HYPERTENSION

90-95% Essential Hypertension

- Affects 26% of adults > 18 years
- Incidence increases sharply with age (90% of 90 year olds are hypertensive)
- 35% polygenic
- 65% environmental
  - BMI and sodium most important environmental risk factors
  - Insulin resistance and the metabolic syndrome common

5-10% Secondary Causes

- Chronic kidney disease
- Primary renal disease
- Primary aldosteronism
- Renovascular disease
- Obstructive Sleep Apnoea
- Phaeochromocytoma
- Coarctation of the aorta
- Drugs
- Cushings Syndrome
- Primary hyperparathyroidism
- Hyper and Hypothyroidism

Rare Causes of Hypertension (0.1%)

Monogenic

- Glucocorticoid responsive hyperaldosteronism
- Apparent mineralocorticoid excess (Hereditary)
- Progesterone-induced hypertension (Activating MR Mutation)
- Liddle's Syndrome
- Gordon's Syndrome (PHA 2)
- Congenital adrenal hyperplasia

Acquired

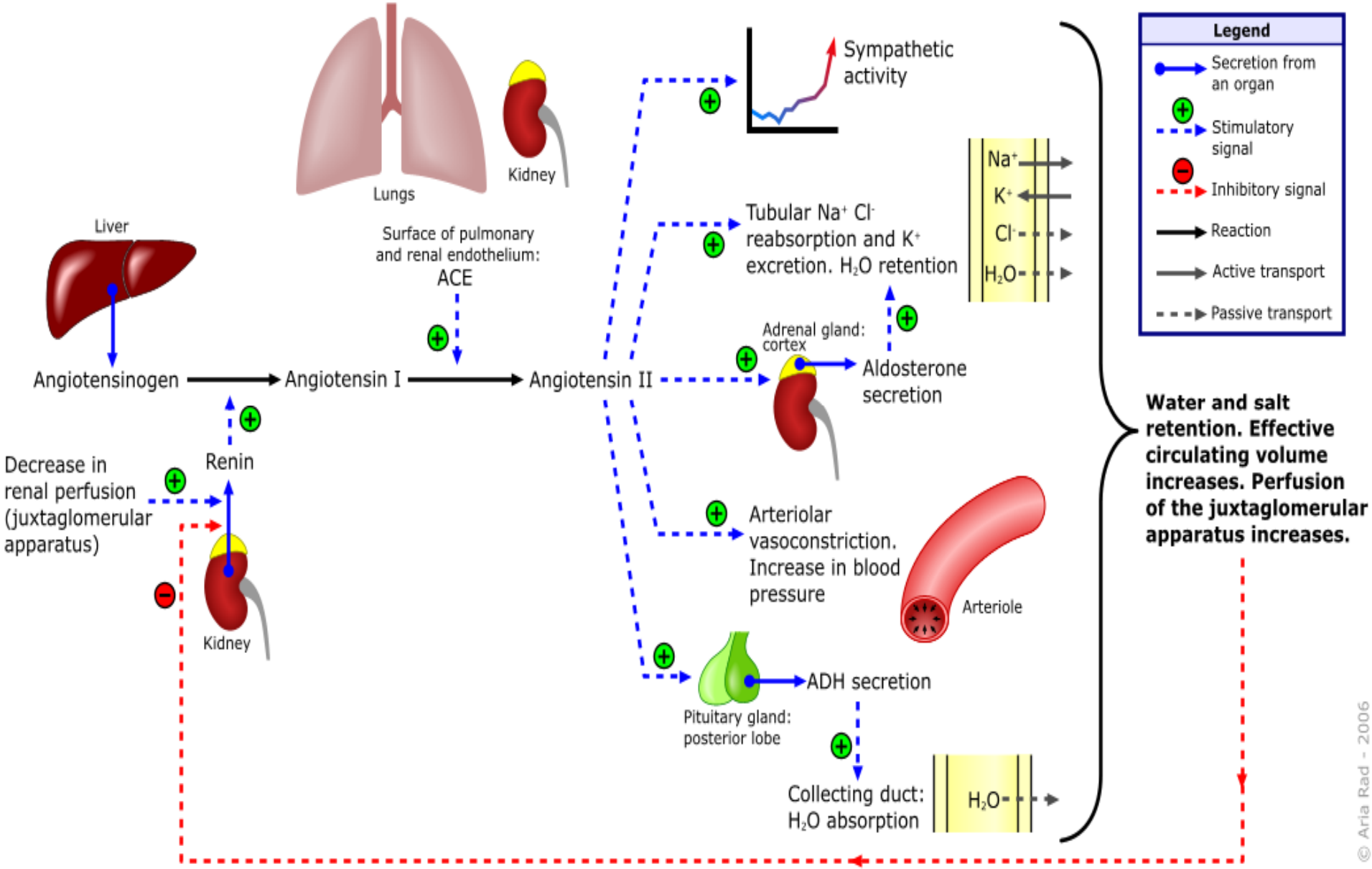
- Apparent mineralocorticoid excess (Acquired)
- Reninoma

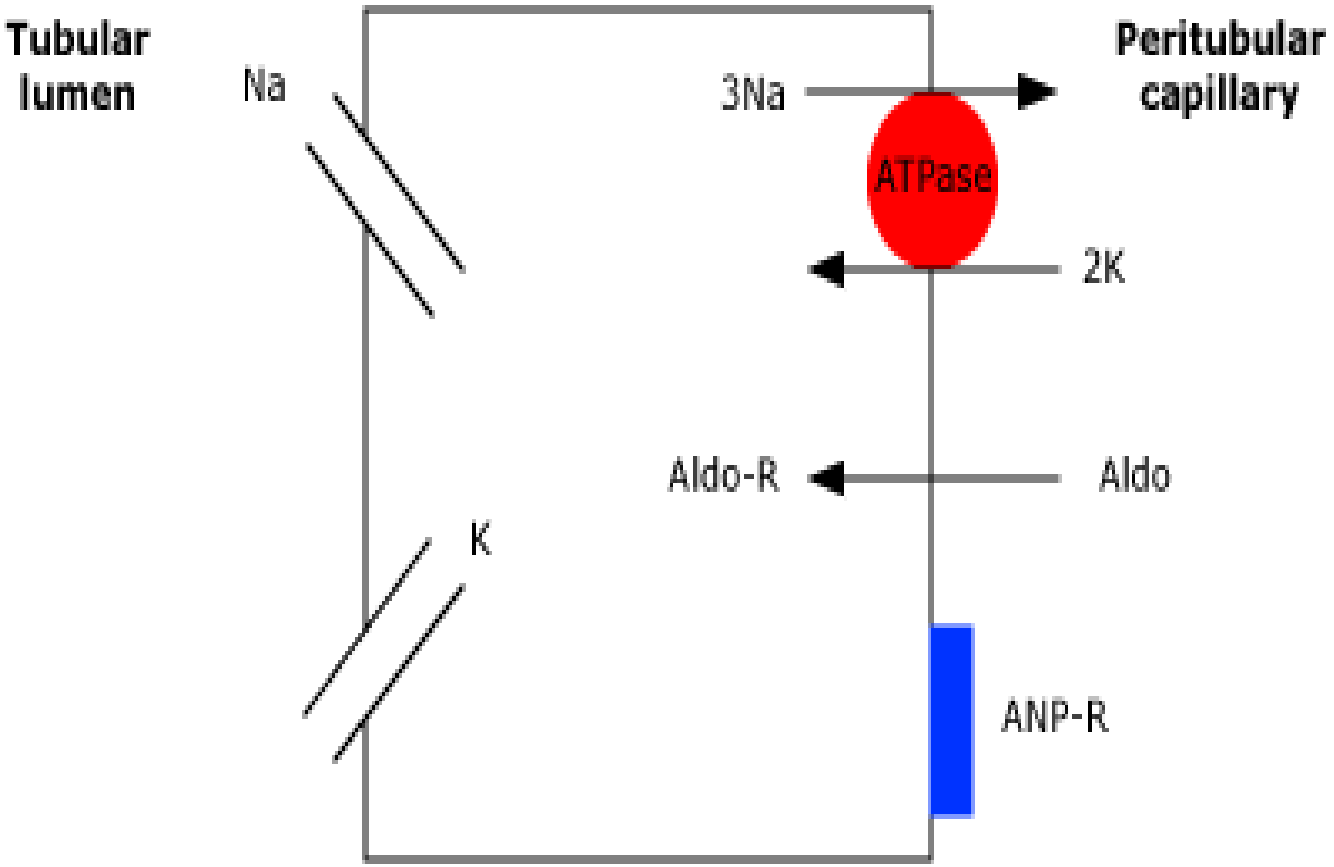
Monogenic causes of hypertension

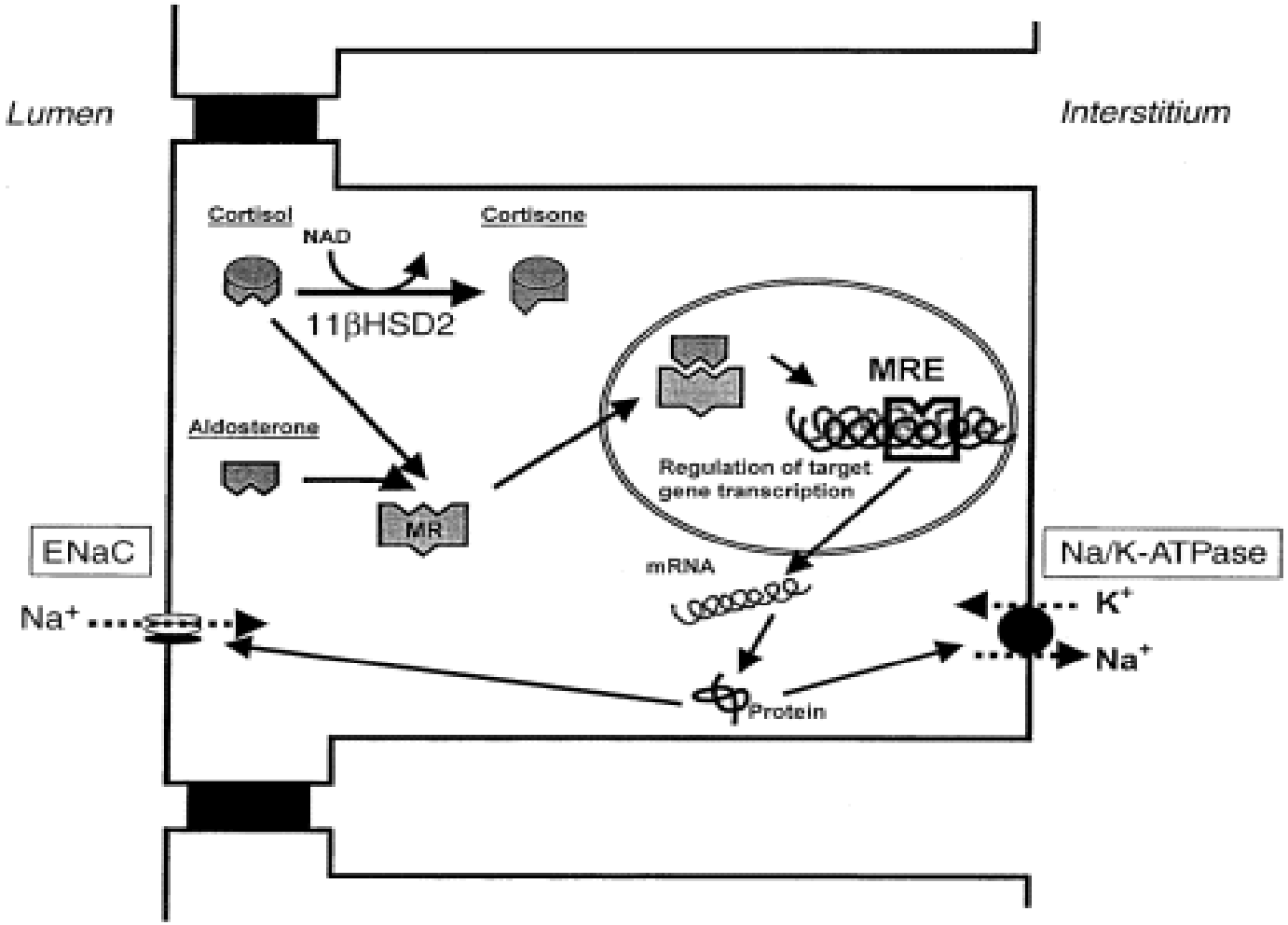
Characterised by abnormalities in steroid biosynthesis or metabolism or abnormalities of the CCT epithelial cell sodium channel

- present as real or apparent minerallocorticoid overactivity
- clinical phenotypes include hypertension from birth, apparent volume expansion, suppression of plasma renin, and variable hypokalaemia

Renin-angiotensin-aldosterone system




Tubular lumen
Na
3Na
Peritubular capillary
ATPase
2K
Aldo-R
Aldo
K
ANP-R


Lumen
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Cortisol
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Regulation of target gene transcription
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Na+
K+
Na+
Protein

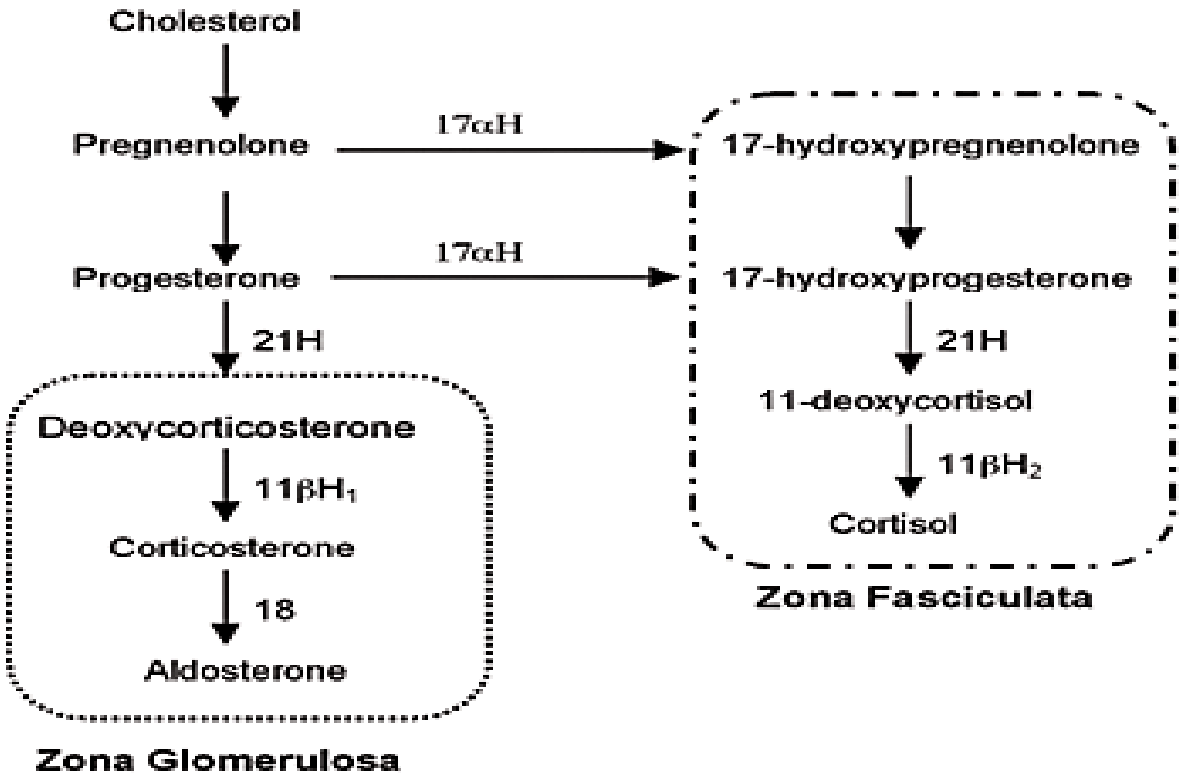
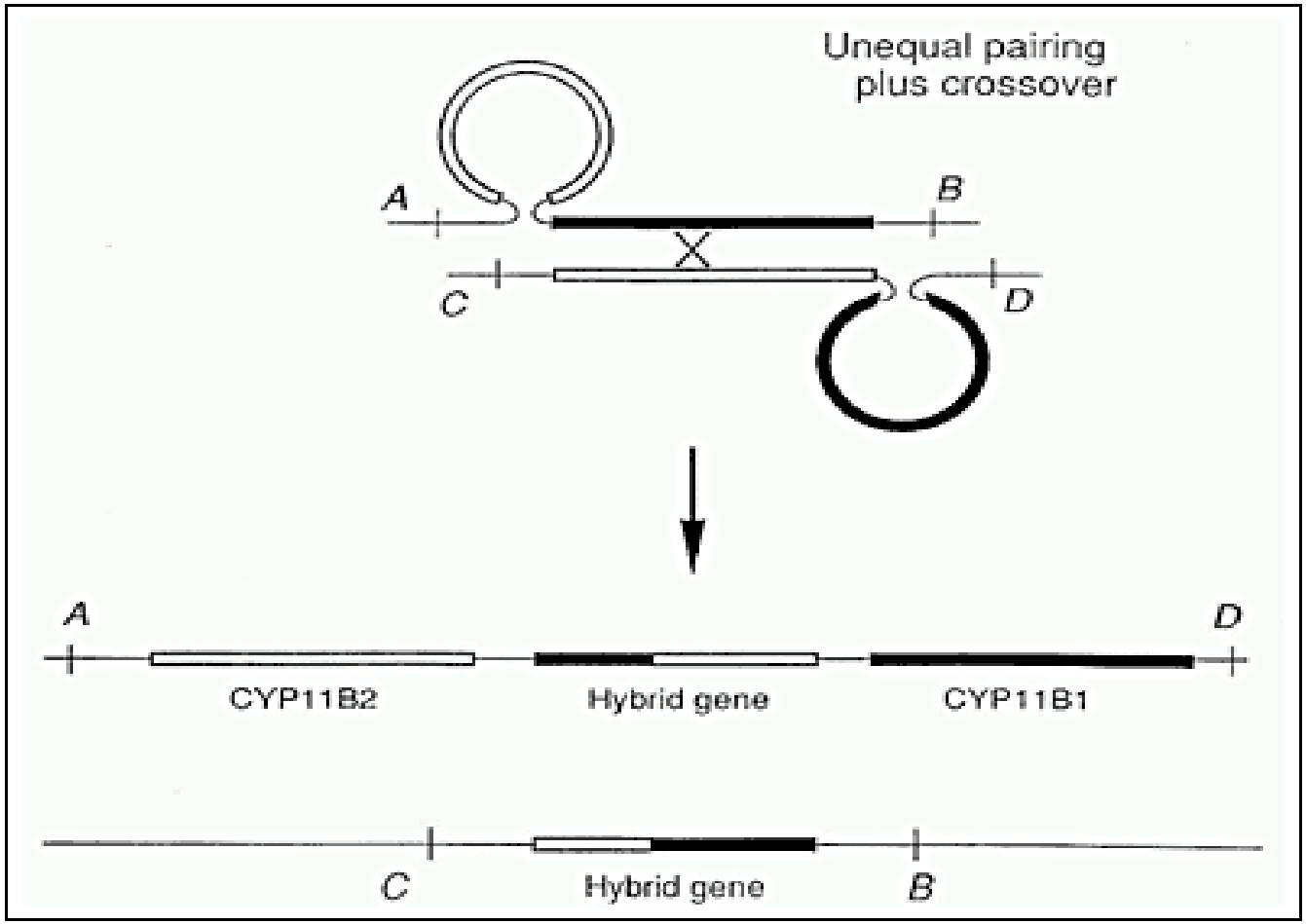


Figure 1. Normal biosynthetic pathways for cortisol and aldosterone. $11\beta H_1$ and aldosterone synthase are present only in the *zona glomerulosa*, and are regulated by angiotensin II. $11\beta H_2$ is present solely in the *zona fasciculata* and is regulated by ACTH. 21H= 21-hydroxylase. $11\beta H_{1\&2}$= 11β-hydroxylase isoenzymes 1 & 2; 18 = 18-hydroxylase/ aldosterone synthase. 17αH= 17α-hydroxylase.


Unequal pairing
plus crossover
A
B
C
D
A
D
CYP11B2
Hybrid gene
CYP11B1
C
Hybrid gene
B

- 25 y/o male with new onset hypertension
- BP 200/115 HR 88, hypertensive retinopathy
- 1 + proteinuria
- Na 140 K 2.7 Cl 97 HCO_3 30 pH 7.44 pCO_2 45 Cr 90umol/l
- Spot urine K 40mmol/l
- Plasma renin 3mU/l (low) aldosterone 150ug/l (low)

What is the diagnosis?

Clue:

unresponsive to spironolactone, but responsive to low Na diet and triamterene

21 year old man with hypertension on 3 drugs and remains poorly controlled. Ongoing search for a secondary cause so far negative. Renin and Aldo levels are pending and in the meantime he is started on spironolactone 25mg daily which results in a severe exacerbation of his hypertension – necessitating urgent withdrawl of the drug

Later that year, his 24 year old previously normotensive sister develops severe hypertension and hypokalaemia late in the second trimester of pregnancy. Her renin and aldosterone levels are both low.

What is the diagnosis?

17 year old boy from Glen Eden with extended family in Northland presents to ED with a minor sporting injury. BP noted to be 180/110. He is admitted and BP does not settle below 160/90. Auntie says there is a family history of high blood pressure and strokes on his father's side.

Na 144 K 3.1 urea 5 creatinine 80 venous bicarb 31

Renin < 3mU/L (low) Aldosterone 650 ug/l (high)

Saline suppression test aldo. non-suppressible

Contrast CT shows adrenals mildly hyperplastic but no focal ademoma

Kidneys normal size and shape

What are the 2 diagnostic possibilities?

What additional test is indicated before treatment plan is finalised?

17 year old girl with BP 170/110

Family history of difficult hypertension

Na 140 K 6.1 creatinine 70 Cl’ 114

pH 7.3 HCO3’ 14 PCO2 32

Renin 2mU/l (low) Aldosterone 175ug/l (low)

What is the diagnosis?

A 13 year old boy is referred from Samoa with severe hypertension

His father died in his 20's of unknown cause.

He is hypokalaemic and alkalaemic

Plasma renin < 2miu/l

Aldosterone 50pmol/l (low)

He is unresponsive to most antihypertensive drugs but prior to referral has been started on spironolactone which has been worked up to 200mg daily and his BP is mow relatively well controlled

What is the diagnosis?

5 year old boy with precocious puberty hypertension and hypokalaemia

What is the likely diagnosis?

- 25 y/o male with new onset hypertension
- BP 200/115 HR 88, hypertensive retinopathy
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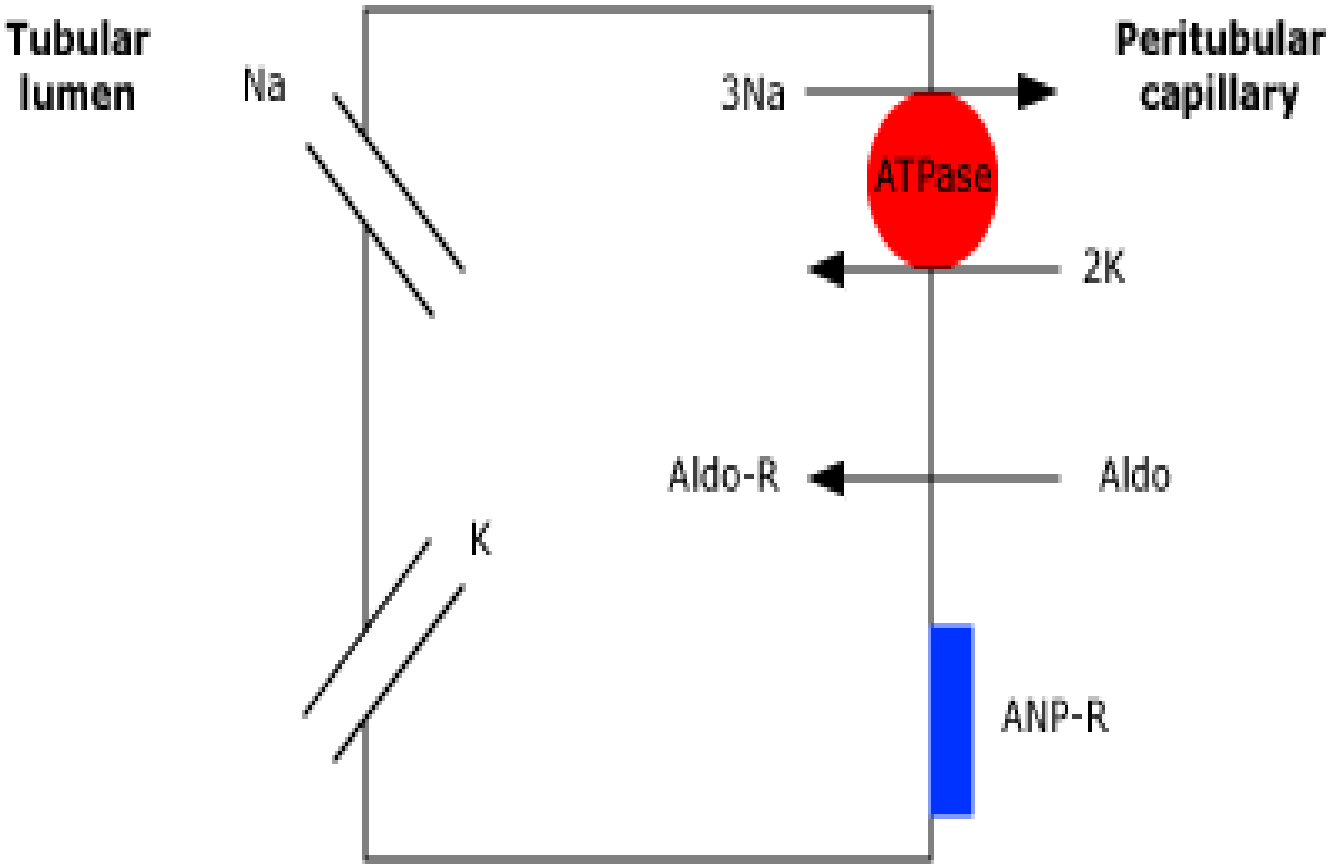
Liddle’s Syndrome

(Pseudohypoaldosteronism type 1)


Tubular lumen
Na
3Na
Peritubular capillary
ATPase
2K
Aldo-R
Aldo
K
ANP-R

Liddle's Syndrome: Characteristic Features

- Prevalence < 1% hypertensives

- Mechanism

    Autosomal Dominant activating mutation(s) in ENaC of collecting duct

    Impaired regulatory mechanism leads to increased no. ENaC channels on luminal membrane

-Presentation: severe salt sensitive hypertension, hypokalaemia, low renin + aldosterone

- Presents in children and young adults

- Diagnosis – Genetic analysis of ENaC gene

- Treatment

    Responds to low protein diet and triamterene

    Cured by renal transplant

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Later that year, his 24 year old previously normotensive sister develops severe hypertension and hypokalaemia late in the second trimester of pregnancy. Her renin and aldosterone levels are both low.

What is the diagnosis?

Mineralocorticoid Receptor Mutation *(Geller's Syndrome) (Pregnancy-Associated Hypertension)*

Rare genetic familial disorder where there is point mutation of the minerallocorticoid receptor resulting in a partially activated receptor.

Causes severe hypertension

Progesterone and spironolactone act as partial agonists

Suspect in women who present with severe hypertension and hyopkalaemia in 2nd or 3rd trimester of pregnancy.

The syndrome was discovered in a young male hypertensive whose 2 sisters experienced severe exacerbations of hypertension in pregnancy.

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Glucocorticoid Remediable Hyperaldosteronism

Suspect in patients with early onset familial hypertension

Biochemically indistinguishable from other causes of Primary Aldosteronism

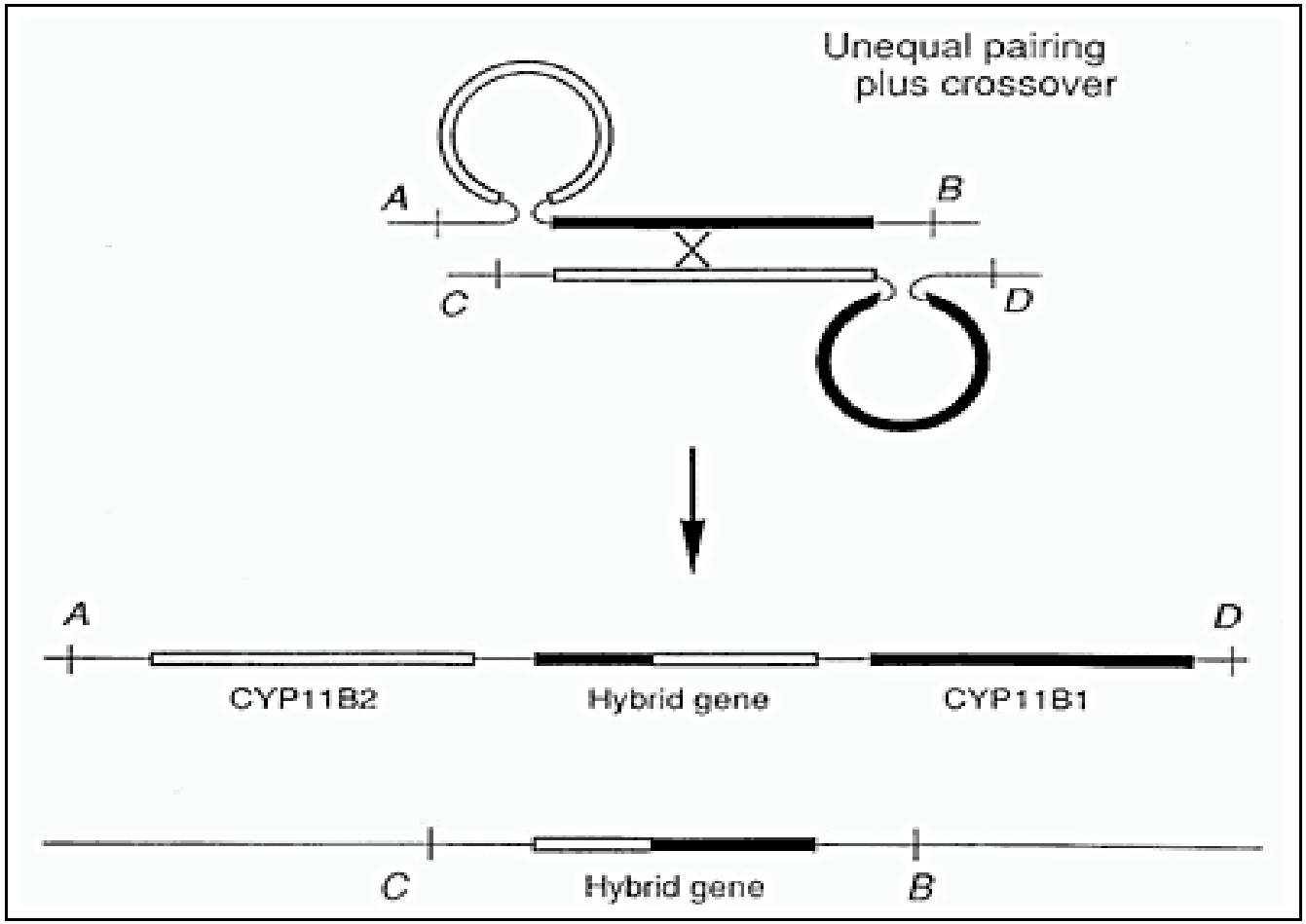
-Adrenals normal or diffuse hyperplasia on CT

Diagnosis – PCR for the chimeric gene

Treatment

Low dose dexamethasone

Also responds to aldosterone antagonists and amiloride


Unequal pairing
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B

Table 1. Algorithm for GRA diagnosis and treatment.

Screening	
Recommended for hypertensive individuals who: - are diagnosed with primary hyperaldosteronism without demonstrable tumor - are young (especially children) and have suppressed plasma renin activity - have a family history of cerebral hemorrhage or hypertension before age 30 years - have refractory hypertension (hypertensive on 3 classes of agents including a diuretic) - are members of known GRA kindreds	
↓	
Diagnosis	
Dexamethasone suppression test	Easily performed. Dexamethasone 0.5mg every 6hrs x 2 days, normally aldosterone < 4ng/dl on day 3 at 8am
Genetic Test	Can be arranged through the international GRA registry (http://www.brighamandwomens.org/gra)
24 hour urinary 18-hydroxycortisol & 18-oxocortisol levels	Impractical since assays only available in specialized centers. Elevated > 2x upper limit of normal; a urinary level of 18-hydroxycortisol > 10nmol/l is diagnostic (5)
↓	
Treatment	
Glucocorticoids	Dexamethasone 0.125-0.25mg, or prednisolone 2.5-5mg daily, titrated to normotension.
Mineralocorticoid receptor antagonists	Eplerenone and spironolactone are effective treatment choices.
Sodium epithelial channel antagonists	Amiloride and triamterene have also been used successfully.
Non-directed anti-hypertensives	β-blockers and ACE-inhibitors are less likely to be efficacious in the setting of a suppressed renin-angiotensin system (9). Dihydropyridine calcium channel blockers can be useful adjunctive treatments to the above diuretic agents.

17 year old girl with BP 170/110

Family history of difficult hypertension

Na 140 K 6.1 creatinine 70 Cl’ 114

pH 7.3 HCO3’ 14 PCO2 32

Renin 2mU/l (low) Aldosterone 175ug/l (low)

What is the diagnosis?

Gordon's Syndrome (Pseudohypoaldosteronsim type 2)

Familial hypertension/ Autosomal Dominant

Hyperkalaemia + metabolic acidosis (*one of the few causes of persistent hyperkalaemia with completely normal renal function*)

Normal (low) aldosterone levels

Responsive to NaCl restriction

Responsive to diuretics – especially thiazides

Possible mechanisms:

- Too much NaCl absorption by DCT
- Too much Cl^- absorption by collecting duct/ shunting voltage with less K secretion
- Impaired collecting duct apical K channel – less K secretion causes more NaCl absorption

(Mutant WNK proteins are though to be involved + could underlie any of these mechanisms)

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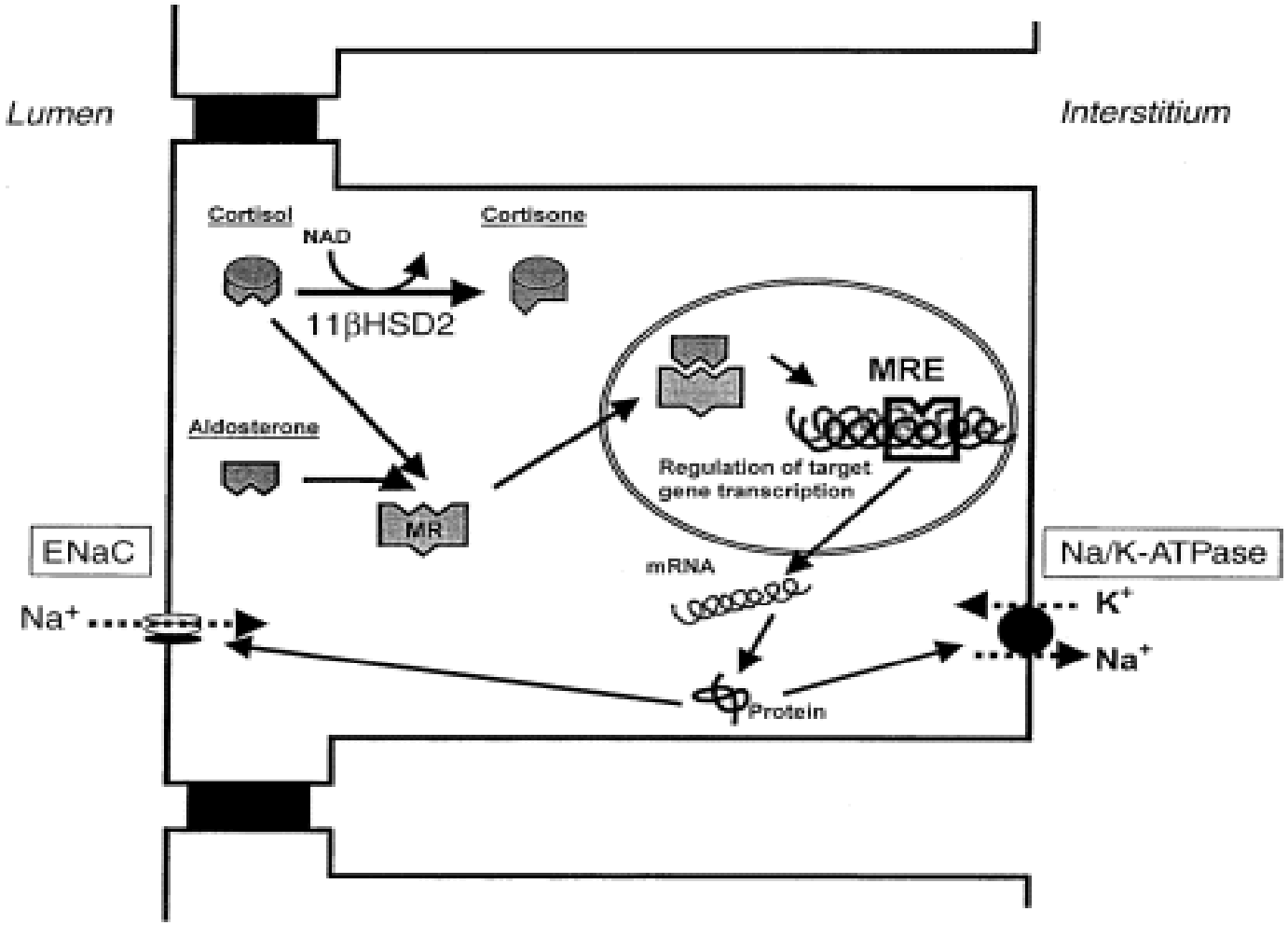
What is the diagnosis?

Apparent Mineralocorticoid Excess (Hereditary)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Aldosterone
MR
MRE
Regulation of target gene transcription
mRNA
ENaC
Na/K-ATPase
Na+
K+
Na+
Protein

Apparent Mineralocorticoid Excess – Hereditary

- Prevalence < 1%
- Mechanism: Autosomal dominant inheritance of inactivating mutation in 11beta hydroxysteroid dehydrogenase 2
- Presentation
  - Severe salt-dependent hypertension with hypokalaemia, low plasma renin and aldo, usually in childhood, can present in adulthood
- Diagnosis: Increase ratio of urinary tetrahydrocortisol (THF + 5 alpha THF) to tetrahydrocortisone (THE): ranga 6-50 (N = 1)
- Treatment High dose MR antagonists

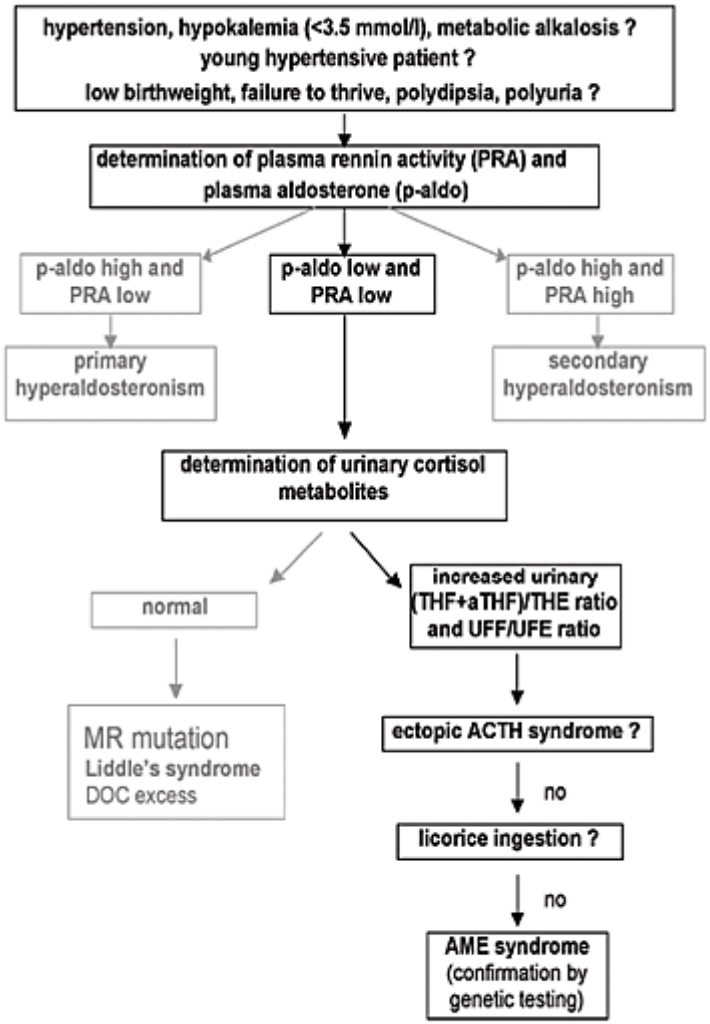
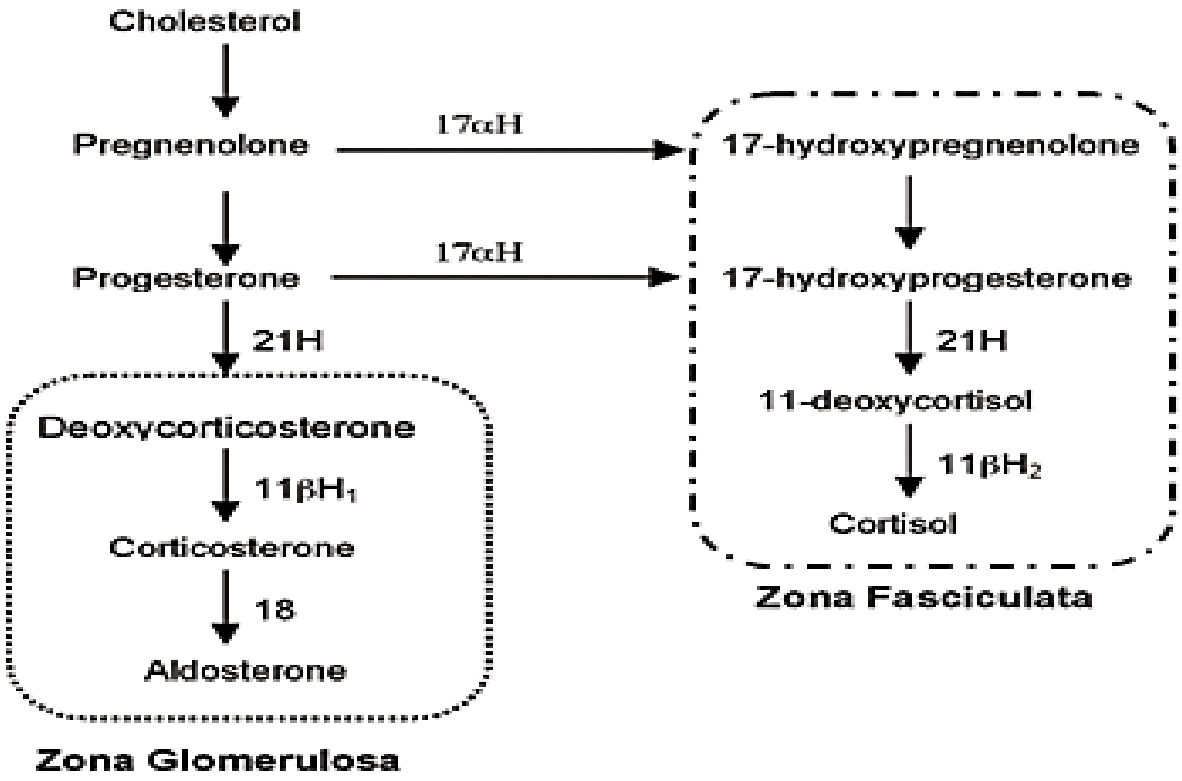


Figure 6. Flowsheet with guidelines for detecting Apparent Mineralocorticoid Excess (AME) syndrome. THF= tetrahydrocortisol; aTHF= allo-tetrahydrocortisol; THE= tetrahydrocortisone; UFF= urinary free cortisol; UFE= urinary free cortisone.

5 year old boy with precocious puberty hypertension and hypokalaemia

What is the likely diagnosis?

Congenital Adrenal Hyperplasia



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Rare Causes of Hypertension – Acquired

- Apparent Minerallocorticoid Excess
- Reninoma

62 year old woman with D2M for 12 years and hypertension for 10 years

Office BP 180/110

Today: Na 144 K 2.6 Bicarb 35 Cl 95

6 months ago: Na 138 K 4.5 Bicarb 26 Cl 101

Meds Valsartan, Frusemide, Verapamil, Vitamin E, Vitamin C, Ibuprofen, Herbal preparation

20 year old woman with BP 170/110 on routine check. BMI 23

Na 142mmol/l K 3.0mmol/l urea 5mmol/l creatinine 66umol/l
Plasma metanephrines normal
24-hour urinary free cortisol normal
renin 350miu/l, aldosterone 800pmol/l

Duplex ultrasound – no evidence or renal artery stenosis

What to do next?

62 year old woman with D2M for 12 years and hypertension for 10 years

Office BP 180/110

Today: Na 144 K 2.6 Bicarb 35 Cl 95

6 months ago: Na 138 K 4.5 Bicarb 26 Cl 101

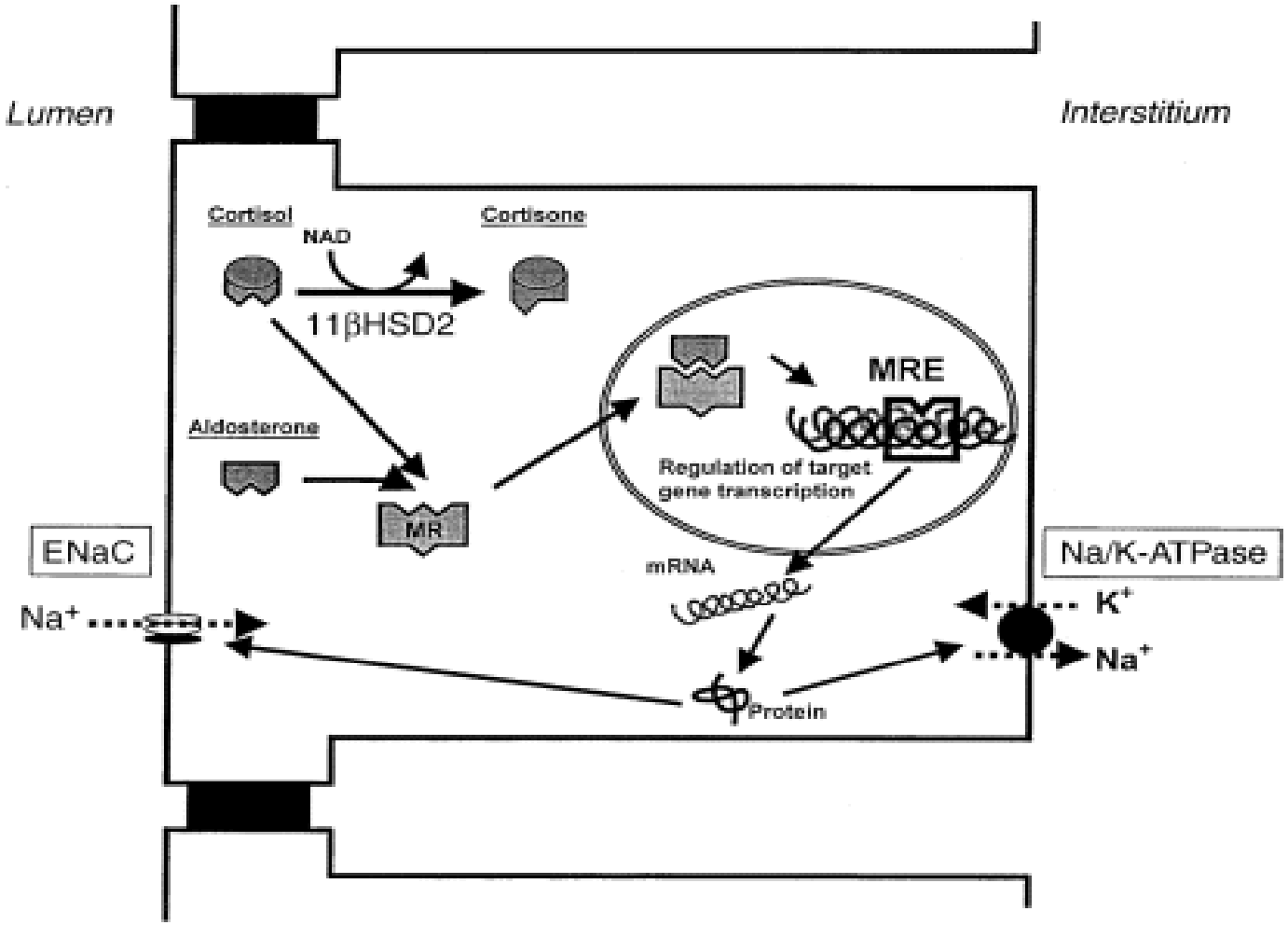
Meds Valsartan, Frusemide, Verapamil, Vitamin E, Vitamin C, Ibuprofen, Herbal preparation

Apparent Mineralocorticoid Excess – acquired

Glycyrrhizic Acid (Licorice)

- Blocks 11BHSD 2
- Increases access of cortisol to minerallocorticoid receptor causing sodiun retention + potassium loss

Glycyrrhizic Acid (50x sweeter than sugar) present in many herbal preparations to improve palatability, candies, medications, chewing tobaccos, teas, and present in 2/3 of Chinese herbal formulas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Plasma metanephrines normal
24-hour urinary free cortisol normal
renin 350miu/l, aldosterone 800pmol/l

Duplex ultrasound – no evidence or renal artery stenosis

What to do next?

CT shows a 2cm solid renal mass in subcapsular location, lower pole of right kidney

What is the likely diagnosis?

How to proceed?

Bilateral renal vein sampling shows lateralisation of renin secretion in a ratio of 6:1 for the right kidney

CT-guided biopsy showed a renal tumour composed of uniform polygonal cells with little nuclear polymorphism or mitotic activity. Renin production confirmed by immunofluoresence antibody testing.

At surgery encapsulated tumour identified and excised

Subsequently BP normal on no treatment

Reninoma

Rare
Tumour of JG apparatus producing renin autonomously
Hypotension and hypokalaemia
50% present before age 20
High renin and aldosterone
Imaging – often see a small renal mass in subcapsular location
Tumours occasionally extrarenal (eg in pelvis)

Treatment – partial nephrectomy usually curative

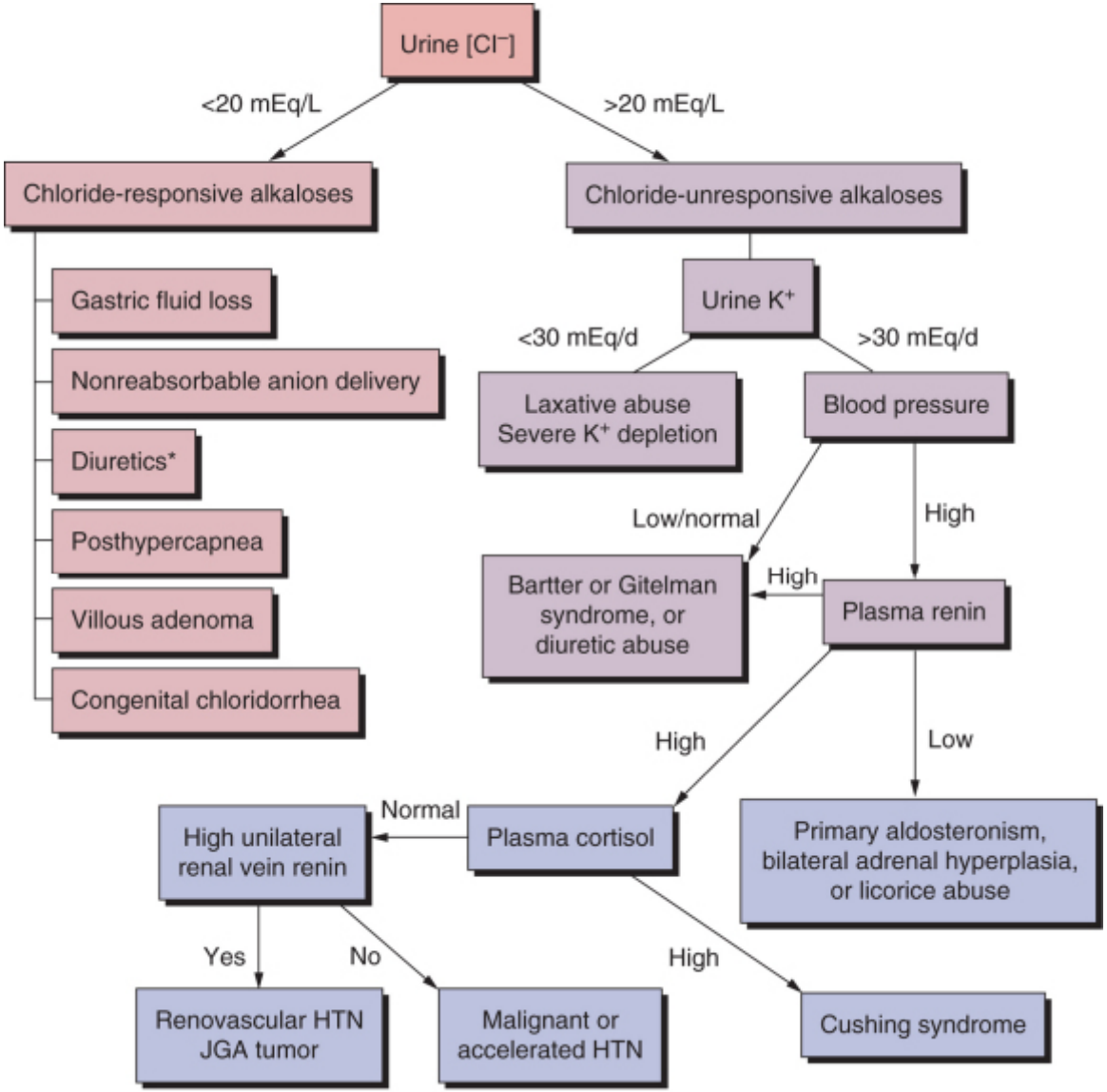
Hypertension and hypokalaemia

↓

Measure renin and aldosterone

↓

↑ renin + aldo	N or ↓ renin + ↑aldo	↓ renin + ↓aldo
↓	↓	↓
Malignant hypertension	Primary aldosteronism	Apparent mineralocortocoid excess – genetic (11BHSD2 mutation) – acquired (glycerrhetinic acid)
Renovascular	Idiopathic aldosteronism	
Diuretics	Glucorticoid remediable hyperaldosteronism	Cushing's Syndrome
Coarctation		DOC Excess
Renin-secreting tumour	Congenital adrenal hyperplasia	Liddle's Syndrome
Renal infarct		Activating MR Mutation
Vasculitis		


Urine [Cl⁻]
<20 mEq/L
>20 mEq/L
Chloride-responsive alkaloses
Chloride-unresponsive alkaloses
Gastric fluid loss
Nonreabsorbable anion delivery
Diuretics*
Posthypercapnea
Villous adenoma
Congenital chloridorrhea
Urine K⁺
<30 mEq/d
>30 mEq/d
Laxative abuse
Severe K⁺ depletion
Blood pressure
Low/normal
High
Bartter or Gitelman syndrome, or diuretic abuse
High
Plasma renin
High
Low
Normal
High unilateral renal vein renin
Plasma cortisol
Primary aldosteronism, bilateral adrenal hyperplasia, or licorice abuse
Yes
No
High
Renovascular HTN
JGA tumor
Malignant or accelerated HTN
Cushing syndrome
* After diuretic therapy