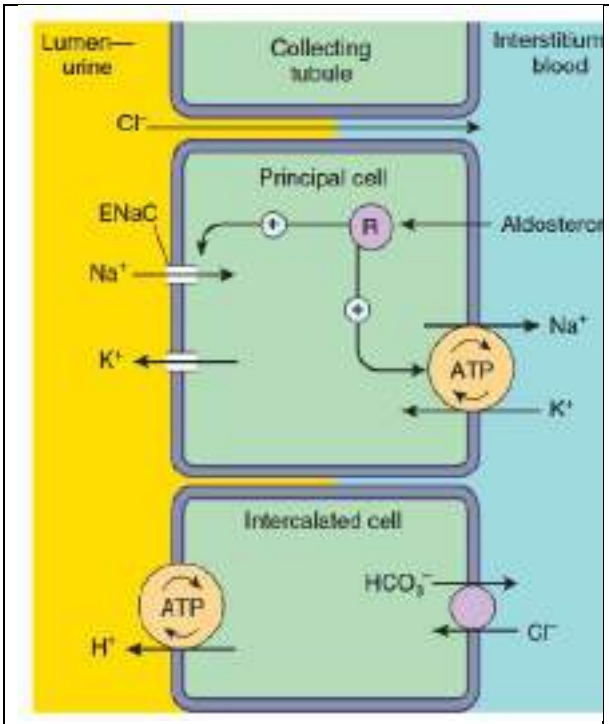


Figure (1-4): Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells (Basic and Clinical Pharmacology 16th Edition).

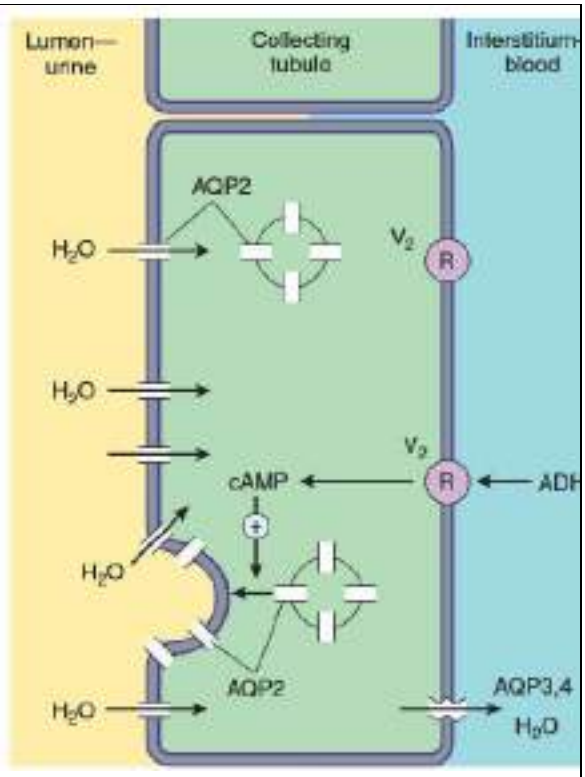


Figure (1-5): Water transport across the luminal and basolateral membranes of collecting duct cells (Basic and Clinical Pharmacology 16th Edition).

Aldosterone antagonist	Inhibitors of renal epithelial Na^+ channel
Spironolactone & Eplerenone	Triamterene & Amiloride
• Spironolactone antagonize aldosterone action at mineralocorticoid receptors (MRs) in the collecting tubules. Therefore, it inhibits reabsorption of Na+ and secretion of K+ and H+.	• They block renal epithelial Na+ channels at late distal tubules and collecting ducts leading to increase in the excretion of NaCl and reduces the net driving force for potassium secretion (decrease excretion of K+).

IV-OSMOTIC DIURETICS

- *Mannitol* (prototypical; given IV), *glycerin and isosorbide (*used orally).
- It increases the renal excretion of water by exerting high osmotic pressure within tubular lumen without Na loss.

Therapeutic uses:

1. **Increased intracranial pressure** (cerebral edema & cerebral tumors).
2. **Glaucoma:** In cases of acute glaucoma and before eye surgery, it reduces IOP.
3. They are used to **maintain urine flow** in cases acute toxicity-induced acute renal failure
4. **Dialysis disequilibrium syndrome:** Administration of mannitol shifts water back into the extracellular compartment and consequently relieves this syndrome.

Adverse effects:

- Dehydration and extracellular water expansion that cause hyponatremia until diuresis occurs.

V- CARBONIC ANHYDRASE INHIBITORS (CAIs)

 # Members:

- **Acetazolamide** (orally used)
- **Methazolamide** (orally used)
- ***Dorzolamide*** (topically used)
- ***Brinzolamide*** (topically used)

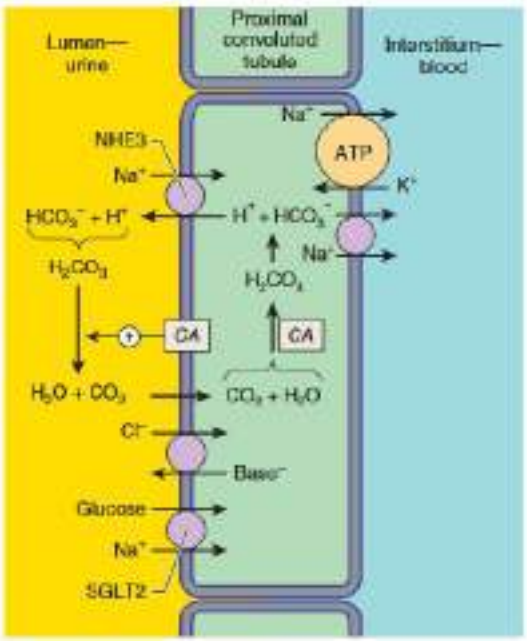


Figure (1-6): Effects of carbonic anhydrase located in proximal tubules (Basic and Clinical Pharmacology 16th Edition).

 # Mechanism of action:

- They act by inhibition of carbonic anhydrase enzyme in the proximal tubules of kidney, so they inhibit bicarbonate reabsorption and increase its secretion as sodium bicarbonate.
- CAIs can inhibit carbonic anhydrase–dependent bicarbonate transport at the **ciliary body** of the eye that secretes bicarbonate from the blood into the aqueous humor and hence reduce the formation of aqueous humor. Therefore, used in glaucoma.
- They also block the formation of cerebrospinal fluid by the **choroid plexus** involves bicarbonate secretion into the cerebrospinal fluid

 # Indications:

1- **Glaucoma:**

- ***Topically*** active carbonic anhydrase inhibitors (***dorzolamide, brinzolamide***) are available. These topical compounds reduce intraocular pressure without systemic metabolic effects.

2- **Acute Mountain Sickness:**

- Weakness, dizziness, insomnia, headache, and nausea can occur in mountain travelers. In more serious cases, pulmonary or cerebral edema develops.
- Acetazolamide enhances performance status and diminishes symptoms.
-

 # Adverse effects:

Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. They decrease urinary excretion of NH4 and may contribute to the development of **hyperammonemia** and **hepatic encephalopathy** in patients with cirrhosis.

VI- ADH (VASOPRESSIN) ANTAGONISTS

- Vasopressin antagonists such as Conivaptan (block V1a and V2) and used I.V. and Tolvaptan (block V2) used orally are used in nephrogenic diabetes insipidus.
- Demeclocycline is nonspecific ADH antagonists and rarely used in cases of syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

VII- SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

 # Examples:

- Dapagliflozin, canagliflozin, empagliflozin and ipragliflozin

 # Mechanism of action:

- Almost all filtered glucose is reabsorbed in proximal tubules by SGLT2 transporter. Inhibition of SGLT2 results in excretion of glucose by about 30-50 % accompanied by water excretion.

 # Therapeutic uses:

- Currently, the only indication for the use of these drugs is as third-line therapy for diabetes mellitus SGLT2 inhibitors will reduce the hemoglobin A_{1c} by 0.5–1.0%, similar to other oral hypoglycemic agents.

 # Adverse effects:

1- SGLT2 inhibitor therapy is associated with a low incidence of hypoglycemia (3.5% versus 40.8% with glipizide).

2- There is a 6 fold increased incidence of genital fungal infection in women and a slightly higher risk of urinary tract infections.

3- They have no or minimal effects on serum electrolyte concentrations.

DIURETIC COMBINATIONS

- Several fixed dose combination of ***K-depleting diuretics*** as thiazides or loop diuretics with ***K-sparing diuretics*** (e.g., spironolactone) or ***ACE inhibitors or ARBs*** is recommended and available in the market e.g., aldactazide, Modiuretics, Capozide, Co-diovan, etc. The value of this combination is that hypokalemia cancel hyperkalemia with additive diuretic activity, i.e., antagonism of side effects and addition of therapeutic effects.

II- NEPHROTOXICITY

Factors affecting the susceptibility of the kidney to toxicants:

1- High renal blood flow

2- Concentration of chemicals in tubular fluid

3- Reabsorption and/or secretion of chemicals through tubular cells

4- Activation of protoxicants to reactive and potentially toxic metabolites

Examples of nephrotoxicants:

1- Metals:

- Many heavy metals are potent nephrotoxicants, and relatively low doses can produce toxicity characterized by glucosuria, aminoaciduria, and polyuria. As the dose increases, renal necrosis, anuria, and death will occur.

- Several mechanisms operate to protect the kidney from heavy metal toxicity.

- After low dose exposure and often before detectable signs of developing nephrotoxicity, significant concentrations of metal are found bound to renal lysosomes resulting in tissue damage.

A- Cadmium:

- In humans, exposure to cadmium is primarily through food or industrial exposure to cadmium dust.

- In Japan, a disease called Itai-itai Byo is known to occur among women who eat rice grown in soils with very high cadmium content. The disease is characterized by anemia, damage to proximal tubules, and severe bone and mineral loss.

B- Lead:

- Lead, as Pb2+, is taken up readily by proximal tubule cells, where it damages mitochondria and inhibits mitochondrial function, altering the normal absorptive functions of the cell.
- Complexes of lead with acidic proteins appear as inclusion bodies in the nuclei of tubular epithelium cells. These bodies, formed before signs of lead toxicity occur, appear to serve as a protective mechanism.

C- Mercury:

- Mercury exerts its principle nephrotoxic effect on the membrane of the proximal tubule cell. In low concentrations, mercury binds to the sulfhydryl groups of membrane proteins and acts as a diuretic by inhibiting sodium reabsorption.
- Organomercurial diuretics were introduced into clinical practice in the 1920s and were used clinically into the 1960s. Despite their widespread acceptance as effective therapeutic diuretics, it was well known that problems related to severe kidney toxicity were possible.
- However, in the absence of other effective drugs, the organomercurials proved to be effective, sometimes life-saving, therapeutic agents.
- More recently organomercurial chemicals have been implicated as environmental pollutants, responsible for renal damage in humans and animals.

D- Uranium.

- About 50 % of plasma uranium is bound, as the uranyl ion to bicarbonate, which is filtered by the glomerulus.

- As a result of acidification in the proximal tubule, the bicarbonate complex dissociates, followed by reabsorption of the bicarbonate ion; the released UO_2^{2+} then becomes attached to the membrane of the proximal tubule cells.
- The resultant loss of cell function is evidenced by increased concentrations of glucose, amino acids, and proteins in the urine

2- Aminoglycosides

- Certain antibiotics, most notably the aminoglycosides, are known to be nephrotoxic in humans, especially in high doses or after prolonged therapy.
- The group of antibiotics includes streptomycin, neomycin, kanamycin, and gentamycin.
- Aminoglycosides are polar cations that are filtered by the glomerulus and excreted unchanged into the urine.
- In the proximal tubule, the aminoglycosides are reabsorbed by binding to anionic membrane phospholipids, followed by endocytosis and sequestration in lysosomes
- It is thought that when a threshold concentration is reached, the lysosomes rupture, releasing hydrolytic enzymes that cause tissue necrosis.

3- Amphotericin B

- With some drugs, renal damage may be related to the drugs' biochemical mechanism of action.
- For example, the polymycins, such as amphotericin B, are surface-active agents that bind to membrane phospholipids, disrupting the integrity of the membrane and resulting in leaky cells.

4- Chloroform

- Chloroform is a common industrial organic solvent that can be a hepatotoxicant or a nephrotoxicant in both humans and animals.
- As a nephrotoxicant it is both species and gender-dependent. For example, following chloroform administration male mice develop primarily kidney necrosis whereas female develop liver necrosis.
- As a nephrotoxicant, chloroform most probably undergoes metabolic activation in the kidney itself. Chloroform is metabolized to phosgene by a cytochrome P450-dependent reaction.

- Phosgene is capable of binding to cellular proteins to produce the cellular necrosis associated with chloroform toxicity to the kidney.

5- Hexachlorobutadiene

- Hexachlorobutadiene is an industrial solvent and heat-transfer agent. It is a widespread environmental contaminant that is a potent and relatively specific nephrotoxicant.
- Hexachlorobutadiene first forms a glutathione conjugate, which is further metabolized by to a cysteine conjugate. In the kidney, the cysteine conjugate is cleaved to a reactive intermediate.

6- Tetrafluoroethylene

- The nephrotoxic mode of action of tetrafluoroethylene is similar to that of hexachlorobutadiene.
- It is first metabolized to a cysteine conjugate, which is metabolized to a reactive product that can bind to cellular macromolecules.

References

- First aid for the basic sciences, Chapter 8 Page(s) 91-95, 670- 673
- First aid for the basic sciences, Chapter 8 Page(s) 675
- Lippincott® Illustrated Reviews: Pharmacology South Asian Edition
- Basic and Clinical Pharmacology 16th Edition

Part 7
Medical Microbiology and Immunology

Part I

Urinary tract infections

*Objectives

-Identify the epidemiology of UTIs

-Recognize risk factors for UTIs.

-Recognize classification of UTIs.

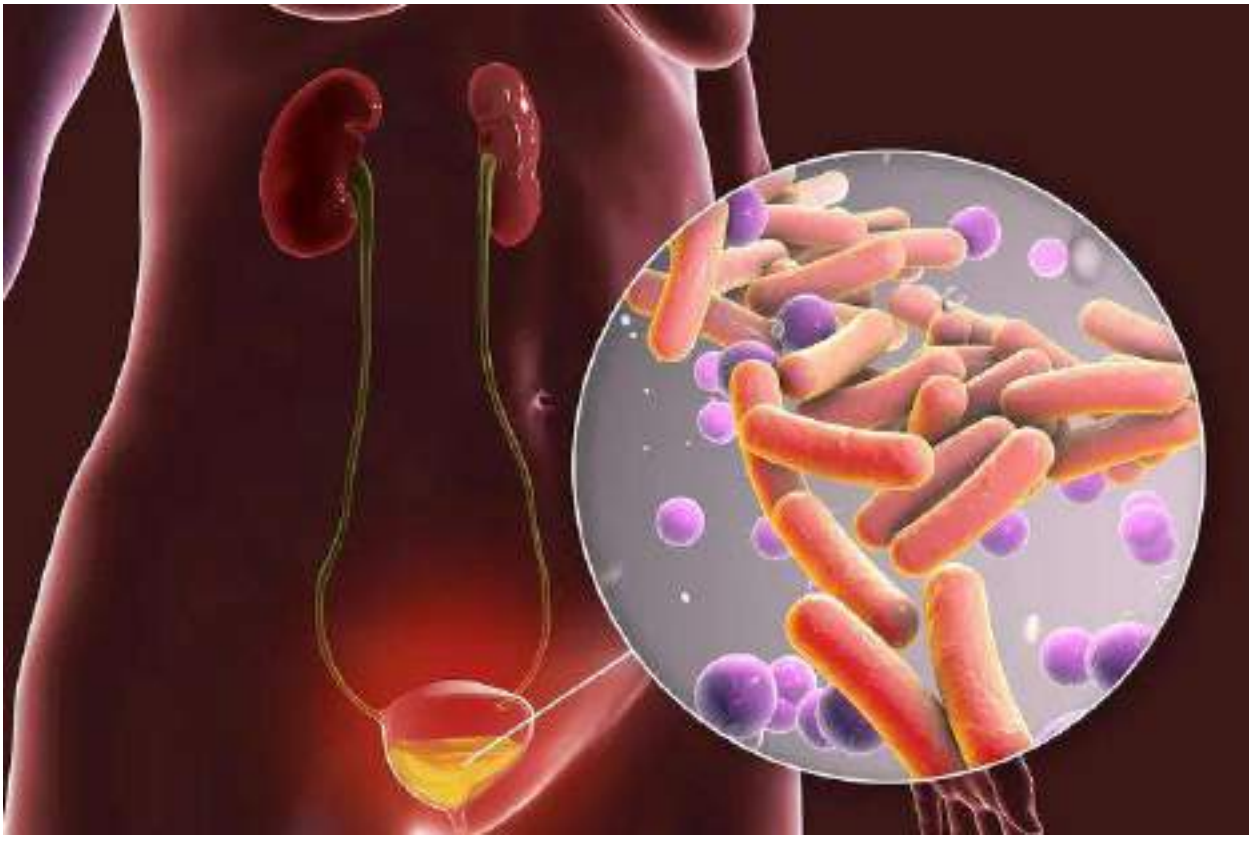
-List the commonest causative agents (Pathogens) of UTI.

-Explain the mode of transmission of UTI.

-Explain the pathogenesis of UTI.

-Describe clinical manifestations of UTI.

-Outline the laboratory diagnostic approach in different UTIs.



*Epidemiology

According to age: UTI is more common in elderly, and infants.

According to sex: UTI is more common in women (due to short urethra).

*Classification of UTI infections

There are several methods of classification:

Lower UTI: cystitis, urethritis, prostatitis

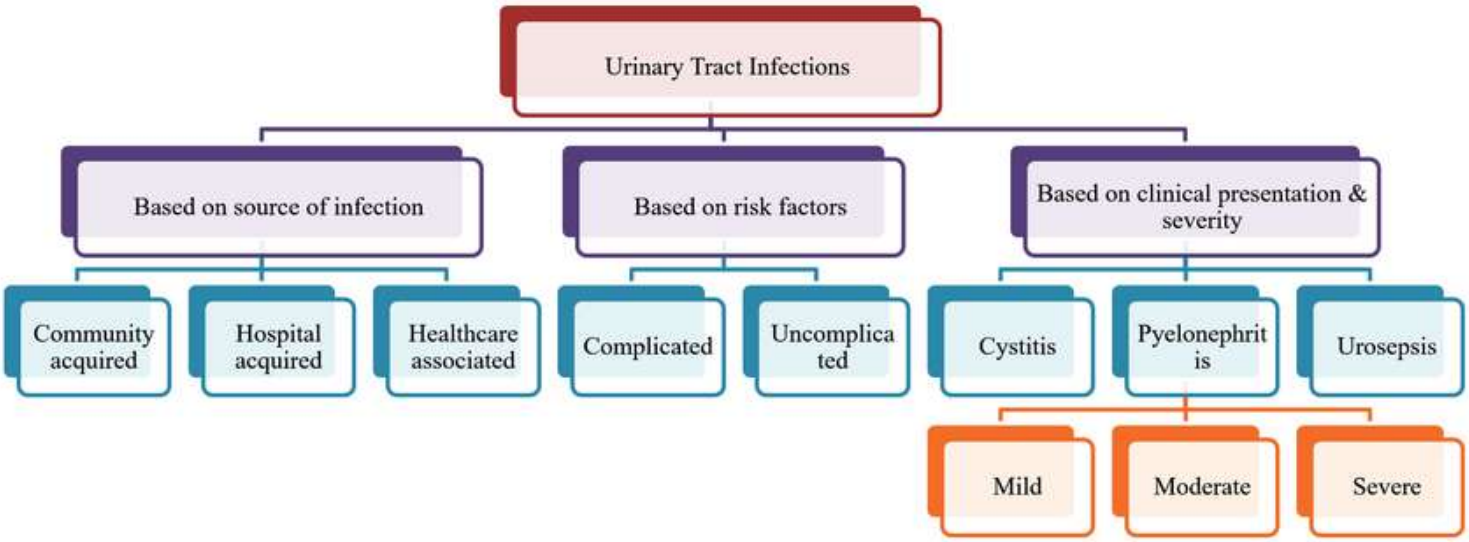
Upper UTI: pyelonephritis, intra-renal abscess, perinephric abscess (usually late complications of pyelonephritis).

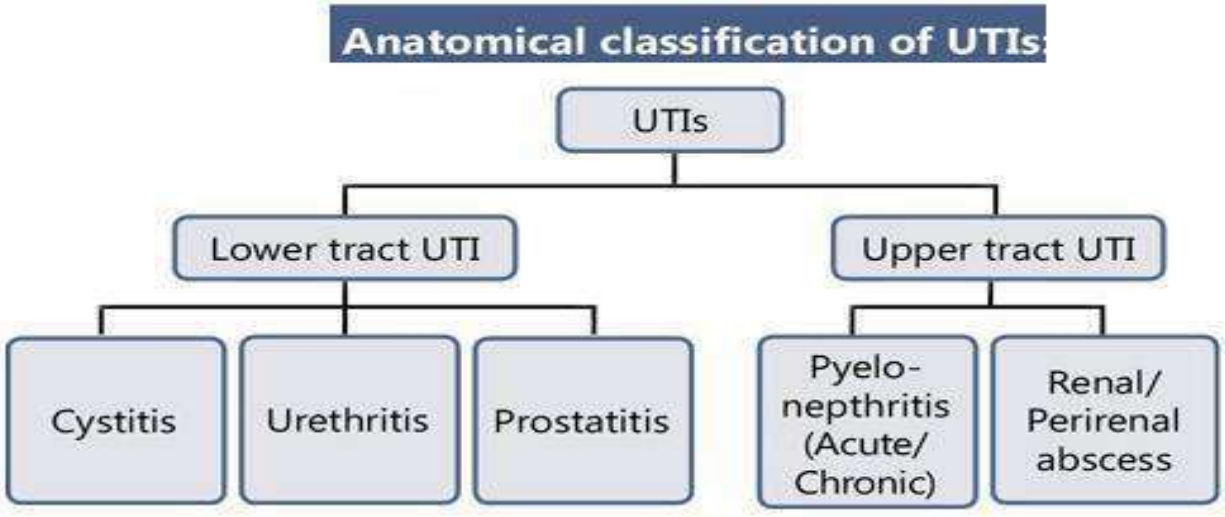
Uncomplicated UTI: Infection in a structurally and neurologically normal urinary tract. Simple cystitis of short (1-5 day) duration

Complicated UTI: Infection in a urinary tract with functional or structural abnormalities (ex. indwelling catheters and renal calculi). Cystitis of long duration or hemorrhagic cystitis.

Community Acquired: 80% are due to E.coli.

Nosocomial infection or hospital acquired: is due to E coli, Pseudomonas, Enterococcus species. It is the fourth most common nosocomial infection and mostly commonly caused by indwelling urinary catheters.


Urinary Tract Infections
Based on source of infection
Based on risk factors
Based on clinical presentation & severity
Community acquired
Hospital acquired
Healthcare associated
Complicated
Uncomplicated
Cystitis
Pyelonephritis
Urosepsis
Mild
Moderate
Severe


Anatomical classification of UTIs
UTIs
Lower tract UTI
Upper tract UTI
Cystitis
Urethritis
Prostatitis
Pyelo-nepthritis (Acute/ Chronic)
Renal/ Perirenal abscess

*Mode of transmission of UTI

1- Ascending route:

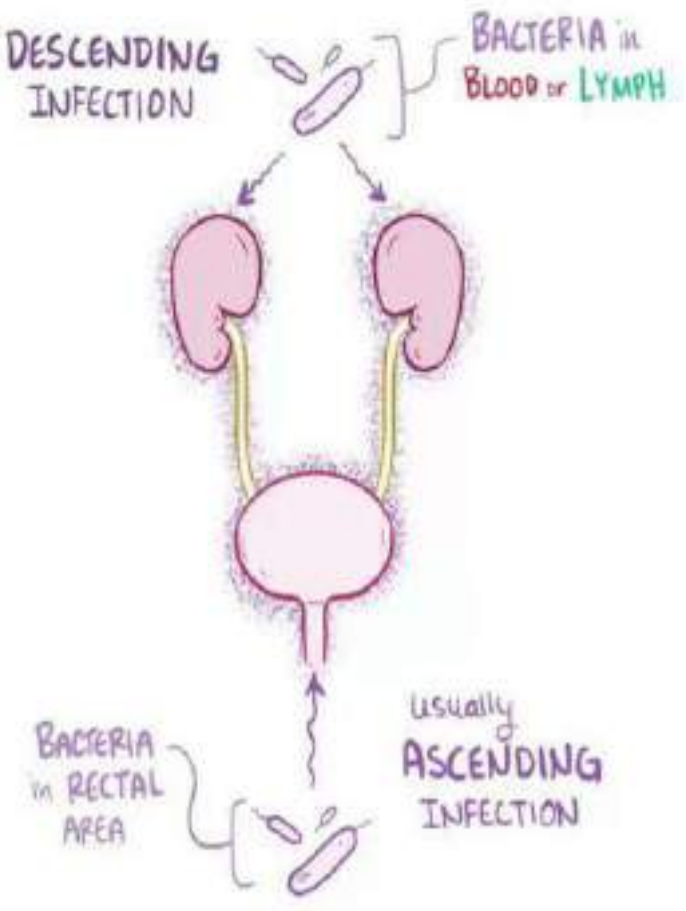
- Bacteria can ascend from the anus to the urethra (urethritis) especially with *E coli*.
- From the urethra to the bladder (cystitis).
- Through the ureter and infect the kidney causing a renal parenchymal infection (pyelonephritis).

2- Descending route:

- Through blood or lymph **(***Staph aureus, Candida*, T.B)

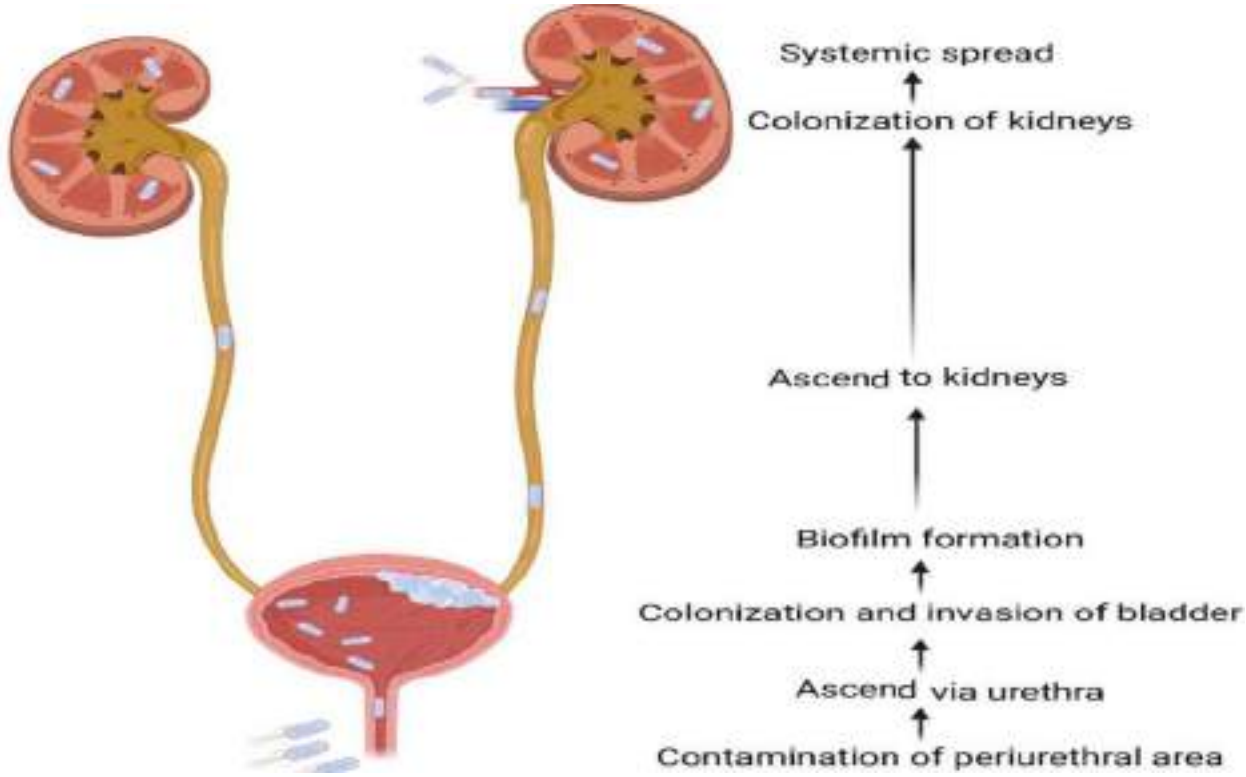
3- Direct extension:

- From intestinal fistula.



*Pathogenesis of urinary tract infections (UTIs)

- Begins when uropathogens able to colonize the urethra contaminate the periurethral area (step 1).
- Bacterial migration to the bladder (step 2).
- Expression of pili and adhesins results in colonization and invasion (step 3).
- Host inflammatory responses, including neutrophil infiltration begin to clear extracellular bacteria (step 4).
- Some bacteria evade the immune system and resist the neutrophils so these bacteria undergo multiplication (step 5).
- Biofilm formation (step 6).
- These bacteria produce toxins and proteases that induce host cell damage (step 7).
- bacterial survival and ascending to the kidneys (step 8).
- Kidney colonization (step 9).
- Bacterial toxin production and host tissue damage (step 10).
- UTIs can progress to bacteraemia, If left untreated (step 11).

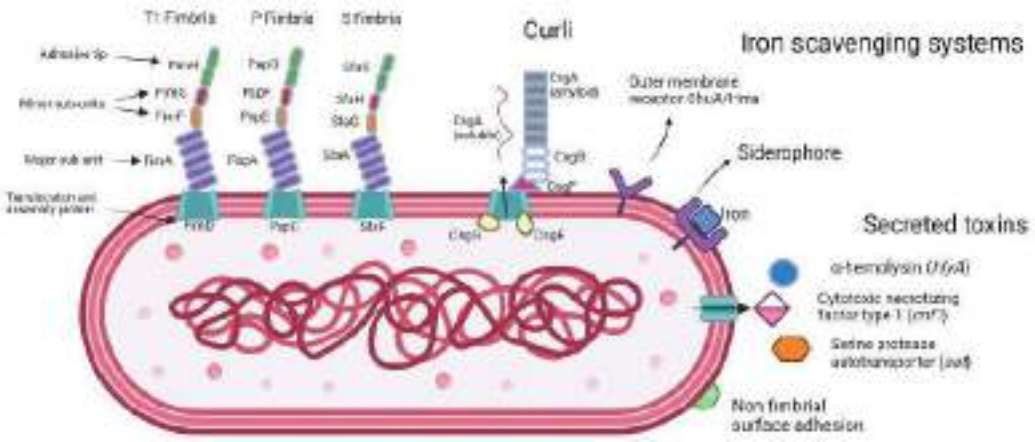


*Risk factors:

- Any cause of urinary stasis or any foreign body predisposes (tumors/stones/strictures/prostatic hypertrophy/neurogenic bladder).
- Sexual intercourse in women ("honeymoon cystitis")
- Catheters are a major cause, and the risk is directly related to the length of catheterization (3–5% per day).
- Women > men (due to short urethra).
- More common in childhood.
- Pregnancy, Postmenopausal (decrease in estrogen).
- Immunocompromised patients.
- Diabetes mellitus.

*Bacterial Virulence Factors allowing initiation of UTI

- Adherence of E. coli to receptors on uroepithelial.
- Cells by adhesins on pili (fimbria).
- Capsular polysaccharides with antiphagocytic activity e.g. *Klebsiella*.
- Enhanced motility by means of flagella.
- Production of hemolysins (membrane damaging toxins) e.g. E coli induces pore formation in cell membrane.
- Production of urease and changing the urinary PH into alkaline is correlated with pyelonephritis and stone formation e.g. *Proteus*.


Curli
Iron scavenging systems
Siderophore
Iron
Secreted toxins
Non fimbrial
surface adhesion

Part II

*Common pathogens causing UTI

Urethritis:

- Gonococcal urethritis caused by *Neisseria gonorrhoeae.*
- Nongonococcal urethritis caused by *Chlamydia trachomatis* (50%).
- *Ureaplasma urealyticum* (20%), *Mycoplasma hominis* (5%), *Trichomonas* (1%), or herpes simplex

Cystitis:

- E. coli in >80%; second are other coliforms (gram-negative bacilli) such as *Proteus, Klebsiella, Enterobacter, Pseudomonas aeruginosa* etc.; enterococci occasionally, and Staph. saprophyticus in young women

Pyelonephrites:

- *E. coli* is most common pathogen; others include *Klebsiella, Proteus,* and Enterococcus. Patients who are immunosuppressed and subjected to indwelling catheters are more prone to *Candida*.

Other pathogens:

- *Staphylococci: S. aureus, S. epidermidis, S. saprophyticus*.
- TB
- Leptospira.

Viruses:

- Adenovirus, mumps, HIV, cytomegalovirus can cause hemorrhagic cystitis in children and immunocompromised patients.

*Clinical manifestations of UTIs

Urethritis:

- Purulent urethral discharge
- Dysuria
- Urgency and frequent urination.

Cystitis:

- Dysuria
- Urgency and frequent urination.
- suprapubic pain.
- Hematuria (less common).
- On examination → suprapubic tenderness (but no flank tenderness).

Acute bacterial Pyelonephrites:

- Chills and fever.
- Flank pain (costovertebral angle tenderness).
- Dysuria
- Increased frequency in urination.

Characteristics of bacteria causing UTI

A. Gram negative bacilli:

***Escherichia coli*:**

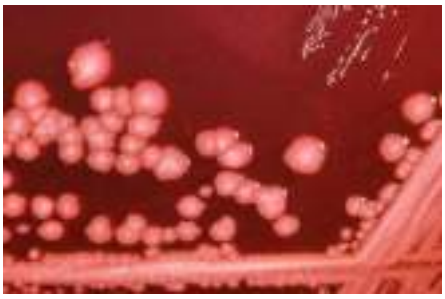
Distinguishing Features:

1. Gram-negative rod.
2. Facultative anaerobic, oxidase negative.
3. *E. coli* is a lactose fermenter: colonies with metallic green sheen on EMB.

Virulence:

1. Uropathic specific adhesion by fimbria, which is specific for cystitis, and pilli production.
2. Capsular Ag and hemolysin.

PROTEUS:



Distinguishing Features:

1. Gram-negative rods, non-lactose fermenting.
2. Highly motile; "swarming" motility on surface of blood agar.
3. Urease produced.
4. Facultative anaerobe (Enterobacteriaceae), oxidase negative.

Pathogenesis:

1. Urease raises urine pH to cause kidney stones (staghorn renal calculi).
2. Motility may aid entry into bladder.
3. Endotoxin causes fever and shock when septicemia occurs.

Pseudomonas aeruginosa:

Distinguishing Features:

1. Oxidase-positive, Gram-negative rods, nonfermenting.
2. Pigments: pyocyanin (blue-green) and fluorescein.
3. Grape-like odor.
4. Non–lactose fermenting colonies on EMB or MacConkey.
5. Biofilm, Slime layer
6. Associated with nosocomial infection and urinary catheterization.

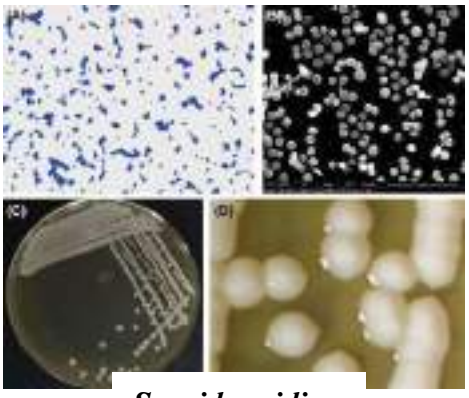
STAPHYLOCOCCUS:

1. Gram-positive *cocci* in clusters.
2. Catalase positive (streptococci are catalase negative).
3. Species of Medical Importance:

• *S. aureus.*

• *S. epidermidis.*

• *S. saprophyticus.*



S. epidermidis

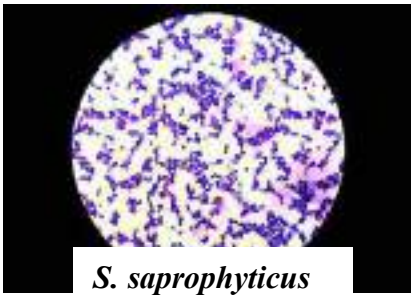
Coagulase negative *Staphylococci*:

***S. epidermidis*:**

1. Coagulase (-); gram (+) cocci.
2. Novobiocin sensitive.
3. Infections of catheters/shunts.

***S. saprophyticus*:**

1. Coagulase (-), gram (+) cocci.
2. Novobiocin resistant.



S. saprophyticus

ACUTE BACTERIAL PYELONEPHRITIS

Clinical findings:

Chills, fever, flank pain, nausea, vomiting, costovertebral angle tenderness, increased frequency in urination, and dysuria.

Diagnosis:

Clean-catch urine for urinalysis, culture, and sensitivity. In most cases, >100,000 bacteria/mL of urine. Routine imaging is not required, but if there is no improvement in 48–72 hours or complications are suspected (obstruction, renal, or perinephric abscess), consider U/S or CT.

Glomerulonephritis (GN):

- Glomerulonephritis (GN) are the most common cause of chronic kidney disease.
- Most GN occur as the result of an autoimmune (immune complex) disorder.
- The most well characterized mechanism of GN is post streptococcal glomerulonephritis (GN): Occur after Streptococcus pyogenes (throat and skin infection).

GN can be classified as follows:

- ❑ Primary disease without systemic illness (e.g. IgA nephropathy)
- ❑ Secondary disease due to systemic illness (e.g. post-infectious GN, diabetic nephropathy, lupus nephritis)

It may be further classified as follows:

1. **Nephritic "acute GN":** hematuria, RBC casts, edema, hypertension, and renal failure (e.g. post-infectious GN).
2. **Nephrotic:** heavy proteinuria, hyperlipidemia, edema, and hypertension (e.g. diabetic nephropathy).
3. **Rapidly progressive GN:** usually nephritic, accompanied by sub-acute renal failure (over 1-2 weeks).

Leptospirosis (Weil's disease):

Leptospirosis is a rare bacterial disease that is acquired by contact with the urine of rodents.

It is caused by bacteria of the genus Leptospira.

Manifestations:

Renal and liver failure

Myositis

Diagnosis:

Serology with ELISA

*Laboratory diagnosis:

Urinalysis:

Specimen:

• Midstream urine (MSU) is necessary to avoid contamination with vaginal or perineal skin flora and must be before starting antibiotic.

• Suprapubic aspiration or urinary catheter aspiration collected in sterile container can a lso be performed if a clean catch cannot be obtained without contamination (e.g., in children who are not toilet trained.)

1-Dip stick urine test:

Urease positivity:

Urine pH > 7 (alkaline) suggest Proteus mirabilis infections.

Protein:

Proteinuria may be caused by glomerular or tubular disease, although glomerular disease leads to greater amounts. The lower limit of detection for protein on the UA is 300 mg/24 hours.

Nitrites:

Gram-negative bacteria reduce nitrate to nitrite, which is a marker of urinary infection.

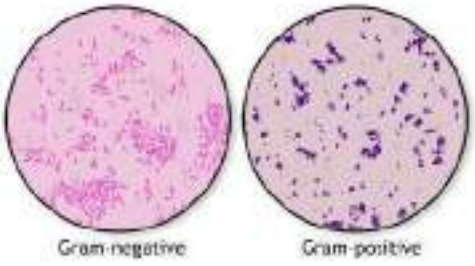
2-Urinalysis with microscopy:

Examination of wet preparation:

White blood cells (WBCs), red blood cells (RBCs),casts, crystals, yeasts, eggs and bacteria (in fresh urine only)

Gram staining:

When bacteria or WBCs (pus cells) are seen in wet preparation.



White blood cells (WBC):

May be due to pyelonephritis, cystitis, or intrarenal inflammation. If due to bacterial infection, the WBC should be accompanied by visible bacteria, but this may not be the case with all microorganisms (e.g., TB).WBCs count is ≥ 10 WBC/high power field (hpf).

Heme and red blood cells:

(RBC) Red cells can be found in the urine from any cause of disease in the urologic system. Hematuria is also from infections such as cystitis or prostatitis. Proteinuria and **RBC casts** are pathognomonic for glomerulonephritis.

Diagnostic criteria for UTI:

• **Pyuria:** ≥ 5-10 WBC/ hpf

• **Bacteriuria:**

Presence of bacteria on Gram stain (most commonly, gram-negative rods).

• **Leukocyte casts:**

Should be absent in lower UTIs (cystitis), however it is a diagnostic finding of an upper UTIs (e.g., pyelonephritis).

3-Urine culture: Culture on specific media.

Bacteriuria:

By itself, the isolated finding of bacteria in the urine is of very limited significance.

The most important exception is in pregnant women, since 30% of those with bacteriuria progress to pyelonephritis.

• Negative culture is associated with TB, viruses, and recent antibiotic treatment.

• **Diagnostic criteria for UTI:**

- significant bacteriuria defined as ≥ 105 colony forming units (CFU)/mL serves to confirm a UTI.
- Any bacteriuria in urine from a suprapubic aspiration of the bladder is abnormal.

4- Antibiotic sensitivity tests in case of recurrent infections.

Test your knowledge:

Which of the following statements about infection-related acute glomerulonephritis is false?

1. Viral infections are most commonly implicated
2. It is post-streptococcal glomerulonephritis
3. It is associated with *Streptococcus pyogenes* throat and skin infections
4. Its main mechanism is immune complexes deposition

References:

Kaplan Medical USMLE® STEP 1, 2021

Pages: 205, 232, 233, 246, 252.

Kaplan Medical USMLE® STEP 2, 2021

Pages: 573, 574, 586, 587, 588, 589, 590, 640, 644, 645, 668, 669.

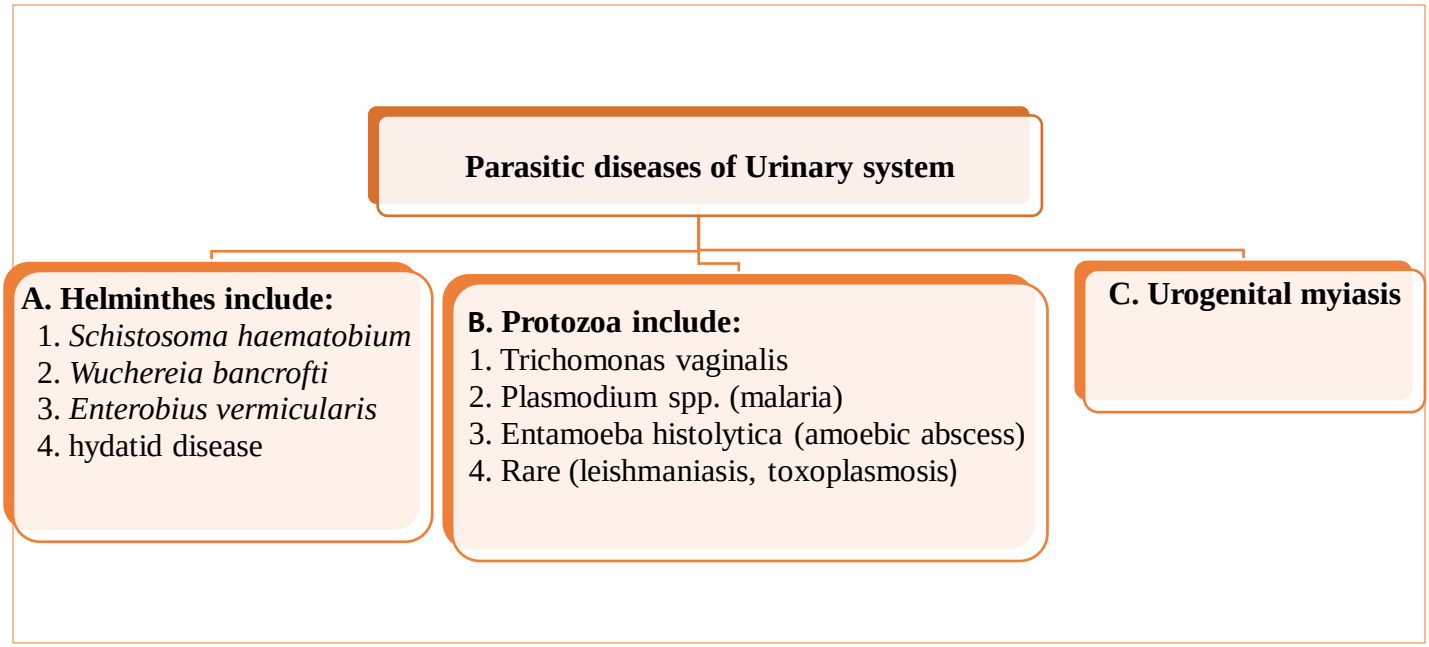
Part 8
Medical parasitology

Medical parasitology

Parasitic Infections of the Urinary System

By the end of this lecture, students should be able to:

1. List parasites causing urinary tract infections.
2. Recall and differentiate the infective and diagnostic stages of each parasite.
3. Identify mode of infection for each parasite
4. Demonstrate the pathological lesions caused by each parasite on the urinary system.
5. Explain host-parasite relationships (pathogenesis and main clinical presentations)
6. Describe laboratory diagnosis, imaging and pathological studies of the disease related to each parasite
7. Recall treatment and prevention of them.



Parasites causing focal renal pathology including

1. hydatid disease
2. amoebic abscess.

Parasites causing diffuse renal pathology including

1. Schistosomiasis (schistosoma haematobium)
2. Malaria (Plasmodium spp)
3. Trichomoniasis (Trichomonas vaginalis)
4. Enterobiasis (Entrobius vermicularis)
5. Urogenital myiasis,

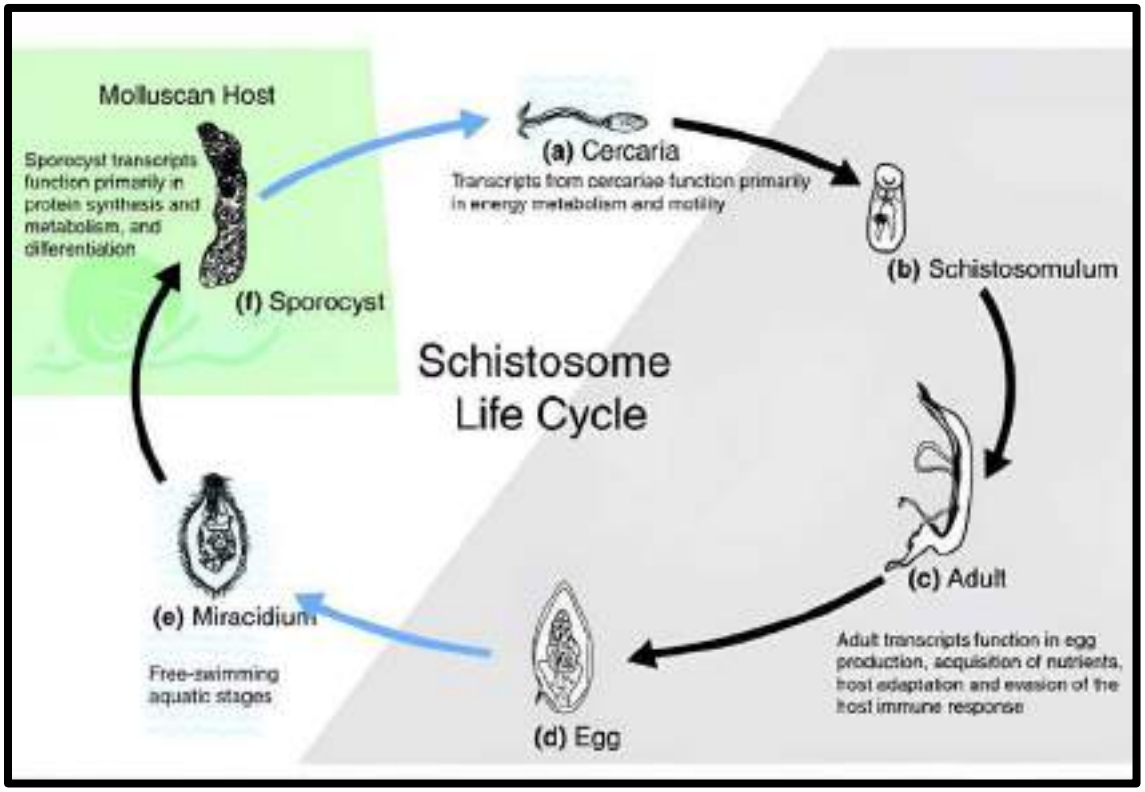
1. Urinary Schistosomiasis (bilharziasis)

The causative parasite	***Schistosoma haematobium*** **(Blood fluke)**
Geog. distribution	Africa, Middle East and Southern Europe. Upper and Middle Egypt
Final host **Reservoir host**	✓ Man ✓ primates, experimentally monkey**.**
Intermediate host	*Bulinus truncatus* snail
Habitat	✓ Adults → Portal veins ✓ Oviposition → Vesical and pelvic venous plexuses.
Infective stage	furcocercous cercariae
Mode of infection	Penetration of skin or mucous membrane by furcocercous cercariae
Diagnostic stage	Eggs with terminal spine in urine

Life cycle:

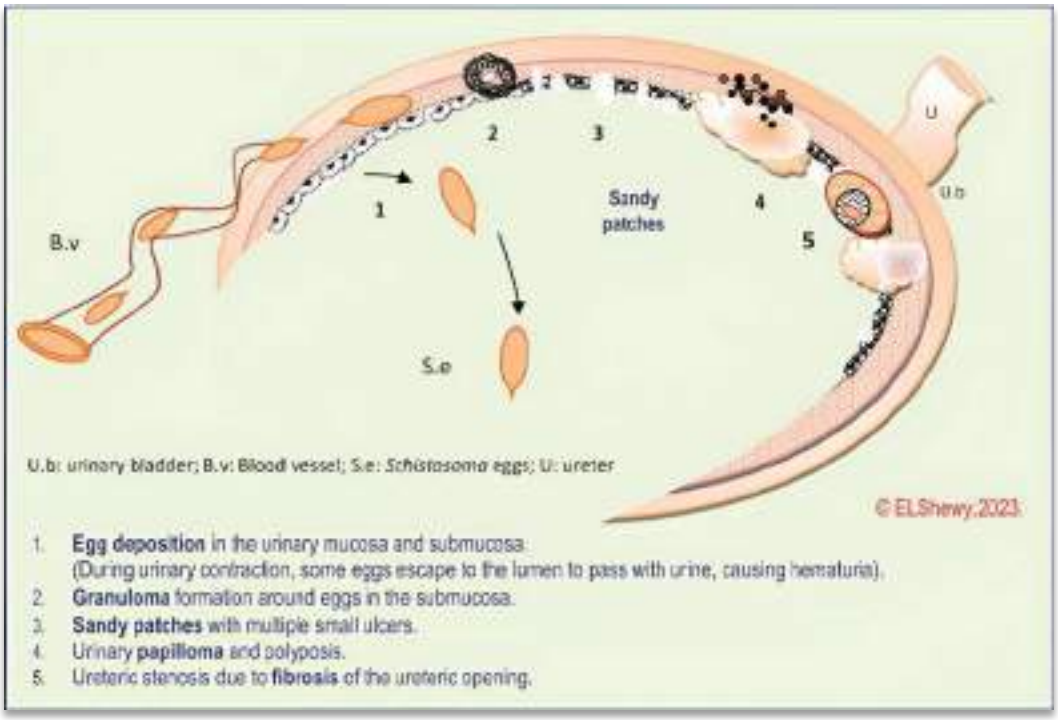
- ✓ Infection occurs by penetration of the skin or mucous membrane by furcocercous cercariae during contact with water or with drinking contaminated water.
- ✓ During penetration, cercariae shed their tails and develop into schistosomules, which get access to circulation and are carried into the heart then to the lungs and finally to the portal vein.
- ✓ In the portal veins, juvenile males take juvenile females into their gynaecophoric canal, a very important step for their maturation.
- ✓ After mating, paired flukes migrate against the blood stream to the pelvic and vesical plexuses. When they reach the smallest blood vessel that will not allow the thick male to go on it stops, blocking the flow of blood, while the thin female leaves the male and proceeds into the vessel to start egg laying.
- ✓ The female stretches the blood vessel around its body, lays one egg, draws back, recoil of the stretched blood vessel occurs and thus the egg becomes “pinned” to the intima of the blood vessel. When the blood vessel becomes loaded with eggs, the female goes back to the waiting male where they mate again, and the male directs the female to another blood vessel.

- ✓ The laid eggs reach into the urinary bladder aided by lytic enzymes secreted by miracidia and the repeated muscular contractions of the bladder during micturition.
- ✓ When the bladder contracts, the spine scratches the mucosa giving rise to (terminal haematuria) near the end of micturition, last drops of urine usually accompanied by few drops of blood.
- ✓ When these eggs reach the fresh water, living miracidia hatch → the miracidium swims in water looking for the snail
- ✓ In the snail intermediate host (*Bulinus truncatus*), the miracidia develop into sporocysts, daughter sporocysts and finally furcocercous cercariae (infective stage) are formed.
- ✓ The cercariae are shed during daylight hours. Thousands of cercariae may be shed by a single snail.
- ✓ Completion of the life cycle must be fulfilled within few hours by penetration of cercaria to the skin or mucous membrane of a human host.



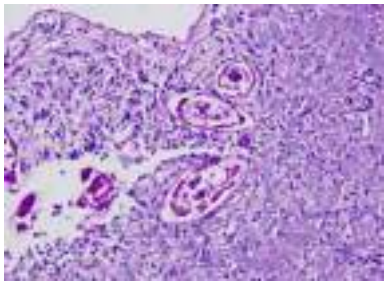
Pathogenesis and clinical picture:

1. The adult worms migrate against blood flow to the vesical venous plexus , where they the female worms begin laying eggs.
2. Some eggs are squeezed through the wall of the urinary bladder by the aid of lytic enzymes secreted by miracidia and vigorous contraction of the urinary bladder into the lumen and leading to **terminal haematuria, burning micturition and dysuria** and the eggs are discharged into urine.
3. Other eggs are trapped under mucosa causes cellular infiltration, inflammation and **granuloma formation**, which undergo **calcification** and **fibrosis** producing **sandy patches** appearance.
4. The trapped eggs create also pseudo-tubercles formation in the bladder mucosa and then nodules and polypoid masses develop (cauliflower polypi, caused by repeated formation of bilharzial polyps).
5. Ulcerative lesions caused by shedding of the atrophic mucosa of sandy patches & those of the polyps.
6. Secondary bacterial urinary infection (*Salmonella* organisms) and kidney damage, ulcers and strictures of ureters, urinary calculi (stones) may occur.
7. Urinary schistosomiasis may be complicated by squamous or transitional cell carcinoma of the urinary bladder.
8. Ureteric inflammation and fibrosis result in **stricture** which might obstruct the ureter → **hydroureter → hydronephrosis + infection → pyonephrosis** → reflux **nephropathy and renal failure** may occur.
9. Hepatosplenomegaly, portal hypertension, hematemesis and anemia



Diagnosis:

1. Clinical History: A history of exposure to fresh water in an endemic region.
2. **Parasitological diagnosis** to detect the characteristic egg in urine sample containing the last drops of urine.
3. **Serological test:** Enzyme linked immunosorbent assay **(**ELISA), Indirect fluorescent antibody test (IFA), Indirect hemagglutination test (IHA) and Circumoval precipitation test (COP).
4. **Urinary bladder** biopsy to detect granuloma surrounding the eggs and diagnosing complicating squamous cell carcinoma.



Treatment

1. **In acute schistosomiasis** (Katayama fever) praziquantel is administered under steroid cover.
2. **Chronic schistosomiasis** is treated with praziquantel; which is repeated within several weeks to eradicate any schistosomes that may have survived the first course of treatment.

Prevention and control:

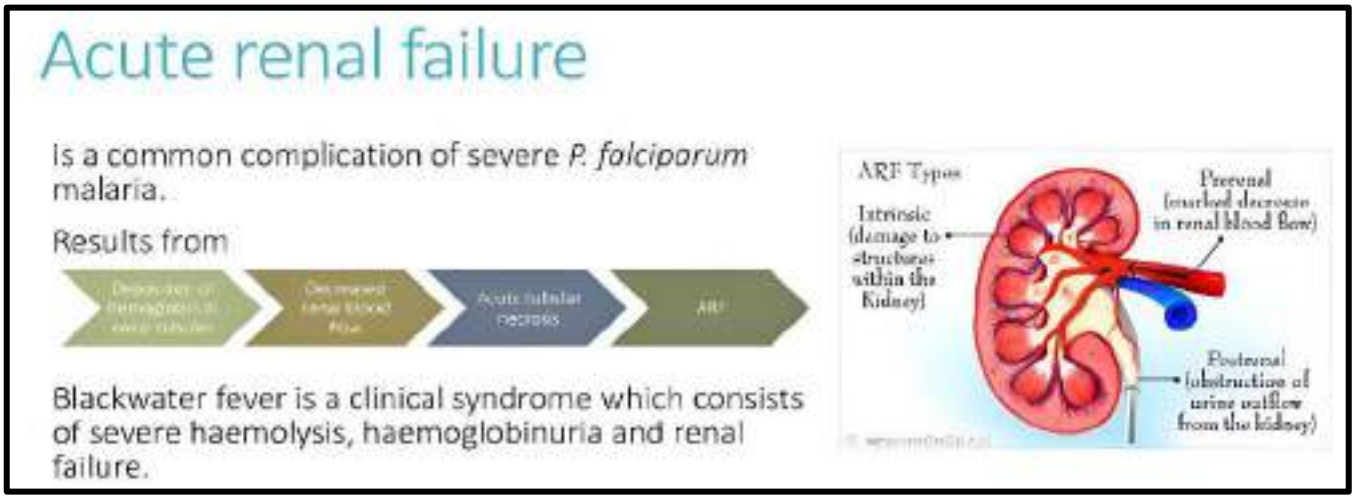
1. For man: mass treatment, avoid urination and defecation in canals. provision of clean water and sanitary latrines. Avoid swimming in pools in the villages. Health education demostrating the life cycle and mode of infection. Improving the social conditions of villages.
2. For the intermediate host (the snail):
    a. Periodic closure of irrigation canals.
    b. Plantation of some plants such as Balanites aegyptica (toxic to snails).
    c. Apply molluscicides such as Baylucide (Niclosamide) 2 p.p.m in canals containing snails

2. Malaria

Causative parasite	***Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium falciparum***
Definitive host **Intermediate host**	**female *Anopheles* mosquito** **man**
Habitat	liver cells and RBCs
Infective stage	Sporozoites, schizont and merozoite
Diagnostic stage	Erythrocytic stages
Mode of infection	1. Through the bite of female *Anopheles* mosquito. Infective stage is the sporozoite**.** 2. Blood transfusion of an infected donor or among drug addicts. Infective stage is the schizont or merozoite**.** 3. Congenital through placental defects or during labour (connatal). Infective stage is the merozoite.

Pathogenesis and clinical picture:

- In ***Plasmodium malariae:*** renal involvement during malaria infection is generally characterized by membrano-proliferative type of glomerulonephritis due to deposition of immune complexes (antigen-antibody complexes). Clinically the patient presents nephrotic syndrome (edema, particularly around the eyes and lower limb edema, foamy urine due to proteinuria, fatigue and loss of appetite.
- In ***Plasmodium falciparum*** malaria; causing acute kidney injury such as tubular necrosis, hemoglobin and cellular casts in tubules, and interstitial edema. These lesions are due to impaired blood flow because of sequestration of infected RBC, leading to a blockage of microcirculation, causing ischemia and subsequent tissue damage in the kidneys. Clinically the patient presents by acute renal failure with or without overt haemoglobinuria black water fever (decreased urine output, fluid retention, lower limb edema, shortness of breath, fatigue, confusion, nausea, weakness, irregular heartbeat, chest pain and seizures or coma).



Diagnosis:

1. **Clinical picture**: The characteristic paroxysms of cold stage (a shaking chills), followed by a fever stage (40– 41°C), and finally a wet stage (profuse sweating). The patient is exhausted but well until the next cycle of fever begins. Other symptoms include tender **hepatosplenomegaly and anemia**.
2. Standard diagnostic method is **thin blood film** for characteristic erythrocytic stages.
3. **Sternal puncture examination** in case of malignant malaria when the parasite does not appear in blood films.
4. **Serological tests:** Fluorescent antibody test and ELISA.

Treatment:

1. **Prophylaxis:** proguanil, daraprim, resochin.
2. **Clinical cure:** chloroquine.
3. **Radical cure:** Primaquine.
4. **If drug resistance occurred:** a combination of pyrimethamine and sulphadoxin.

Prevention and control:

1. Treatment of patients.
2. Destruction of breeding places by draining ponds or by filling them with earth or by using larvicidal oil.
3. The use of small fish (Gambusia) which eat mosquito larvae.
4. The use of insecticides on the inner walls of houses to destroy adult mosquitoes.
5. Screening houses and the use of bed nets.

6. Application of skin repellents over exposed areas of skin.

3. Trichomoniasis

Causative protozoa	***Trichomonas vaginalis* (Urogenital flagellates)**
Geog. Dist.	**Cosmopolitan.**
Definitive host:	**Man.**
Habitat:	➢ **Vagina and urethra of female.** ➢ **Prostate, seminal vesicles and urethra of male.**
Infective stage: **Diagnostic stage:**	➢ **Trophozoites.** ➢ **Trophozoites.**
Mode of infection:	• **Sexual intercourse (Sexually Transmitted Infection -STI).** • **Contaminated toilet articles and toilet seats.**

Pathogenesis and clinical picture:

- *T. vaginalis* affects the urogenital system of both sex; females of child bearing period are more affected.
- The infection, once established, persists for long periods in females but only for a short time in males.
- *T. vaginalis* principally infects the squamous epithelium of the genital tract .
- The parasite produces deterioration of the cells of the vaginal mucosa, resulting in low-grade inflammation and persistent vaginitis.
- The parasite may find its way to the **lower urinary tract causing profuse purulent urethritis and cystitis. Clinically,** infection is largely **asymptomatic**, or may be **acute or chronic.**

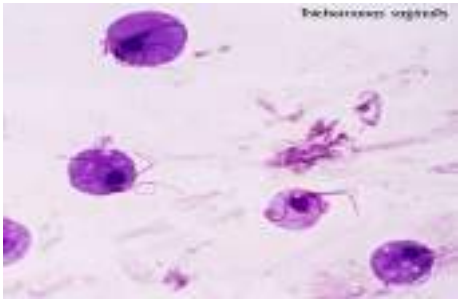
➢ **In females**; dysuria and pruritus with diffuse vulvitis with leucorrhea (white or yellow fuzzy discharge).

➢ **In males**; mild dysuria; pruritus and minor urethral discharge.

➢ Complications include prostatitis, epididymitis, endometritis, cervical erosion, low birth weight and infertility.

Diagnosis:

1. **Examination of urine or prostatic secretions;** for detection of *Trichomonas* trophozoites in wet mount and Giemsa-stained smears.
2. **Culture**: on CPLM (Cysteine, Peptone, Liver, and Maltose) media.
3. **Serology:** of suspicious urine sample; ELISA.
4. PCR using specific primers.



Treatment: The most effective drug for both sexes is Metronidazole.

Prevention and control:

- Attention to personal hygiene is the most important preventive measure.
- Detection and treatment of infective asymptomatic carriers' partner help in reducing infections.

4. *Enterobius vermicularis*

Geog. distribution	**most frequent helminth parasite worldwide**
Disease	Enterobiasis.
Host	Man, especially children,
Habitat	Large intestine mainly caecum, colon, rectum and appendix.
Infective stage	Mature egg
Diagnostic stage	Mature egg
Mode of infection	Ingestion of infective mature eggs through: *1.* Autoinfection a) **external autoinfection**: contaminated hand to mouth. b) **Retro infection,** eggs hatch in the peri-anal region and larvae migrate back through the anus to the large intestine 2. Contaminated food or drinks. 3. Contaminated objects as doorknobs, toilet seats or clothing.

	4. Air-borne infection through inhalation of eggs in dust particles.

Pathogenesis and clinical picture:

- ✓Worms may migrate to the urethra and urinary bladder leading to irritation and inflammation (urethritis and cystitis).
- ✓**Clinically;** dysuria, increased frequency of urination and pruritus are the common presentations.

Diagnosis:

1. **Urine examination**: eggs and adult worms (females) may be seen.
2. **Immunodiagnosis** of suspicious urine sample; ELISA.
3. **Molecular Diagnosis:** PCR using specific primers.

Treatment:

Pyrantel pamoate; Flubendazole or Mebendazole as a single oral dose. A second dose should be given after 2 weeks in resistant cases.

Prevention & control:

1. Personal hygiene: Cutting nails short and washing hands after using a toilet and before meals.
2. Infected children should wear tight-fitting trousers (clothes), their underwear and bedding carefully handled and washed.
3. Food and drink should be protected from dust & flies.
4. Mass treatment of all individuals in any infected community, e.g. family or school.

5. Urogenital Myiasis

Definition: It is an infestation of human's urogenital organs by larvae of diptrous flies.e.g. ***Eristalis tenax, Dermatobia hominis.***

Pathogenesis and clinical picture:

- ➢ It is usually a self-limited condition.
- ➢ It is usually associated with poor general health and hygiene, restricted mobility, and ulcerating lesions.

- Adult flies oviposit on external offices of urinary tract, eggs hatch and larvae lives on live cells or dead tissues.
- Habitation and living of larvae into the lower urinary system occur.

Clinically: patients presented wit: itching, dysuria, polyuria (bladder irritative symptoms) and hematuria.

Diagnosis:

- Identification of fly larvae either by:
  1. Characteristic morphological features of the larvae.
  2. Rearing of larvae to adult stage and identification of the adult.
- Cystoscopy to reveal any associated complications as secondary infection.

Treatment: Bladder wash, antibiotic and ivermectin.

6. Filariasis

Urinary filariasis is a manifestation of lymphatic filariasis, caused by ***Wuchereria bancrofti*** and ***Brugia malayi***.

Pathogenesis: is directly linked to

- the recurrent **lymphadenitis, lymphangitis, and fever** can be seen in mild disease, and these cause swelling especially in the legs and feet (elephantiasis)
- Acute glomerulonephritis occurs which is immune complex mediated.
- In severe disease, obstruction of major lymphatic vessels may cause **chyluria** with elephantiasis. **Chyluria** (milky white urine) is caused by rupture of dilated abdominal lymphatics into the urinary system.

The diagnosis is established clinically, and serologically

- **Treatment** with diethylcarbamazine (DEC) and ivermectin.

Refences:

1. Kaplan USMLE Step1 Lecture Notes Immunology and Microbiology 2021. Pages 134, 149,
2. First aid for USMLE step 1. Student to student guide 2019. Pages: 159, 160, 165. 665, 751
3. Oxford handbook of Medical Sciences 2017. Pages: 443, 453, 448, 718, 810, 819
4. Garcia, Lynne Shore, and David A Bruckner. Diagnostic Medical Parasitology. New York: Elsevier, 2016. Pages: 335, 381,384, 458, 607-610