Biochemistry

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Note: memorize the important bits

1. Biochemistry in Practice

2. Calcium and Phosphate

- Body Calcium:
  - 99% bone
  - 1% (Total [Calcium]): Free [Ca2+] (50%), Complexed (10%), Bound (40%)
- Measurement: Total Ca (2.15-2.60 mmol/l)
  - Albumin can affect [Calcium] but not [Ca2+]: ↑ [albumin] → ↑ [Calcium] cos bound
  - ↓ pH → loss of ability to bind Ca → ↑ [Ca2+]
  - Corrected calcium means takes account of albumin levels = 0.02(40-albumin)

Homeostasis

PTH

- Parathyroid chief cells
- ↑ if: ↓ [Ca2+],
- ↓ if: ↓ Mg, ↑ Vit D
- Net ↑ Ca, ↓ PO4:
  - Bone: ↑ Ca, ↑ PO4. by stimulating osteoclasts. Requires vit D
  - Kidney: ↑ Ca, ↓ PO4. ↑ reabsorption of Ca. ↓ reabsorption of PO4. 1 alpha hydroxylation of vit D

Vitamin D

- 25 alpha hydroxylation in liver
- 1 alpha hydroxylase stimulated by: ↓ PO4, ↑ PTH,
- Net ↑ Ca, ↑ PO4:
  - Gut: ↑ absorption Ca and PO4
  - Bone: ↓ Ca, ↓ PO4. by ↑ mineralisation bone
  - Kidney: ↑ Ca, ↑ PO4. ↑ reabsorption Ca and PO4

Calcitonin

- ↑ if ↑ [Ca2+]
- Net: ↓ Ca, ↓ PO4
- Use: tumour marker, hypercalcaemia

Hypercalcaemia

- Worse than hypocalcaemia
- Px: Bones (pain), Stones (Urinary calculi cos calcium oxalate), psychic moans (confusion, depression), abdominal groans (pain due to peptic ulcer/constipation/N+V)
  1. Renal: Polyuria, calculi
  2. CVS: ↓ HR, block
- Causes:
  1. Artefact: dehydration
  2. ↑ Bone resorption: 90% {primary hyperparathyroidism, malignancy (bony mets activate osteoclasts)}, thyrotoxicosis, immobilisation
     - Primary hyperparathyroidism: commonest cause of hypercalcaemia. Men > women. Ix: Serum Ca, ↑ PTH. 24 urine.

        - Malignancy: i. Humeral hypercalcaemia of malignancy (bone resorptive factors eg TNF) ii. metastatic hypercalcaemia
    3. ↑ Intake/absorption: ↑ Vit D, sarcoidosis (produces 1 alpha hydroxylase)
    4. ↑ Renal reabsorption: thiazide diuretics, familial
    - Rx:
        - ↑ Circulating vol ċ 0.9% saline
        - Loop diuretics: promote Ca loss
        - Bisphosphonates: Mainstay. Inhibit bone resorption.
        - Also: Steroids (↑ renal excretion), oral phosphonates

Hypocalcaemia

- Px: Neuro {lethargy, depression, psychosis, tetany, paraesthesiae}, CVS {arrhythmia}, Soft tissue {cataracts, brittle nails/hair}
- Si: Chvosteks {tapping facial N causes facial twitching}, Trousteau's {inflating sphyg causes hand spasm}
- Causes:
    1. Artefact: ↓ albumin
    2. ↓ Intake/absorption: ↓ Vit D
        - Vit D deficiency: commonest cause hypocalcaemia. Rx: Diet. Oral vit D. IV calcium gluconate.
            - ↓ Intake/absorption: Malnutrition/malabsorption, ↓ sunlight
            - Impaired vit D metabolism: renal, anticonvulsants
    3. ↓ Flux from bone:PTH deficiency/resistance. Rx ċ antiresorptives
        - Hypoparathyroidism:
            - PTH deficiency: surgical, congenital (Di George)
            - PTH resistance: ↓ Mg, pseudohypoparathyroidism
    4. ↑ Flux to bone: post parathyroidectomy and removal of chronic stimulus (“hungry bone syndrome”)
    5. Extraskeletal: acute pancreatitis (loss of albumin to ecf, pancreatic enzymes to abd cavity)

3.The Lab in Diagnosis and Management of DM

Classification

- Type I DM:
    - Autoimmune beta cell destruction. Absolute insulin deficiency. DKA prone (MEM: Ketone bodies in type one)
    - Most before 20y. C peptide -ve (cos ↓ insulin).
- Type II DM:
    - Insulin resistance or relative deficiency. 90% of DM.
    - Rfs: age, obesity, ↑ BP, dyslipidaermia
    - Px: HONK. Rx: Diet, drugs, insulin
- Others/secondary: pancreatic, endocrinopathies, gestational

Diagnosis

- Blood tests: NB whole blood (finger prick) < plasma
- HBA1C not good cos ↑ interindividual variation
- oGTT (gold std): 75mg glucose given after overnight fast. Samples @ 0m, 120m.
- If no hyperglycaemic sx requires 2nd day confirmation. Should not be based on samples taken during stress.
- Results:
    - Random plasma glucose >= 11.1 mmol/l
    - Fasting plasma glucose >= 70 mmol/l
    - 2h plasma glucose >= 11.1 during OGTT

HBA1C and Self monitoring

- (+): Helps assess hypoglycaemic sx, allows Rx regime to be adapted alters behaviour if pt sees ↑ glu etc
- (-): Wash hands and calibrate meter
- HBA1C:
    - Glycated Hbg. Cannot be inhibited or upregulated → good marker
    - Expressed as % of total Hbg
    - Over last 2-3m
    - Knowledge of HBA1C changes behaviour
- Other glycated Hbgs exist: fructosamine: last 3w. Useful in preg/children

Diabetic Complications

- Renal: plasma creatine (50-150 micromol/l), urine “microalbumin” (should be < 30 microg in resting overnight sample)

- Lipids: TGs, cholesterol
- Thyroid function tests

Nephropathy

- 1/3 will develop ESRF
- All annually screened. If +ve → exclude infx (MSU), pyrexia, hrt failure
- Microalbuminuria (amount, not size!).
  - RF for nephropathy, hrt failure, mortality
  - Reversible
  - Ix: Semi-quantitative and quantitative assays

DKA

- Pathophysiology: (often) illness → ↓ insulin and ↑ counter reg hormones→
  - Carbs {↑ glycogenolysis, ↑ gluconeogenesis, ↓ tissue uptake} → hyperglycaemia → ↑ osmolarity ↑ → glycosuria → osmotic diuresis {loss of Na, H2O, K} → hypovolaemia → dehydration/thirst
  - ↑ Proteolysis → ↑ urea
  - ↑ Lipolysis and ketogenesis →sev acidosis {hyperventilation = kussmaul breathing} and acetone on breath, vomiting
- Ix:
  - Blood: ↑ glucose, ↑ K (but ↓ total body K), U+E{↑ urea, ↓ Na (diuresis)}, ↑ ketones, ABG {↓ HCO3, ↓ pH, ↓ pCO2 (met acidosis)}
  - Urine: glycosuria, ketonuria, osmotic diuresis
  - FBC, Blood culture (initial insult?), CXr, ECG {arrhythmias}
- Rx:
  - Insulin, saline (replace fluid), IV K, (HCO3- unnecessary), heparin sliding scale
  - Monitor: Blood glucose, ABG, U+E/creat esp K

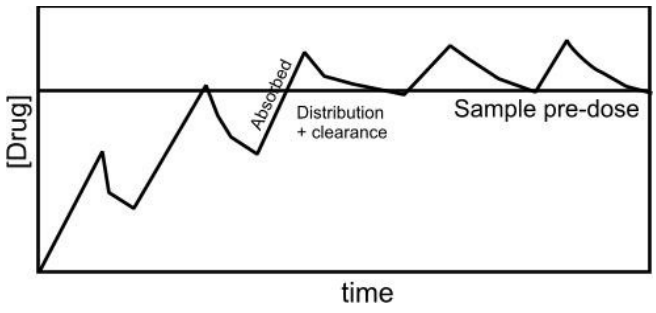
HONK

- Enormous diuresis due to osmosis → ↑ thrombosis risk → 50% mortality. Rx: Similar

4. Drugs and Poisoning

Therapeutic Drug Monitoring

- Useful when:
  - drug does not correlate ċ clinical effect (pharmacokinetic variability)
  - [plasma] does not correlate ċ clinical effect (pharmacokinetic variability)
  - clinical effect difficult to measure:
- When to measure drug concentrations:
  - Routine: specific drugs (eg Li, Warfarin), variable pharmacokinetics (old/ill/interactions)
  - Lack of efficacy: eg anticonvulsants (phenytoin, carbamazepine), theophylline
  - Sx of toxicity: eg anticonvulsants, Digoxin (arrhythmia), aminoglycosides, gentamicin
- Dose and timing of sample: Measure @ steady state (usually after 6 half lives). Generally sample pre-dose (trough) except when peak level important



- Steady state: where amount cleared = amount taken in. (NB Loading doses can be used to get to steady state quicker)

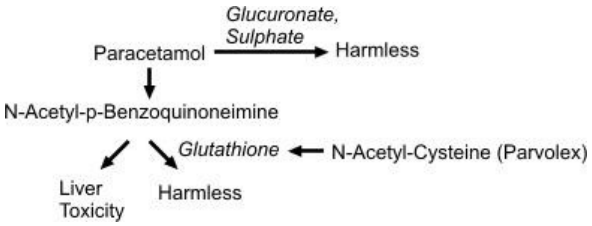
Drugs of Abuse Screening

- Use: i. Clinical suspicion: psychiatric disturbance, acute poisoning ii.Employment screening:
- Samples: urine (still there after left blood, easily available), other
- Screen for: opiates, methadone, cocaine, amphetamines, benzo's
- Problems:
  - False (+): Substitutions (eg methadone), additions. Occurs ċ opiates (from codeine), amphetamines (deriv cold cures)

    - False (-): Substitutions, dilution
- The measurement of metabolites can help discriminate

Acute Poisoning

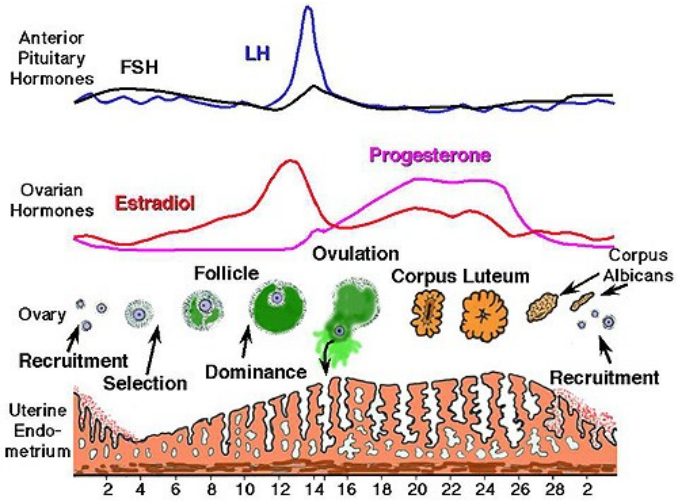
- Source: environmental, household, pharmaceutical. Accidental vs deliberate
- Route: Inhalational (eg mercury), ingestion (eg household), absorption (eg organoposphates)
- Hx: Exposures, claims, previous o/d, psychiatric
- Ix:
    - Unexplained met acidosisis {paracetamol, salicylate, methanol}, renal/liver failure
    - Specific drug assays (may need antidote or ↑ elimination)
- Rx:
    - ABC
    - C = Collect blood + urine
    - E = Examine Pupils {big eg TCAs, small eg opiates}, GCS, needle marks, hrt
    - All need supportive care
    - Techniques to ↓ absorption:
        - ↓ Absorption: i. Gastric lavage (ineffective except Fe and Li) ii. Activated (↑ SA) charcoal
        - ↑ Elimination: i. Repeat dose charcoal ii. Dialysis
    - Specific antidotes: Paracetamol (n-acetyl cysteine), lead (calcium edetate), benzo's (flumazenil), iron (desferrioxamine), opiates (naloxone), digoxin (monoclonal ab's), methanol (ethanol)



5. Enzymes and Biomarkers

6. Fertility and Pregnancy

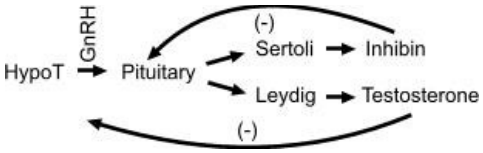
Subfertility in Women



- Causes:
    - Not enough time (85% conceive @ 12m)
    - Egg (25%), Tube (14%), Sperm (24%)
    - Other inc endometriosis, coital failure, mucal defects
- Assessment:
    - Assess ovulation: Progesterone @ 21d, need to repeat as may be normal
    - Exclude uterine abn's/pregnancy
    - Assess ovarian failure
        - Primary: ↓ E2 → ↑ LH/FSH. Causes: premature ovarian failure, post-menopausal. Others inc autoimmune, iatrogenic, dysgenesis (Turners)
        - Secondary: ↓ LH/FSH → ↓ E2. Causes LHRH deficiency (often Kallmans = congenital), pit tumours (prolactinoma), secondary hypopituitarism (eg iatrogenic), functional (↓ wt, exercise), systemic (↑ thyroid)

- PCOS: Px: Obese, insulin resistant, hirsute, oestrogenisation. Ix: ↑ LH:FSH ratio, USS {cysts around ovary} Rx: Clomiphene/metformin

Subfertility in Men



- Assessment
  - Semen analysis (if normal virtually excludes man)
  - LH/FSH, prolactin, testosterone
    - Testicular: Hypergonadotrophic hypogonadism (gonadal failure) {↓ T, ↑ LH/FSH, biopsy}, isolated germinal compartment failure {Normal T/LH, ↑ FSH}, non-endocrine {eg obstructive}
    - Hypothalamic/pituitary: Hypogonadotrophic hypogonadism: ↓ T/FSH/LHG

Lab aspects of Pregnancy

Effect on Ix

- Chemical: ↑ alk phos/hormone binding proteins. ↓ albumin/creatine/urea
- Physiological: ↑ plasma vol/CO/GFR (early. ↓ fasting glu (early preg)
- Endocrine: ↑ E2/P (wall)/prolactin (breasts)/hCG (placenta). ↓ FSH/LH (not needed)

Gestational DM

Pregnancy induced Hypertension

- Ix: Early {↑ BP, ↑ urate,}, Late { ↓ GFR, proteinuria, ↑ urea/creatine, HELLP (haemolysis, elevated liver proteins, low platelets)}

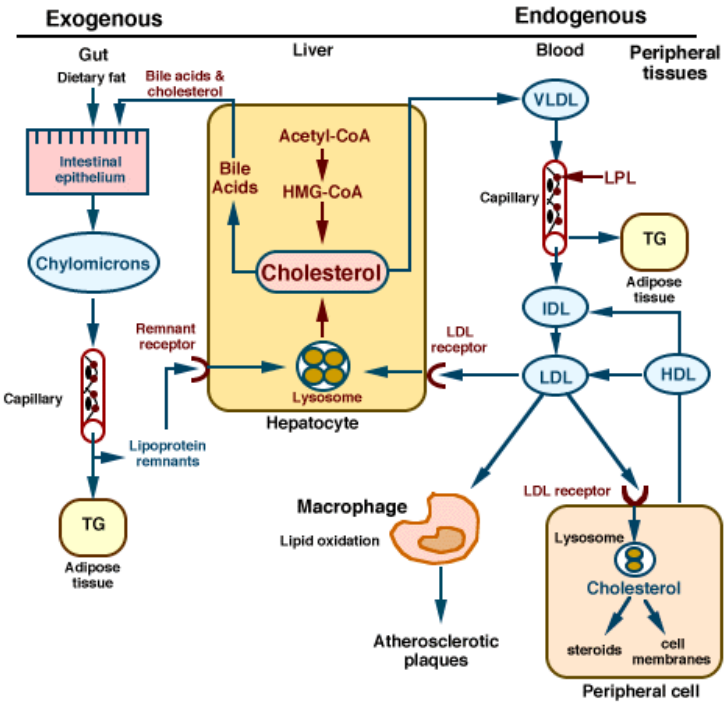
Obstetric Cholestasis

- Px: Pruritis. Ix: ↑ Bile acids/ALT/AST. Rx: Deliver

Antenatal Screening

- Neural tube defects: ↑ AFP (MEM: leaks out of tube into womb). Ix: USS
- Trisomy 21: ↓ AFP, ↑ hCG, ↑ Inhibin. Ix: Nuchal translucency

7.Hyperlipidaemia



- ↑ VLDL when ↑ liver triglyceride synthesis (eg post big meals)
- LDL rec is ApoB100. Liver is <u>regulated</u> uptake, extrahepatic is <u>unregulated</u>. Broken down extrahepatically by lipoprotein lipase.
- HDL hoovers excess lipids/cholesterol

Hyperlipidaemia

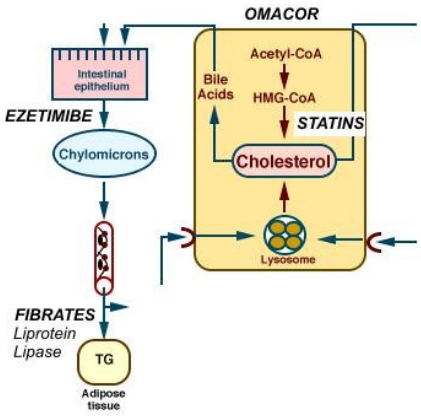
Primary (genetic)

- Type I Hyperlipidaemia
  - Rare. Lipoprotein lipase deficiency → hyperchylomicronaemia
  - Px: Lipaemia retinalis, eruptive xanthomata, pancreatitis
  - Rx: Diet. Fibrates.
- Type III Hyperlipidaemia
  - Apo E2:E2 genotype, needs eg alcohol for expression. ↑ IDL (ch and TGs)
  - Rx: Diet. Fibrates. Statins
- Familial Hypercholeserolaemia
  - LDL rec defect → ineffective hepatic clearance of LDL
  - Px: Tendon xanthomata (pathognomic), corneal arcus, premature CHD
  - Rx: Family screening. Diet. Statins. Ezetimibe.
- Familial Combined Hyperlipidaemia
  - Moderate ↑ Ch/TGs
  - Px: Xanthomata, lipaemia retinalis (milky white line in retinal vessels due to chylomicrons), premature CHD
  - Rx: often resistant

Secondary

- Common: DM, liver disease (removes fat), renal (↑ albumin synthesis causes ↑ ch), hypothyroidism
  - Diabetic: metabolic syndrome {I resistance, central adiposity, ↑ TGs, ↓ HDL, LDL, ↑ BP}, pathology?
- Also: HIV, anorexia, alcohol, drugs (thiazide, BBs, steroids)

Drugs



- Statins {HMGCoA reductase inhibitors}: benefits independent of age and initial ch level. For everyone ċ vascular disease or ↑ CHD risk
- Fibrates: for ↑ TGs or mixed
- Ezetimibe {Ch absorption inhibitor}
- Omacor (Fish oils) {FFA → x TGs in liver}
- Nicotinic acid {niaspan}: For ↑ ch

- Consider primary prevention {genetic/RFs} and secondary

8. Adult Hypoglycaemia

- Pathophys: Imbalance btw factors raising and lowering blood glu. ↑ Food, counter Hs. ↓ insulin/oral meds, exercise
- Definition
  - Venous plasma glu < 2.5 mmol/l (but threshold varies btw ppl, many normal ppl below this)
  - Whipple's triad: i sx hypo ii. ċ ↓ glu iii. sx relieved by administration glu
- Sx:
  - Often non-specific. Depend on degree, rate, age (counter Hs), muscles
  - SNS {immediate}: tremor, palpations, sweating, hunger, anxiety, nausea
  - Neuroglycopenic {more gradual drop}: confusion behaviour changes, tired/headache, seizures/neuro, coma

Hypoglycaemia and DM

- Causes: missing/delaying meal, inadequate carb intake, ↑ ↑ insulin/OHA, ↑ exercise, ↑ alcohol, vomiting
- If @ night often slept through ċ rebound hyper in morning. Px: morning headaches, nocturnal sweating.

- Rx: monitor closely. Ensure sufficient CHO. if sev (eg unconscious): glucagon

Classification

MEM: here's how to EXPLAIN a hypo:

1. E = Exogenous drugs : insulin/OHA, alcohol, quinines. Ix: ↑ C-Peptide (exogenous except sulphonylurea)
2. P = Pituitary insufficiency: no GH or cortisol
3. P = Post-postprandial
    - Post gastrectomy there is rapid transit of glu to SI and release of Hs that stimulate ↑ ↑ insulin
4. L = Liver failure: no glycogen stores
5. A = Adrenal: no cortisol
6. I = Insulinoma
    - Most 20-60y, solitary, benign
    - Px: diplopia, blurring, sweating, palpitations, weakness, confusion
    - Ix: Measure {glu, insulin, C-peptide} @ sx and fasting.
7. N = non-islet cell tumour eg mesothelioma. Some produce ↑ IGF-2 {→ acts @ insulin rec and inhibits counter Hs}

9. Pituitary and Adrenal

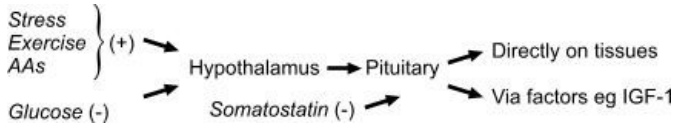
Hypothalamic Pituitary Axis

- Releasing factors: CRF → ACTH, Thyrotropin Releasing Factor → TSH, LHRH/GnRH → LH/FSH, GHRH → GH
- Releasing Inhibiting Factors: Somatostatin →x GH, Dopamine →x Prolactin

Ant Pituitary Disorders

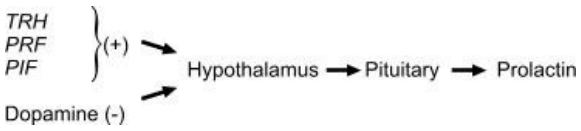
1. Pituitary Tumours:
    - Usually benign/slow growing. Functional/non-functional
    - Px: Local {visual field, headaches...}, endocrine
2. Hyperfunction:
    - Secondary is due to ↓ negative feedback. If LH, TSH, FSH likely to be secondary
    - Usually single H
3. Hypofunction
    - Usually generalised (pan)
    - Occasionally isolated (GH, LH/FSH, ACTH)
    - Causes: tumours, infarction (Sheehans), iatrogenic, meningitis
- Ix:
    - Basal H measurements: Pituitary, target. But can overlap ċ normal.
    - Stimulation testing: ACTH {hypoglycaemia, CRF}, TSH {TRH}, LH/FSH {LHRH}, GH {hypoglycaemia}
    - Suppression testing: ACTH {dexamethasone}, GH {glucose}

Growth Hormone



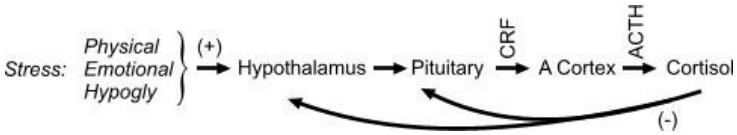
- Effects:
    - Normal body growth
    - Protein synthesis: muscle, cartilage, viscera
    - Carb: insulin antagonism
    - Lipid: lipolysis
    - Ca absorption
- Excess:
    - Prepubertal = giant. Postpubertal = acromegaly {Px: generalised= coarsening (look at old photos), sleep apnoea (obstructive). Also: ↑ BP (↑ reabsorption H2O and cardiomegaly), diabetes, calcium stones}
- Deficiency:
    - Px: short stature in children
    - Causes: lesions (tumour, iatrogenic), functional {psychosocial, endocrine, Laron Dwarfism (↓ IGF)
- Ix:
    - Basal GH, IGF-1 (non-pulsatile)
    - Stimulation: Insulin is gold std (clonidine in children) (make hypoglycaemic and want ↑ GH)

Prolactin



- Hyperprolactinoma
  - Physiological: pregnancy, stress, drugs {dopamine rec antagonist (phenothiazines), dopamine depleting (methyldopa, oestrogen), macroprolactin (means no activity)
  - Pathological: Prolactin secreting pit adenoma {micro=small. macro=big}, lesions to hypo/pit stalk, primary hypothyroidism (↑ TRH), chronic renal failure
  - Ix: < 700 normal. > 6000 = macroprolactinoma

Adrenal



- Hormones: Medulla: catecholamines. Cortex: aldosterone, cortisol, androgens
- Synthesis: complicated. All steroids come from cholesterol.
- Cortisolism
  - Most important H.
  - 90% protein bound (inactive). Free is active
  - Effects:
    - Carb: insulin antagonist, gluconeogenesis. Net ↑ glucose
    - Protein catabolism
    - Immunosuppression
    - Permissive for catecholamines, water clearance
  - ↓ in night ↑ in morning

Hypo-cortisolism

- Causes:
  1. Primary (↑ ACTH): selective destruction {ab's}, total/Addisons {TB/bact/fungus/mets}, enzyme {congenital adrenal hyperplasia}
     - CAH
       - 21 hydroxylase deficiency (needed to make aldosterone and steroids). But can still make testosterone/oestrogen → ↑
       - Px: Girls {semi-formed male genitalia}. Boys {big/strong, salt losing crises}. Adults: hirsuitism/menstrual abn's
       - Ix: blood {17-alpha-hydroxyprogestorone (precursor), ↑ K/ ↓ Na, ↑ glu, ↑ androstenedione, ↑ T, renin}, urine {electrolytes, steroid profile}, karyotype
  2. Secondary (↓ ACTH): adrenal insufficiency: due to ↓ pit
- Px: Lethargy/anorexia, pigmented gums (MSH), dehydration, N+V
- Ix:
  - Na (↓ aldosterone), ↑ K (in exchange), ↓ BP and ↑ urea (↓ vol: ↓ ADH, loss of H2O to correct ↓ Na → eventually ↑ ADH when vol depleted)
  - ACTH: differentiates primary from secondary
  - Serum cortisol: but may be in normal range
  - Short synacthen (synthetic ACTH) test: 250 microg im. Should rise > 500 nmol/l @ 30m
  - Long synacthen: depot. Addison's failure to reach 600 nmol/l @ 8h. Atrophy: delayed/stepwise increase

Hypercortisolism

- Causes:
  - ↑ ACTH: Pituitary (Cushings disease) , ectopic (most often lung)
  - ↓ ACTH: Adrenal adenoma/carcinoma (Cushings syndrome), iatrogenic
  - Pseudo-Cushings (appearance): alcohol, obese, depression
- Px: Mental disturbance, truncal obesity, protein catabolism {osteoporosis, easy bruising}, hyperandrogenism {hirsute, acne, amenorrhoea}, insulin resistance, Na retention (↑ BP)
- Ix:
  - Serum cortisol (midnight). Urine free cortisol {but ↑ in illness, stress, obesity}
  - ACTH: see above
  - Overnight dexamethasone suppression of pituitary (if not suppressed then possibly adrenal/Cushings syndrome)
  - Yanovski: Dexamethasone then CRF (suppress pituitary, stimulate adrenal) →exaggerated response ċ Cushings

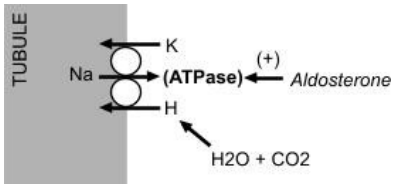
syndrome, ↓ ċ ectopics
    - BiL inf petrosal sampling {give CRF, if pit then measure ↑ ACTH cf blood}, pituitary imaging

10.Potassium

Metabolism

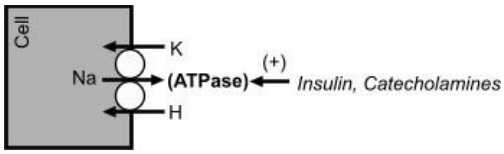
- Stored:
    - Intracellular: 98% (NB: so serum K+ says little about total body K. but when acid-base normal, hypoK usually depleted)
    - Extracellular: 2% → interstitial, plasma (0.5%)
- Flux
    - Intake: 30-100 mmol/d. Absorbed in PCT, excreted in DCT
    - Out-take: Urine, skin, faeces (can ↑↑ in disease)
- NB: don't put samples in fridge cos ATPase heat dependent → ↑ K outside cells

Distal Tubule



- When Na absorbed K or H excreted to keep balance. So need enough Na to excrete K
- ↑ Excretion: aldosterone, [K+}, ↓ [H+] (H+ steals transporter in acidosis)

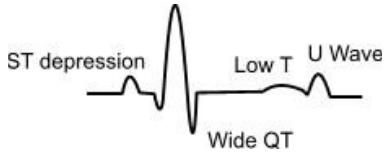
Any Cell



- Many H+ buffered inside cells. As ↑ H+ then K+ displaced to ecf

Hypokalaemia

1. Renal Loss
    (a) Alkalosis (but this usually secondary to K depletion)
    (b) Drugs: Thiazide/Loops
        i. Block Na reabsorption → more Na in DCT → favours K excretion
        ii. Hypovolaemia → aldosterone → K loss
    (c) Mineralocorticoid excess
        i. Primary hyperaldosteronism (Conn's), secondary hyperaldosteronism: ↓ K and ↑ Na
        ii. Cushings: acts on aldosterone rec (just usually broken down)
        iii. Ectopic ACTH: rapid so no cushingoid Px
    (d) Renal Disease
        i. Renal Tubular acidosis: cannot excrete H (obviously) so excrete K
        ii. Interstitial nephritis: block reabsorption K in PCT
        iii. Polyuric ATN: lose electrolytes
    (e) Miscellaneous:
        i. ↓ Mg: needed for ATPase
        ii. ↑ Ca: interfere ċ absorption
2. Extra-renal
    (a) GI (fluids rich in bicarb → acidosis)?: Diarrhoea, villous adenoma, pancreatic fistula
    (b) ECF to ICF shift: insulin, catecholamines
    (c) Inadequate intake: alcoholism, anorexia nervosa
- Px: Muscle weakness, paralytic ileus, exacerbation of hepatic encephalopathy, polyuria



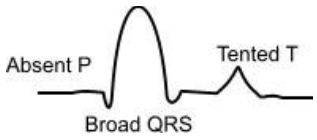
- ECG: Flat T waves, ST depression, U waves, wide QT

- Rx: Oral (unpleasant). IV (only if oral impossible)

Hyperkalaemia

1. Renal
   (a) Renal failure: Acute/end stage chronic
   (b) Drugs:
      i. K sparing diuretics: amiloride, spironolactone (inhibit aldosterone)
      ii. ACE Inh's: Block aldosterone
   (c) Mineralocorticoid deficiency
      i. Addisons
      ii. Hyporeninaemic hypoaldosteronism: diabetic nephropathy, ↓ renin
2. Extrarenal
   (a) Pseudohyperkalaemia: haemolysis, leukocytosis, thrombocytosis
   (b) ↑ K input:
      i. Exogenous
      ii. Endogenous: Tissue necrosis, haemolysis, malignancy, chemoRx
   (c) ICF to ECF shift: acidosis, hypoxia (↓ ATPase), insulin deficiency (DKA)

- Px: Risk of cardiac arrest
- ECG: Tall T waves, absent P waves, broad QRS, sine wave ECG, asystole



- Rx:
  - Calcium gluconate: protects myocardium
  - Insulin (+ glucose): K in to cell
  - Calcium resonium: ion exchange resin
  - Dialysis

11.Proteins: Measurement in diagnosis and monitoring

- Proteins in serum: albumin (most), globulin, immunoglobulins, lipoproteins, complement, fibrinogen, transferrin, haemoglobin
- Indications for protein/albumin analysis: liver synthetic ability, oedema, hydration, concentration of protein bound substance

Albumin

High

- Rare, usually not significant

Low

- Causes
  - ↓ Synthesis: liver dysfunction, malnutrition/malabsorption, immature (neonate)
  - ↑ Loss: nephrotic syndrome, subcutaneous (eg burns), intestinal (protein losing enteropathy)
  - Redistribution: recumbancy, ↑ capill permeability (inflammation)
  - ↑ Catabolism: illness
  - Dilution: iatrogenic, SIADH, pregnancy, artefact
- Consequence:
  - Oedema: ↓ oncotic P
  - ↓ transport of protein
  - More drugs in free form (↑ activity), eg warfarin, phenytoin
  - Changes in total (but not free) Ca
  - ↑ Bilirubin

Liver Disease

- Bilirubin: normally 95% unconjugated
- Hepatocellular damage: aminotransferases:
  - Alanine (ALT): liver specific
  - Aspartate (AST): chronic
- Cholestasis:
  - Alkaline phosphatase (ALP) and GGT
- ↓ Albumin synthesis. ↑ Ig (but non-specific)

Acute phase response

- ↑ in 24h ċ injury, inflammation, infx
- CRP (attracts macrophages, alpha-1-antitrypsin (protease inhibitor), haptoglobin (binds free Hbg), fibrinogen (clotting)
  - CRP: rapid ↑ and ↓. Assess: disease activity, response to Rx. Viral gives lower levels.
- Alpha-1-antitrypsin deficiency
  - Dominant. Formed in liver → protects lungs from damage from elastase
  - Deficiency: (Young) liver disease/hepatitis (abn accumulates), bronchiectasis/emphysema.

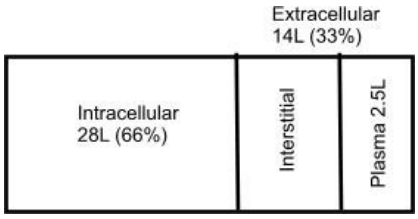
Hypergammaglobulinaemia

- Types:
  - Polyclonal: infx, chronic liver, autoimmune
  - Monoclonal: myeloma, leukaemia
  - Paraprotein
- Ix: Protein electrophoresis: expansion of 1 band ċ monoclonal, ċ lighter surrounding

Proteinuria

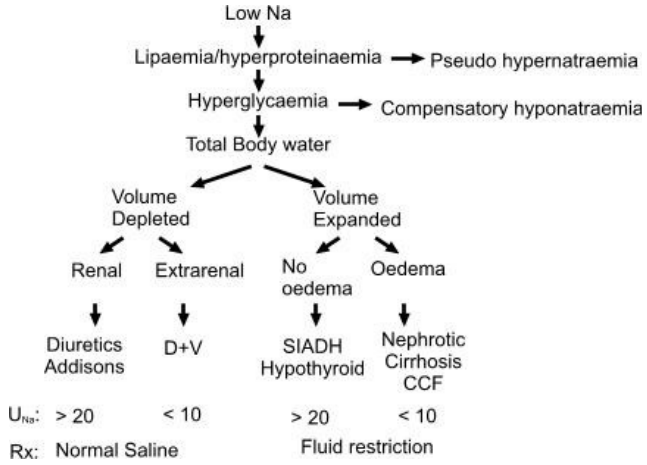
- Causes:
  - False (+) on dipstix: bact contamination, disinfectant, v concentrated sample
  - Extrarenal (usually transient): acute inflammation (↑ permeability) {trauma, surgery, MI}, exercise
  - Overflow (exceed reabsorption capacity). NB dipstix only measure albumin.
  - Glomerular: nephrotic
  - Tubular: impaired reabsorption
  - Post-renal: UTI, seminal fluid/pus/blood

12.Sodium and Water



- Water balance: Losses {skin, lungs, gut, kidneys)} = sources {oxidation, dietary} = 1500ml

Hyponatraemia



- Diuretics: ↑ Na excretion renally drives H2O loss
- Addisons: ↓ aldosterone
- SIADH:
  - Causes:
    (a) Neoplasia
    (b) Pulmonary (stretch rec's)
    (c) Neuro (eg meningitis, head injury) {affect hypothalamus}
  - Ix: hypertonic saline cos ADH not preserve Na
  - Rx: fluid restrict, underlying cause. Demeclocylin (ADH antagonist)

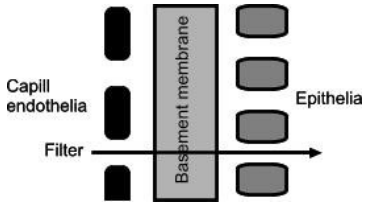
Hypernatraemia

1. Inadequate H2O intake: loss of thirst, inability drink
2. Impaired H2O retention: diabetes insipidus
   (a) Diabetes insipidus: excretion of severely diluted urine
      i. Cranial (↓ ADH production)
         A. Idiopathic: familial, sporadic
         B. Secondary: trauma, tumours, granuloma (eg sarcoid), infx, vascular, autoimmune
      ii. Nephrogenic (insensitivity)
         A. Idiopathic
         B. Secondary: drugs/toxins {Li, demeclocylin}, metabolic {↑ Ca, ↓ K, amyloid}, vascular, pyelonephritis, after ATN
3. Loss of hypotonic fluids: sweat, hyperventilation, watery diarrhoea, burns
4. Excessive Na intake: IV fluids, drugs (Esp IV abx)
5. ↑ Na retention: primary hyperaldosteronism

13.Renal Function

- Normal Functions:
  - Excretion: waste, acid-base, removal of drugs + toxins
  - Fluid/electrolyte balance
  - Endocrine: RAA system, erythropoetin, hydroxylation of vit D

Glomerulus

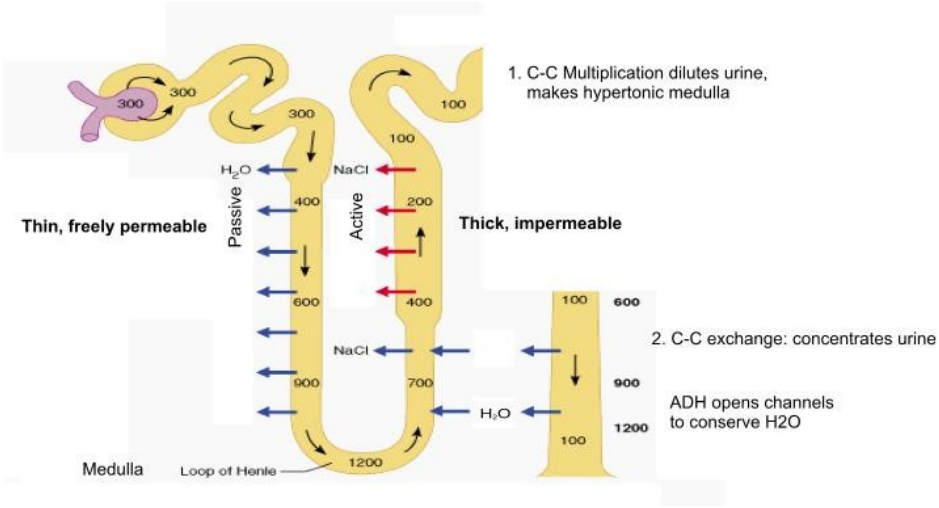


- Normal plasma vol: 3-4 l
- 200 l/24h filtered → 24 h urine = 1.5 l/day
- Permeability: ↓ ċ size {inulin ↑, albumin ↓}
- GFR depends on:
  - Intrinsic (kidney): no. functioning nephrons (infarction), glomerular function (eg fibrosis)
  - Extrinsic {↓ ċ shock, obstruction}: intracapillary P, tubular luminal P

Proximal Tubule

- Reabsorption:
  - 70% of Na, K, Ca, Cl
  - Cl drives isosmotic reabsorption H2O
  - 100% of HCO3, glucose, urate, AAs
- Na reabsorption causes electrostatic gradient: either H+ taken up or Cl excreted

Countercurrent System

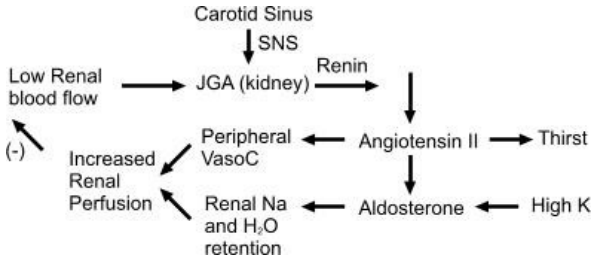


- NB: vasa recta: supply energy without disturbance of osmotic balance

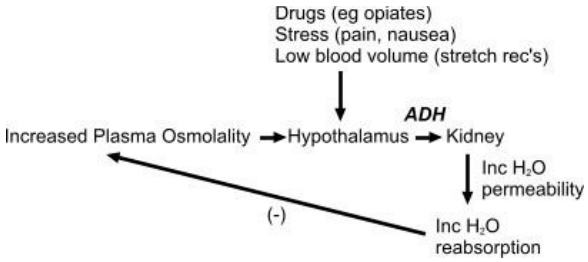
Distal Tubule

- Homoeostatic solute adjustment
  - Na-H-K exchanger → see K lecture
  - isosmotic H2O exchange: water follows Na

Renin Aldosterone System

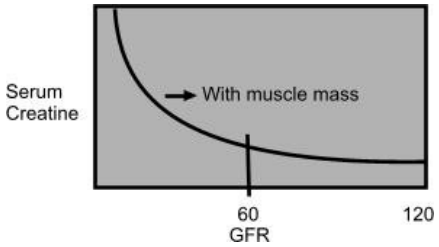


Anti-Diuretic Hormone



Glomerular function Tests

- IF production constant AND excretion entirely by glomerular then raised or rising indicate glomerular dysfunction
- Urea: ↑ catabolic states, GI haemorrhaged (absorption), protein load, dehydration. ↓ Not eating, low protein diet
- Creatine (muscle breakdown): depends on muscle mass



GFR

$$serum\,creatine \propto \frac{1}{GFR}$$

- Clearance of creatine can be directly measured
- Estimates are possible using age, weight, serum creatine. This is useful to create a std value to compare against for drug doses/measure early renal failure

14.Renal Failure

Acute Renal Failure

- Def: Sudden worsening of renal func over hours/days
- Causes:
  - Prerenal: Hypovolaemia (haemorrhage/sepsis), hrt failure
  - Post renal (obstruction): Stones, tumour, prostate
  - Renal: Ischaemia, glomeronephritis, nephrotoxins (drugs/poisons, myoglobin, paraprotein), hepatorenal syndrome (secondary to liver failure)
- Px: non-specific and late. Oliguria. Nitrogenous waste {N+V, confusion}
- Ix:
  - Retain nitrogenous waste products: ↑ u+c
  - Retain salt and water: fluid overload (→ hyponatraemia)
  - Retain acidic waste products of metabolism
  - Retain K

    - No endocrine problems in ARF
- Rx:
    - Correct fluid, electrolytes, acid-base (life threatening)
    - Restore renal perfusion → if cannot restore func then dialysis

Chronic Renal Failure

- Gradual irreversible decline in function
- Causes: DM, ↑ BP, polycystic kidneys, glomeronephritis, pyelonephritis, interstitial nephritis, drugs
- GFR can be decreased 50% before serum creatine rises, and further before clinical
- Assessment renal function:
    - Clearance of creatine
    - Estimated creatinine clearance
- Consequences:
    - Biochemistry changes: ↑ u+c, acidosis, ↑ K, Na/H2O retention(pul oedema, ↑ BP), ↑ phosphate, ↓ Ca
    - Endocrine changes: anaemia (erythropoetin), ↑ PTH (due to ↓ Vit D)
    - Lipids: ↑ Ch and TGs
    - Impaired immune function
    - Renal bone disease:
        - ↓ Ca → osteomalacia
        - ↓ GFR → metabolic acidosis → dissolve bone
        - ↓ GFR → ↑ Phosphate → metastatic calcification
        - ↑ PTH → bone resorption

Renal Tubular Disorders

- Glycosuria: When resorptive capacity exceeded: ↑ [glucose], ↑ GFR, tubular disorder (↓ capacity to reabsorb)
- Aminoacidurias: defect in aa transport
- Renal tubular acidosis
    - Type I (distal): failure to excrete H, excessive K loss. Rx: Bicarb and K
    - Type II (proximal): bicarb leak
    - Type IV: low renin low aldosterone: both H and K excreted

15.Thyroid Disease and Secondary Hypertension

Hypothyroidism

- Ix: ↑ TSH, ↓ T4 (T3 not that helpful)
- Px: lethargy, tiredness, wt gain, cold intolerance, coarsening of hair and skin, slow reflexes, hoarseness, constipation, menstrual abm's, ↓ HR
- Compensated hypothyroidism: ↑ TSH, ↓/normal T4 ± antithyroid peroxidase ab's
- Normal TSH does not exclude secondary hypothyroidism
- Rx: replacement (if TSH> 10). Review and increase if T4 still low.
    - If ↑ TSH and normal T4 → has pt recently taken more on background of not enough

Hyperthyroidism

- Ix: Undetectable TSH, ↑ TSH, ↑ T3 (MEM: Hyper=three)
- Px: weight loss, heat intolerance, palpitations, agitation/tremor, muscle weakness, diarrhoea, thyroid eye disease

Effects of on the thyroid

- Illness:
    - Pattern: ↓ TSH, ↓/normal T3/T4, ↑ reverse T3 (stress shunts T4 → T3)
    - (-) to TSH by: ↓ TRH, IL-1/TNF, somatostatin, glucocorticoids, dopamine
- Drugs: in general ↓ ċ anticonvulsants, BBs, Li, steroids, amiodarone

Hypertension

- Classification
    1. 98% essential
    2. Secondary: (MEM: AD CHAPS)
        (a) A = Adrenal
        (b) D = Drugs (OCP)
        (c) C = Cushings
        (d) H = Hyperaldosteronism
        (e) A = Aorta coarctation
        (f) P = Phaeochromocytoma

(g) S = Stenosis of renal artery

Hyperaldosteronism

- Causes
  - Aldosterone producing adenoma
  - Bilateral idiopathic hyperplasia
  - Aldosterone producing adrenocortical carcinoma
  - Familial hyperaldosteronism
- Ix Screening: ↑ BP ċ ↓ K, ↑ Na, resistant ↑ BP
- Ix:
  - Plasma renin: ↓ ċ primary, ↑ ċ secondary
  - Plasma aldosterone: morning blood sample → again after correcting K and off drugs
  - Aldosterone:renin ratio: ↑ Conn's (tumour of adrenal) → again off drugs
  - Localise tumour: venous catheterisation {aldosterone:cortisol ratio}, imaging

- Drugs and aldosterone: ↑ Diuretics/vasodilators, ↓ Ca Ch blockers, BBs, ACEIs, spironolactone (aldosterone antagonist)

Phaeochromocytoma

- Adrenal medulla tumour. Rare but potential for serious and curable. Most benign, sporadic.
- Ix Screen: paroxysmal persistent ↑ BP, headache, sweating, flushing, palpitations, pallor, tremor. May have symptomatic attacks
- Ix: 24h urine catecholamines proportional to overall production

16.Blood Gas Analysis

- Normal: pH {7.35-7.45}, pCO2 {35-45 mmHg}, HCO3 {23-29 mmol/l}, base excess {± 3 mmol/l}

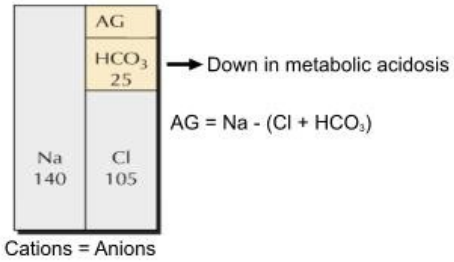
Acid Base Homeostasis

- Acids produced by body: HCl (stomach), lactic (muscles), uric, alpha-ketoacid, proteinuria
- Bases produced by body: Bicarbonate, proteins (ECF), Hbg (ICF), phosphate, ammonia

$$pH \propto \frac{HCO_3}{pCO_2}$$

- Principle 1: changes in PCO2 respiratory
- Principle 2: changes in HCO3 metabolic
- Compensation:
  - Change in pH causes body to compensate
  - If no metabolic compensation then acute process?
  - Primary disorders may be mixed
  - There is never overcompensation
- Analysis:
  - pH: acidaemic or alkalaemic?
  - pH explained by change in pCO2: respiratory?
  - pH explained by change in HCO3: metabolic?
  - Evidence of compensation
  - Calculate anion gap if metabolic acidosis

Anion gap



- Difference btw cations/anions (artefact not reality) used in differential of metabolic acidosis
- Interpretation:
  1. Normal anion gap: there has been compensatory hyperchloraemia
     (a) Diarrhoea (GI loss of HCO3)
     (b) Renal loss of HCO3
     (c) Renal dysfunction (hyperaldosteronism, renal tubular acidosis)

(d) Ingestion: ammonium chloride, total parental nutrition
(e) Alcohol

2. ↑ Anion gap
   (a) Endogenous acidosis
      i. Renal failure (no regeneration HCO3 and build up of acids)
      ii. Ketoacidosis: DM, starvation. alcoholic
      iii. Lactic acidosis: hypoxic (exercise, shock, post seizure)
   (b) Exogenous acidosis: aspirin, paracetamol, metformin, poisons (eg methanol)

Summaries:

1. Metabolic acidosis: (Above)
2. Metabolic alkalosis: H loss → vomiting, gastric aspiration, diuretics, ↓ K, hyperaldosteronism, ↑ alkali administration. Depresses respiration (↑ CO2)
3. Respiratory acidosisis:
   (a) Lung disease (eg fibrosis)
   (b) Mechanical (eg trauma)
   (c) CNS depression (eg drugs)
4. Respiratory alkalosis (hyperventilation):
   (a) ↓ O2 (anaemia, CCF, altitude)
   (b) Pulmonary pathology (infx, oedema)
   (c) Central stimulation (sepsis, toxins, trauma)
   (d) Psychogenic