

NEPHROLOGY 1

Marrow SS Medicine





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Nephrology

Volume - 1

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Contents

Volume - 1

Basics of Nephrology

1. Renal Embryology	1
2. Renal Anatomy	9
3. Renal Physiology	20
4. Clinical Approach To A Renal Disease	29
5. Urine Analysis	32

Vascular Disorders of The Kidney

6. Renal Artery Stenosis	42
7. Thrombotic Microangiopathy	48

Glomerulopathies

8. Approach To Glomerular Disorders	53
9. Minimal Change Disease	61
10. Focal Segmental Glomerulosclerosis (FSGS)	67
11. Membranous Nephropathy	75
12. Membranoproliferative Glomerulonephritis (MPGN)	81
13. IgA Nephropathy	85
14. PSGN	90
15. Goodpasture Syndrome	94
16. SLE : Introduction & Pathogenesis	98
17. SLE : Clinical Features	108
18. SLE : Management	121
19. ANCA Vasculitis - Part 1	128
20. ANCA Vasculitis - Part 2	131
21. Familial Glomerular Syndromes	136
22. Rare Glomerular Disease	141

KDIGO Updates

23. KDIGO Updates : Glomerular Diseases - I	149
24. KDIGO Updates : Glomerular Diseases - II	154
25. KDIGO Updates : Glomerular Diseases - III	164
26. KDIGO Updates : Glomerular Diseases - IV	169
27. KDIGO Updates : Glomerular Diseases - V	179
28. KDIGO Updates : Glomerular Diseases - VI	182
29. KDIGO Updates : Glomerular Diseases - VII	186
30. KDIGO Updates : Glomerular Diseases - VIII	191
31. KDIGO Updates : Glomerular Diseases - IX	195

Hereditary and Cystic Renal Disorders

32. Hereditary and Cystic Renal Disorders	199
---	-----

Acute Kidney Injury (AKI)

33. Introduction To AKI	209
34. ATIN vs ATN	218
35. Septic ATN	226
36. Pigmented Nephropathies and TLS	230
37. Contrast Induced AKI	234
38. Cholestrol Embolism	237
39. Myeloma and Kidney	239
40. Renal Cortical Necrosis	241
41. HRS/CRS	243
42. AKI Complications & Management	249

Tubulointerstitial Diseases

43. Chronic Tubulointerstitial Disease	251
--	-----

Infections and The Kidney

44. UTI and Pyelonephritis	258
45. HIV and The Kidney	270
46. Genito-urinary TB and Schistosomiasis	273
47. Tropical Acute Kidney Injury (AKI)	281

Kidney Health in Women

48. Introduction To Kidney Health In Women	284
49. AKI in Pregnancy	286

Volume - 2

Tubular Disorders and Electrolytes

50. Proximal Tubule & Inherited Disorders	293
51. Potassium Metabolism	304
52. Renal Tubular Acidosis	317
53. Hypokalemia and Alkalosis	324
54. Hyperkalemia	332
55. Magnesium Metabolism	338
56. Calcium Metabolism	341
57. Phosphorus Metabolism	354
58. Disorders of Water Balance	359
59. ADH	362
60. Hyponatremia	366
61. Management in Hyponatremia	371
62. Diabetes Insipidus and Hypernatremia	375

Chronic Kidney Disease (CKD)

63. Introduction To CKD	379
64. Pathogenesis of CKD	382

65. Kidney Protection in CKD	387
66. What to watch out for in CKD	390
67. Hematological Manifestations in CKD	392
68. CKD - Mineral Bone Disease	398
69. Cardiovascular Manifestations in CKD	407
70. Neuroendocrine Manifestations in CKD	412
71. Dermatological Manifestations in CKD	415
Diabetic Kidney Disease	
72. Diabetic Kidney Disease	420
Hemodialysis	
73. Introduction To Dialysis	432
74. Mechanism of Hemodialysis	435
75. Machine Blood Circuit	439
76. Machine - Dialysate Circuit	442
77. Access for Dialysis	448
78. Complications of Dialysis	457
79. Newer forms of Dialysis	460
Renal Transplantation	
80. Adaptive Immunity	469
81. Effector T-Cell Function	484
82. HLA	489
83. Immunological Workup for Transplant	495
84. Small Molecules : Immunosuppression in Transplantation	505
85. Biologics : Immunosuppression in Transplantation	521
86. Recipient and Donor Evaluation	527
87. Beyond 3 Months After Transplant	536
88. Rejection At End of 1st Week To 3 Months	544

89.	Chronic Graft Loss	551
90.	Post Transplant Infections	559
91.	Transplant Surgery and DGF	565
92.	Recurrence After Transplant	572

ACID-Base Balance

93.	Introduction To Acid Base Analysis	577
94.	Methodology and Interpretation of ABG Analysis	582
95.	Metabolic Alkalosis	586
96.	Case Scenarios On ABG	588

Peritoneal Dialysis

97.	Introduction and Physiology of PD	600
98.	The Process of PD	602
99.	Complications After PD	608

Pediatric Nephrology

100.	Posterior Urethral Valves	613
101.	Vesicoureteric Reflex	617
102.	Congenital Nephrotic Syndrome	622
103.	Sickle Cell Nephropathy	625
104.	Congenital Anomalies of Kidney and Urinary Tract	628

Sessions in Nephrology

105.	Urinary Casts	639
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RENAL EMBRYOLOGY

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Development of urogenital system

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mesoderm :

- Intermediate mesoderm : Gives rise to kidneys.
- Paraxial mesoderm : Gives rise to somites (muscles).
- Lateral plate mesoderm : Cavities (Pleura, peritonium, pericardium).
 - Somatopleuric gives rise to parietal pleura, parietal pericardium, etc.
 - Splanchnopleuric gives rise to visceral pleura, visceral pericardium, etc.

Development of urogenital system :

Entire urogenital system is derived from :

- Intermediate mesoderm : Entire kidney is derived from this.
- Cloaca.

Cloaca :

- Cloaca is part of the hindgut that is distal to the allantois.
- Cloaca is completely **endodermal** in origin.
- It gives rise to two structures namely :
 - Primitive urogenital sinus :**
 - Gives rise to vesicourethral canal → Bladder and urethra.
 - The upper part gives rise to the bladder.
 - Pelvic part gives rise to prostatic and membranous urethra.
 - Phallic part gives rise to sponge urethra.
 - Primitive rectum :**
 - Gives rise to rectum and anal canal up to pectinate line.
 - Anal canal below pectinate line is **ectodermal** in origin.

Intermediate mesoderm :

Gives rise to :

- Genital ridge (Gonads).
- Paramesophric duct (Müllerian duct).
- Mesonephric duct/Wolffian duct.
- Urogenital ridge (Nephrogenic cord) : It extends from the cervical to sacral region of the embryo. It is very closely aligned to the Wolffian duct.

Structures derived from mesonephric duct :

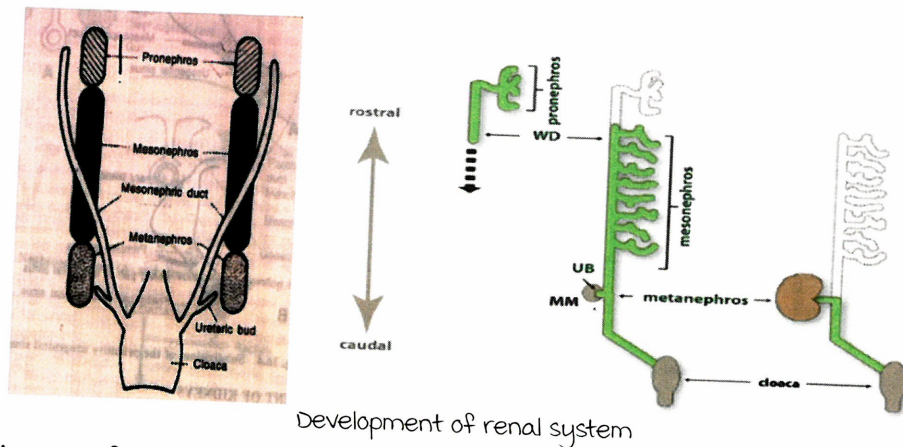
- Seminal vesicle.
- Ejaculatory duct.
- Vas deferens.
- **Trigone of bladder** (Entire bladder is endodermal in origin except trigone).
- **Appendix of epididymis.**
- Ureteric bud.

Note :

Remnants of mesonephric duct are Gartner's cyst, epoophoron and paroophoron.
Remnants of paramesonephric duct are appendix of testis and hydatid of morgagni.

Timelines of development :

- Day 22 : Pronephros appears and regresses in 2-3 days.
- Day 24 : mesonephros appears and regresses in 4 months.
- 5th week :
 - metanephric mesenchyme (Forms the **excretory part** of the kidney).
 - ureteric bud develops from the mesonephric duct (Forms the **collecting part** of the kidney).
- Between 6th to 8th week : **epithelial mesenchymal interaction** occurs.
- End of the 8th week : First fully formed nephron.
- 9-10th week : Urine formation starts.
- 32-26 weeks : Nephrogenesis is completed.
- 18 months : Fetal kidney reaches adult concentrating capacity.
- After birth :
 - New nephrons are not formed, and lost nephrons cannot be replaced.
 - Concentrating capacity is increased even after the birth.
- At 18 months : Adult concentrating capacity is reached.
- metanephros (Adult kidney) :
 - It is initially formed at the level of S1-S2.
 - At around 9-10th week, ascend with rotation occurs and reaches T12-L3 level.



Development of renal system

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Importance of nephron number :

- 60% of nephrons are formed in third trimester.
- $GFR = \text{Single nephron GFR} \times \text{Number of nephrons}$.
- CKD is decrease in nephron number.
- 3 kg at birth : 9,00,000 nephrons in each kidney.
- 2 kg at birth : 2,25,000 nephrons in each kidney.
- Birth weight determines the number of nephrons at birth, after which new nephrons are not formed.

Therefore premature babies are prone to CKD.

- mother's average BP during pregnancy determines birth weight → Determining risk of CKD.

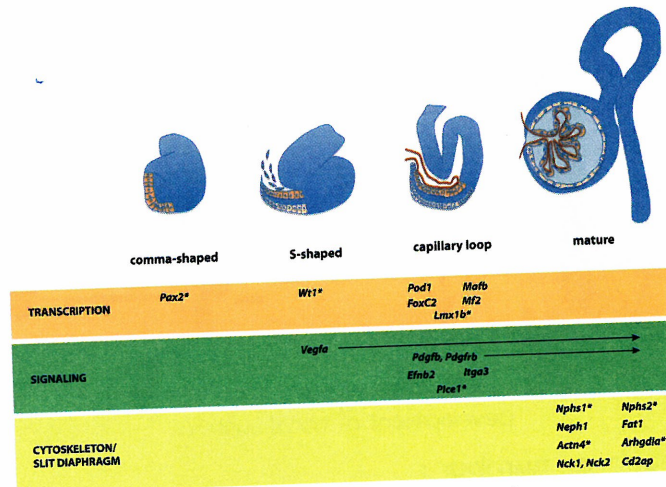
EMI & associated anomalies

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Epithelial mesenchymal interaction (EMI) :

- Epithelial mesenchymal interaction (EMI) is made possible by transcription factors which is expressed from the ureteric bud side or metanephric mesenchyme side.
- Transcription factor required for ureteric bud induction : PAX-2 (mutation causes unilateral renal agenesis).
- VEGF is produced by the podocytes and is required for this progression.
- Homozygous mutation leads to bilateral renal agenesis.
- Transcription factors expressed by :
 - metanephric mesenchyme : WTI, WNT4 and WNT6.
 - ureteric bud : FGF, BMP-7.
- WTI gene on chromosome 11p : mutation leads to :
 - WAGR syndrome.
 - Denys Drash syndrome.

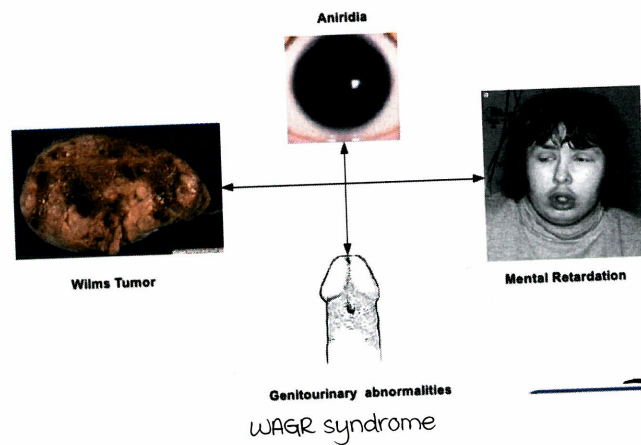
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Epithelial mesenchymal interaction

WAGR syndrome :

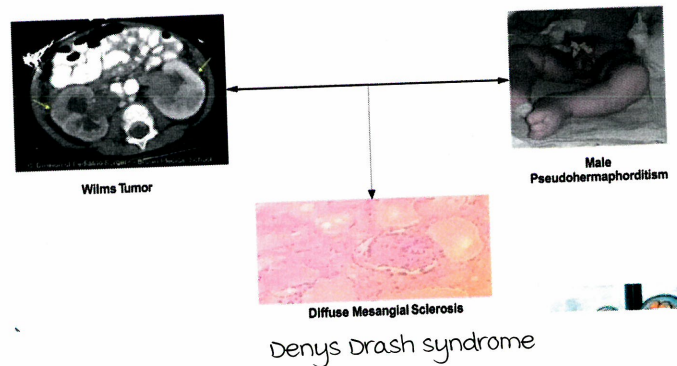
- Wilms tumour.
- Aniridia.
- Genitourinary abnormalities.
- mental retardation.



Denys Drash syndrome :

Characterized by :

- Wilms tumor.
- male pseudohermaphroditism
- early onset renal failure (Diffuse mesangial sclerosis).



Beckwith-Wiedmann syndrome :

Beckwith-Wiedmann syndrome is **not a part of** emi.

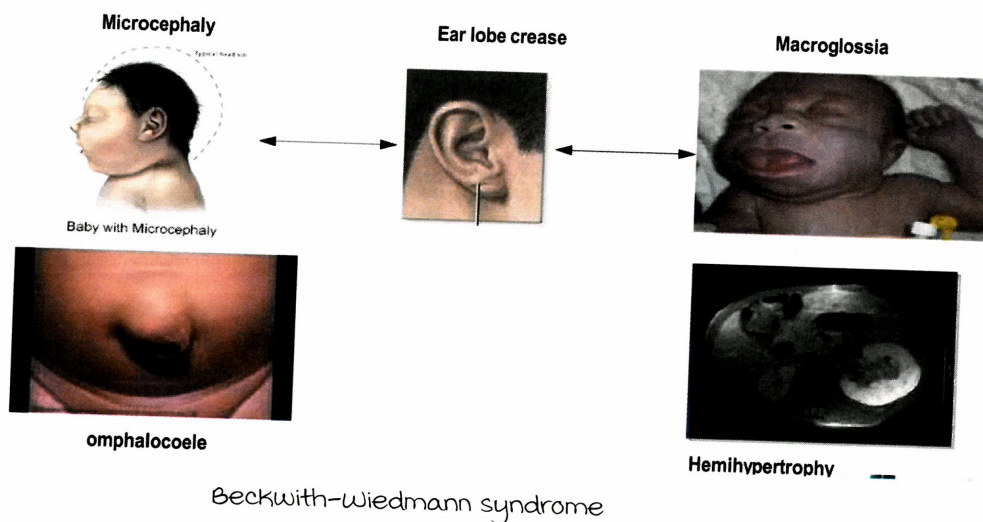
Due to WT2 gene mutation on chromosome 11.

Genomic imprinting abnormalities are present.

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Clinical features :

- **Organomegaly** (Renomegaly, nephromegaly, adrenomegaly, hepatomegaly).
- Omphalocele/umbilical hernia.
- macroglossia.
- Hemihypertrophy of testes (Very closely associated with medullary sponge kidney).



Other mutations :

- WNT4 and WNT6 mutation :
 - Renal hypodysplasia (<2 SD size).
 - Hyperandrogenism
 - mullerian aplasia.
- ACE mutations are associated with tubular dysgenesis.
- HNF1B mutations are associated with MODY 5, renal cysts, genital abnormalities.

Renal agenesis :

Unilateral renal agenesis :

- **Heterozygous PAX-2** mutation : unilateral renal agenesis with optic coloboma.
- Incidence : 1 in 1000 live births.
- Common in females >> males.
- HTN is only the clinical feature.

malformations associated with unilateral renal agenesis :

- Single umbilical artery.
- Absent uterus.
- Absent ipsilateral vas deferens.
- Contralateral vesico-ureteral reflex.
- Contracted kidneys from birth : multicystic dysplastic kidney.

Bilateral renal agenesis :

- RET/GDNF gene mutation.
- Associated with : Oligohydramnios and Potter's syndrome (Bilaterally absent renal artery, disc shaped adrenals).

CAKUT anomalies

00:27:56

Stage of Nephrogenesis	Gene	Associated Phenotype
Ureteric bud induction	EYA1	Branchio-oto-renal syndrome
	GATA3	HDR syndrome
	PAX2	Renal coloboma syndrome, FSGS
	RET	Renal agenesis and Hirschsprung disease
	ROBO2	VUR
	SALL1	Townes-brocks syndrome
	SIX1, SIX5	Branchio-oto-renal syndrome
Mesenchymal to epithelial transition	WNT4	Renal hypodysplasia, müllerian aplasia, hyperandrogenism
	SIX2	Renal hypodysplasia
Branching morphogenesis	ACE	All associated with renal tubular dysgenesis
	AGT	
	AGTR1	
	REN	
As yet unknown	HNF1B	Renal cysts and diabetes syndrome, genital malformations, hypomagnesaemia, abnormal LFTs, gout, autism
	DSTYK	CAKUT
	TNXB	VUR, joint hypermobility
	SOX17	VUR
	KAL1	Kallman syndrome
	FRAS1	Fraser syndrome
	FREM2	Fraser syndrome
	GRIP1	Fraser syndrome

Common congenital anomalies of kidneys and urinary tract.
m/c ESRD in children.

It includes :

- Agenesis : It can be unilateral or bilateral.
- Dysplasia : Abnormal differentiation.
Eg : multicystic dysplastic kidney (Unilateral).
- Hypoplasia : Decrease in size of kidney.

Associated with :

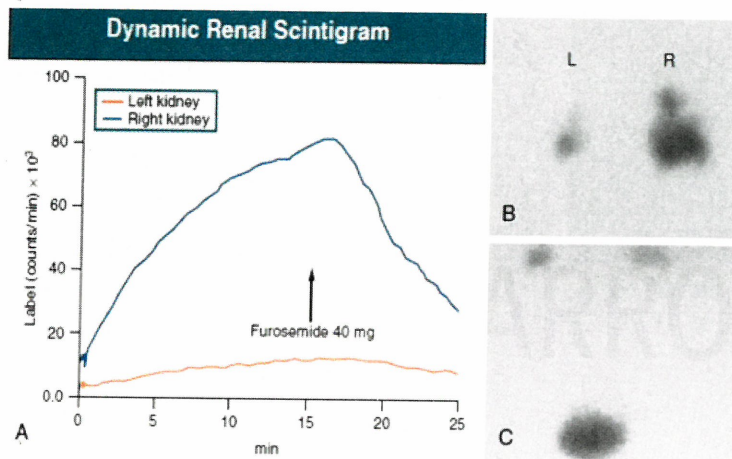
- Normal nephron number.

- **Oligomeganephronia** (Decreased nephron number) : Remaining glomeruli undergo hypertrophy).
- **Segmental hypoplasia** : Associated with HTN in young (Ask up mark kidney).

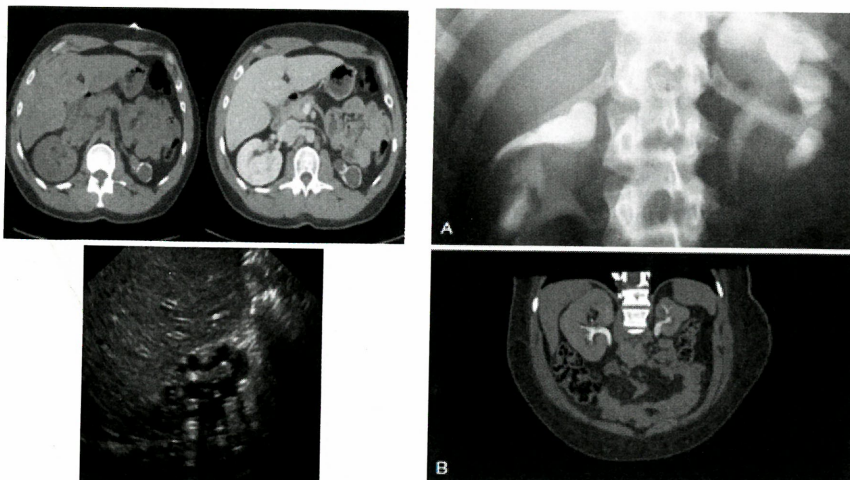
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Note :

Technetium-99m MAG3 scintigram : used to detect PUJ stenosis.



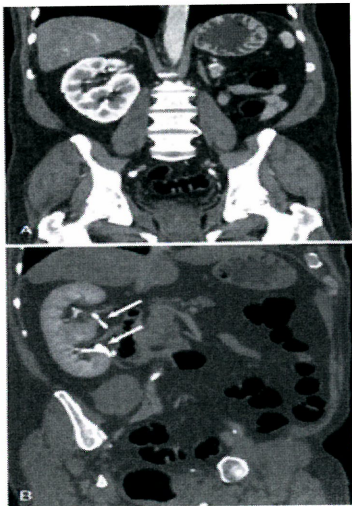
Ectopic kidney



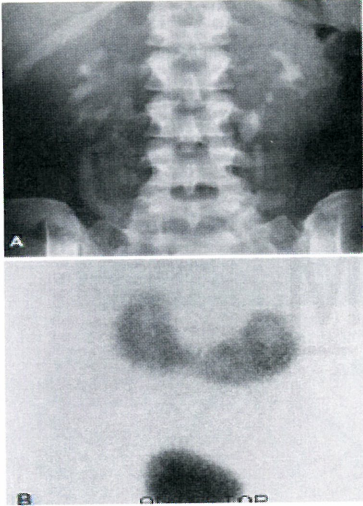
multicystic dysplastic kidney

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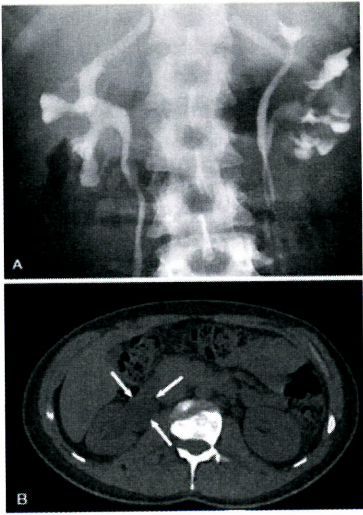
Other kidney anomalies :



Crossed fused ectopic kidney



Horseshoe kidney



Duplex system

RENAL ANATOMY

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Definitions

00:00:21

Nephron

Renal corpuscle :

- Glomerulus : The term used most frequently to refer to the entire renal corpuscle.
- Bowman's capsule

Proximal tubule

- Convulated part.
- Straight part (pars recta) or thick descending limb of Henle's loop.

Intermediate tubule

- Descending part or thin descending limb of Henle's loop.
- Ascending part or thin ascending limb of Henle's loop.

Distal tubule

- Straight part or thick ascending limb of Henle's loop : Subdivided into medullary and a cortical part; the latter contains in its terminal portion the macula densa.
- Convulated part.

Collecting duct system

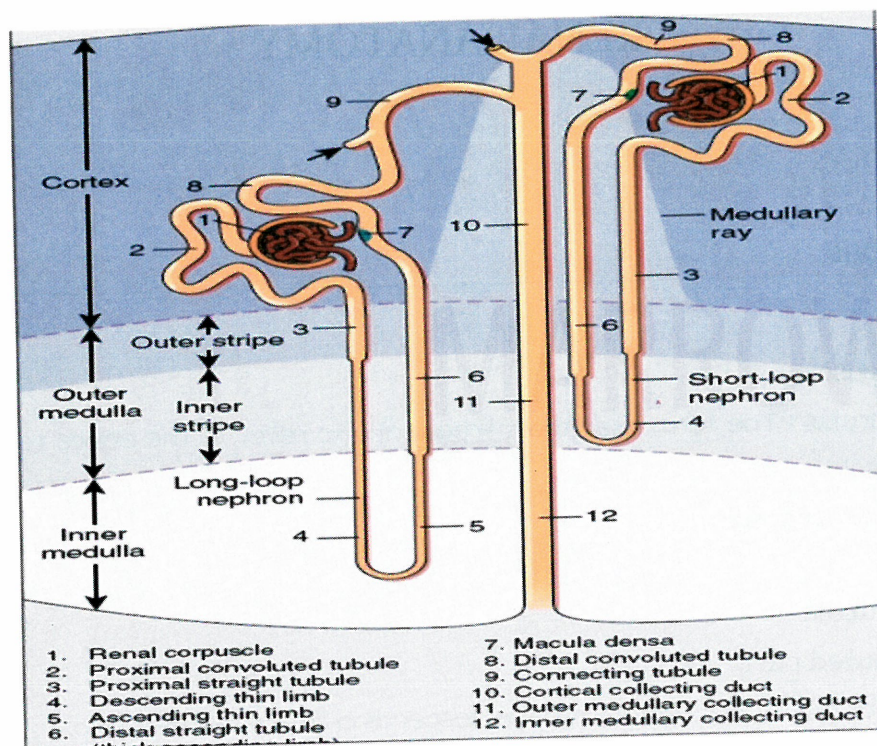
Connecting tubule :

- Includes the arcades in most specie

Collecting duct

- Cortical collecting duct : Outer medullary collecting duct subdivided into an outer and an inner stripe portion.
- Inner medullary collecting duct subdivided into basal, middle, and papillary portions.

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Structures in the excretory part of kidney

1. Glomerulus + Bowman's capsule (renal corpuscle).
 - PCT or pars convoluta.
2. The S1 and S2 segments are parts of PCT. Present in the cortex.
3. PST or pars recta :
 - S3 segment is present in PST. It is present in the medulla.
 - 2 + 3 is called proximal tubule.
 - The main function of proximal tubule is reabsorption.
 - It contains abundant number of mitochondria.
 - The tubule is lined by cuboidal epithelium containing brush border microvilli.
 - PST is the most susceptible to acute tubular injury because of high oxygen requirement needed for reabsorption.
 - Ischemia is the most common cause for acute tubular injury.
4. Thin descending limb of Henle's loop.
5. Thin ascending limb of Henle's loop.
 - 4 + 5 is called intermediate tubules.
 - 85% of nephrons are cortical nephrons and 15% of nephrons are juxtamedullary nephrons.
 - Cortical nephrons are short looped and juxtamedullary ones are long looped based on the location of tip of the loop of Henle.
 - When the tip is at the junction of inner and outer medulla, it is called short looped cortical nephrons.