- **General**
  - Pre-Term Complications (<37wks)
    - Pulm
      - Respiratory Distress Syndrome (RDS)
      - Bronchopulmonary Dysplasia (BPD)
      - Tachypnea
    - ID
      - Infection esp Pneumonia
    - GI
      - Jaundice
      - Necrotizing Enterocolitis (NEC)
    - CV
      - PDA
      - Bradycardia
    - CNS
      - Interventricular Hemorrhage (IVH)
      - Retinopathy of Prematurity (ROP)
  - **Apgar** @1min and @5min which reflects the adequacy of resuscitation (NB never full 10 b/c of acrocyanosis)
    - NB Ballard

APGAR	0	1	2
(**A**ppearance) Color	Cyanotic/Pale	Body Pink & Extremities Cyanotic/Pale	Pink
(**P**ulse) Heart Rate	Absent	<100	>100
(**G**rimace) Reflex Irritability	No Response	Grimace	Cough or Sneeze
(**A**ctivity) Muscle Tone	Limp	Some Flexion	Active Motion
(**R**espirations) Respirations	Absent	Weak Cry or Hypo/Irregular Ventilation	Strong Cry

  - **Guidance**: Sleep on Back to prevent SIDS, Car Seat, No Honey, Childproof Home, Lead Screening, Low Water Heat, No Walkers, Avoid Small Objects and Chemicals
  - **M&M:** <1yo (respiratory distress syndrome, infections, pregnancy problem) vs >1yo (injury)
  - **Feeding**
    - **Breast-Milk/Formula 0-1yo** but longer if mutually desired regardless begin to introduce Gerber's **solid food >6mo** (signs of readiness for solid foods: hand-to-mouth coordination, decreased tongue protrusion reflex on squeezing palms/soles, sits w/ support, improved head control, drooling, opens mouth to spoon) and **Whole/2%/Skim Milk >1/2/5yo** (in general avoid water/juices)
    - Feed on demand or Q2hrs if preterm
    - Urinate >6x/d and BM Qmeal (begin toilet training >18mo)
    - Breast Milk
      - **Colostrum** (birth-3d, yellow sticky, rich in protein and immunologically active substances) then Transition Milk (3d-14d, gradually increasing calories, fat, and lactulose) then Mature Mild (>14d, varies in composition depending on time of day w/ hindmilk more fat/calories and foremilk more protein/immunologically active substances)
      - Contraindications: **HIV** (except in developing countries where the r/o death from Cholera using water to make formula is greater/quicker than that of HIV), **active TB** (not b/c it passes thru breast milk but just b/c you are close to infant and breathing on it), **CMV, active Herpes on Nipple, Illicit Drug Use, Galactosemia in Infant, Very Few Drugs** (Chemotherapeutics, Cyclosporin, Ergotamines, Radioactive Contrast, Lithium), **Breast Cancer**
        - NOT HepB/C, Fever, Jaundiced Infant, Mother Exposed to Chemicals, Mother Taking Contrast, Mother Smoking, Most Drugs
      - Compared to Formula
        - higher in cholesterol
        - **lower in protein, fat, carbs, salts, iron** (give cereal @ 6mo if term or iron supplements at 2mo if preterm), **VitD** (give 300IU/d @ 2mo if infant is never in sun, dark skin, exclusively breastfeeding >6mo), **VitK** (give shot at birth b/c VitK is produced by gut flora which is sterile in neonate), **fluoride** (give 0.25mg/d @ 6mo if levels are <0.33ppm, Low Fl: dental caries vs High Fl:

mottling, staining, hypoplasia of enamel) = **hence at 4mo start giving vitamin supplements**

- Why better than formula?
  - Nutritional: compared to formula a lot on nutrients are low which seems weird b/c you would think that more is better but the nutrients that are there are in their best form and the infant does not require the amount of nutrients in formula
  - Medical: decreased risk of infections during childhood, decreased risk of obesity, decreased HL and CAD in adulthood, decreased risk of autoimmune, inflammatory conditions during adulthood, decreased risk of SIDS, decreased need for orthodontics, better vision, less fussy eaters
  - Intelligence: higher IQ
  - Financial: save ~$1500/yr
  - Maternal: prolactinemia increases motherly instincts, decreased risk of post partum bleeding and anemia, decreased risk of ovarian and breast cancer, decreased risk of osteoporosis, greater post-partum weight loss (b/c mother's weight is going to baby)

- **Growth Milestones** (markers of general well-being, measure FOC/HC from 0-2yo and Weight/Height forever, cross-sectional comparing one pt to all kids at same age vs longitudinal comparing pt to same pt over time, genes kick in at 4mo and are complete at 18mo so during this period infants are crossing percentiles but after **18mo** infant should be locked into a percentile)
  - HR: 94-175
  - RR: 40-60 (often neonates undergo periodic breathing in which there are apneic spells of 5-10sec followed by hyperpnea (benign), >20sec is considered apnea concerning for infection, intracranial hemorrhage, airway obstruction, GER, seizures, hypoxia, pulmonary edema, metabolic disturbances, extreme temperatures, etc but most common is 2/2 preterm infants reflecting immaturity of resp control center in brain (bradycardia is also seen) Tx: tactile stimulation, keep warm, oxygen, oscillating water bed, respiratory stimulants
  - Temp: 36.5-37.0 (Neonates are unable to regulate temperature therefore in presence of infection they are unable to raise temperature to kill bacteria therefore neonates are often NOT febrile during infection)
  - BP: not routinely checked b/c the anxiety makes it unreliable

	Weight	**Height/Length**	**Frontal Occipital or Head Circumference (FOC/HC)**
	Failure To Thrive (FTT) (weight below 3% for age OR inadequate weight gain resulting in downward crossing of 2 major percentile lines but still overall weight gain OR actual weight loss, NB eventually height/length and then FOC is affected) • Low Calorie Intake aka Non-Organic aka Psychosocial (90%) poor family, bad formula, bad feeding techniques, bad mother-child relationship w/ emotional neglect, etc • Impaired Absorption aka Organic (5%) oral anatomic problem, infection, enzyme deficiency, cystic fibrosis, etc • Impaired/Increased Utilization aka Organic (5%) hyperTH, heart dz, infection, malignancy, etc Obesity • Feeding Too Much and Lack of Exercise • Genetic: Prader-Willi/Angelman Syndrome • Endo: HypoTH, Cushing, etc NB SGA (<10th percentile) vs LBW (<2500gm) • Early Onset (<28wks) Symmetric (growth during 1st half of pregnancy is achieved by hyperplasia therefore problems (genetic, infections, toxins) during this period result in symmetric growth) • Late Onset (>28wks): Asymmetric (growth during 2nd half of pregnancy is achieved by hypertrophy therefore problems (malnutrition, placental problems, preeclampsia, multiple gestation, smoking) during this period result in asymmetric growth w/ preservation of FOC	Short Stature • Familial Short Stature = always low percentile, short parents, appropriate bone age • Constitutional Delay = initially low percentile but then jumps to higher percentile, tall parents but they have a h/o delay, delayed bone age • Insult = primary damage to MS system w/ pt below even lowest percentile: Turner's, Trisomy 21, Prader-Willi, Achondroplasia, Russell-Silver Syndrome vs secondary damage to MS system w/ pt initially following along nl percentile but then drops to lower one or even below lowest percentile: malnutrition, major organ dz, endocrine dz, medications) Tall Stature • Familial Tall Stature • Insult = primary stimulation of MS system: Klinefelters, XYY, Marfan, Beck-Wiedemann vs Secondary Stimulation of MS System: endocrine dz NB closure of epiphyseal plate at puberty therefore if premature/delayed puberty	Low: microcephaly, fetal alcohol syndrome, familial, congenital infection aka TORCH, chromosomal abnl, dysmorphogenesis, toxins, ischemic insult, malnutrition, etc High: macrocephaly, hydrocephalus, neurocutaneous disorders, malignancy, etc

	NB LGA (>10th percentile) vs Macrosomic (>4000g) • Postterm, Maternal Diabetes, Beckwith-Wiedemann Syndrome, Genetic Predisposition aka Constitutionally Large, Hydrops Fetalis NB Weight typically drops in the first few days by 5% (15% if preterm) 2/2 extracellular water loss and suboptimal caloric intake. Weight is regained by 1st wk and thereafter 20-30gm/day then below	then shorter/taller NB Bone Age: degree of ossification of epiphyseal centers of metacarpals on x-ray of hand	
0-3mo	1kg/mo		
3-6mo	0.5kg/mo (increase by 100% aka double)		
6-12mo	0.25kg/mo (increase by another 100% aka double again)	(increase by 50%)	
12-24mo	0.2kg/mo		

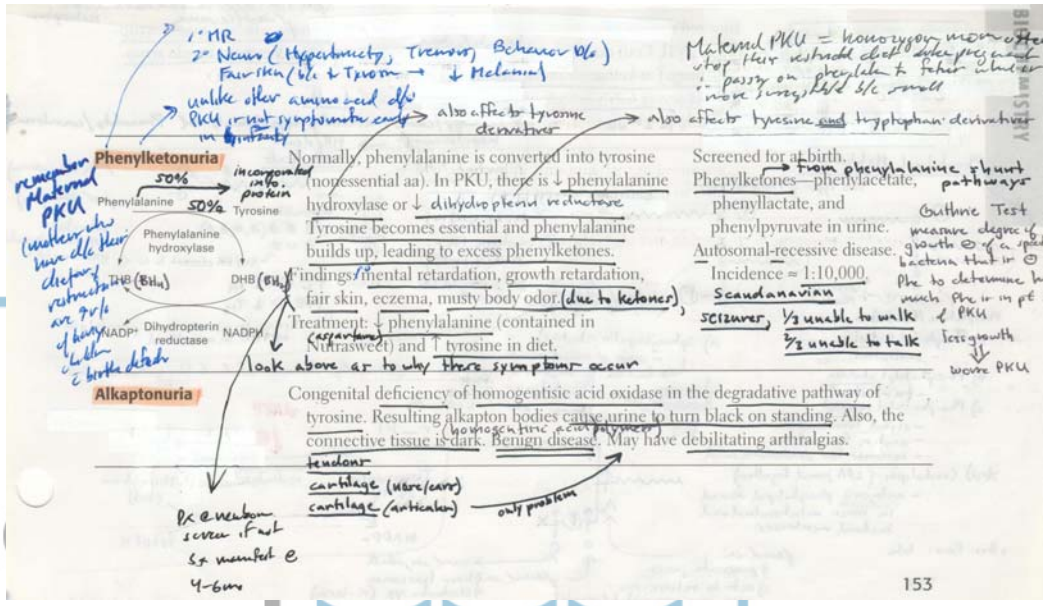
- **Developmental Milestones**
  - when concerned order a formal developmental test
  - if premature reduce the age by the number of months premature up until 2yo

	Language (best predictor of intelligence, language can be speech or any other signal like sign language, etc, Delayed (hearing impaired, perinatal RFs, CNS problem, anatomic problem, environmental deprivation)	**Gross Motor**	**Fine Motor**	**Cognitive**	**Psychosocial**
4mo	R: responds to their name E: laughs/cooing	Sit Up Rolls Front to Back Sits up w/ No Support at 7mo	Hold Rattle in One Hand w/ No Release	Searches for Dropped Objects	Smiles Socially Sleeps thru Night
9mo	R: understand "no", E: indiscriminate 1st baba and then mama	Stand While Holding Onto Something	Hold Rattle in Both Hands w/ Release Pat-a-Cake Waves Bye-Bye	Likes Peek-a-Boo	Plays Stranger Anxiety
1yr	R: 1step command E: discriminate baba/mama, 5 words, one word sentences, imitates other sounds	Walk	Put In and Take Out Can use cup/spoon	Search for Hidden Objects	Consoles easily and does not stiffen when approached Separation Anxiety
2yr	R: 2step command E: 50 words, two word sentences	Climb Run	Stack 6 Blocks and Scribble	Categorize Similarities	Responds nicely when approached
3yr	R: listen to story E: 250 words, three word sentences	Stand on One Foot	Stack 8 Blocks and Write Straight Line	Knows Full Name	Good Eye Contact
4yr		Hop	Stack 10 Blocks and Draw Circle	Can pick out short vs long line	Constantly Moving
5yr		Walk Straight Line	Build a Stair Case w/ Blocks and Copy Simple Images Ties Shoelaces	Knows Colors and Letters	Responds to Discipline, Plays w/ Other Children

  - **Malnutrition**: protuberant belly, flat buttocks, sucking cheek pads, muscle wasting poor muscle tone, poor response to stimuli
  - **Dehydration**: restlessness, weak cry, absent tears, exhausted/apprehensive behavior, rapid/weak pulse, poor skin tugor, sunken dry eyes, sunken anterior fontanel, dry mucous membranes, cold/cyanotic extremities
- Genetic Syndromes (refer)
- Metabolic
  - Inborn Errors of Metabolism

- General S/S: lethargy, vomiting, poor feeding, FTT
- Always rule out: sepsis, electrolyte imbalance, pulmonary problems, neurotoxins, etc
- Types: Urea Cycle Defects, Amino Acidopathies, Beta Oxidation Defects, Galactosemia, Pyridoxine Dependency, Mitochondrial Cytopathies (Unique S/S: metabolic acidosis, ophthalmoplegia, hearing loss, ataxia, hypotonia, seizures) w/ defects in pyruvate metabolism / FA oxidation / respiratory chain enzymes, Organic Aciduries, Branched Chain Amino Acidopathies, Multiple Carboxylase Deficiency

o **Newborn Screening Panel** (must be done w/in 1st month)
- All States: PKU, Hypothyroidism
- Most States: Congenital Adrenal Hyperplasia, Hemoglobinopathies, Galactosemia
- Some States: Homocystinuria, Maple Syrup Urine Disease, CF



Albinism

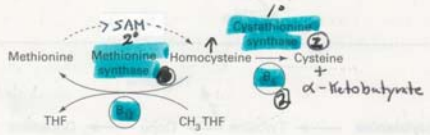
Congenital deficiency of either of the following:
1. Tyrosinase (inability to synthesize melanin from tyrosine)
2. Defective tyrosine transporters (↓ amounts of melanin)
3. Lack of migration of neural crest cells

Lack of melanin results in an ↑ risk of skin cancer.

Homocystinuria/-emia

Defect in cystathionine synthase and/or methionine synthase. 2 forms:
1. Deficiency (treatment: ↓ Met and ↑ Cys in diet)
2. ↓ affinity of synthase for pyridoxal phosphate (treatment: ↑↑ vitamin B_6 in diet)

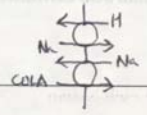
Results in excess homocysteine in the urine. Cysteine becomes essential.
Can cause mental retardation, osteoporosis, tall stature, long fingers and kyphoscoliosis (downward and inward).



Cystinuria

Very common (1:7000) inherited defect of tubular amino acid transporter for Cystine, Ornithine, Lysine, and Arginine in kidneys. Excess cystine in urine can lead to the precipitation of cystine kidney stones.

COLA.
Treat with acetazolamide to alkalinize the urine.



Maple syrup urine disease (MSUD)

Blocked degradation of branched amino acids (Ile, Val, Leu) due to ↓ α-ketoacid dehydrogenase.
Causes ↑ α-ketoacids in the blood and urine
Causes severe CNS defects, mental retardation, and death

Urine smells like maple syrup.
I Love Vermont maple syrup.

OTCD (Ornithine Transcarbamylase Deficiency) and other Urea Cycle Disorders
X-linked not AR
- manifests in first 1-2d of life after starchy protein rich feed (milk)
- progressively lethargic, ↓consciousness, seizures or NH_3↑

(females may have HA/V after protein rich meals if X-inactivation is unequal)
→ often outlive males except if prospectus Tx (based on the 5 pathways)
Tx: fluids, glucose, agents that ↑ alternate pathways for nitrogen excretion
↳ benzoic acid, phenylacetate

Disorders of galactose metabolism

Galactosemia (AR)

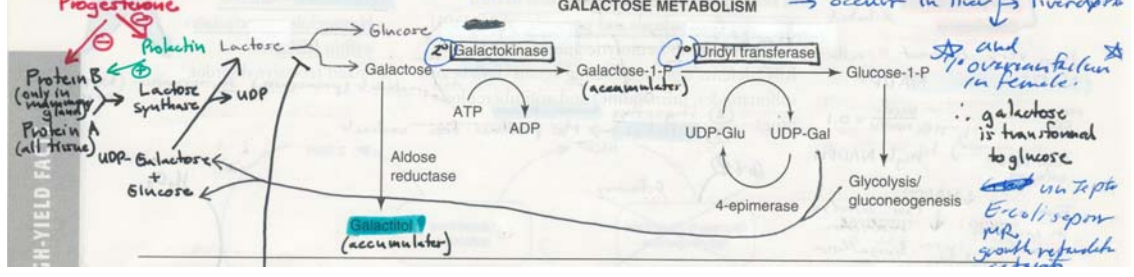
Absence of galactose-1-phosphate uridyltransferase. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol) rather than absence of an essential compound.
Symptoms: cataracts, hepatosplenomegaly, mental retardation.
Treatment: exclude galactose and lactose (galactose + glucose) from diet.
Causes galactosemia and galactosuria

Pregnancy [↑] After Birth [↓]

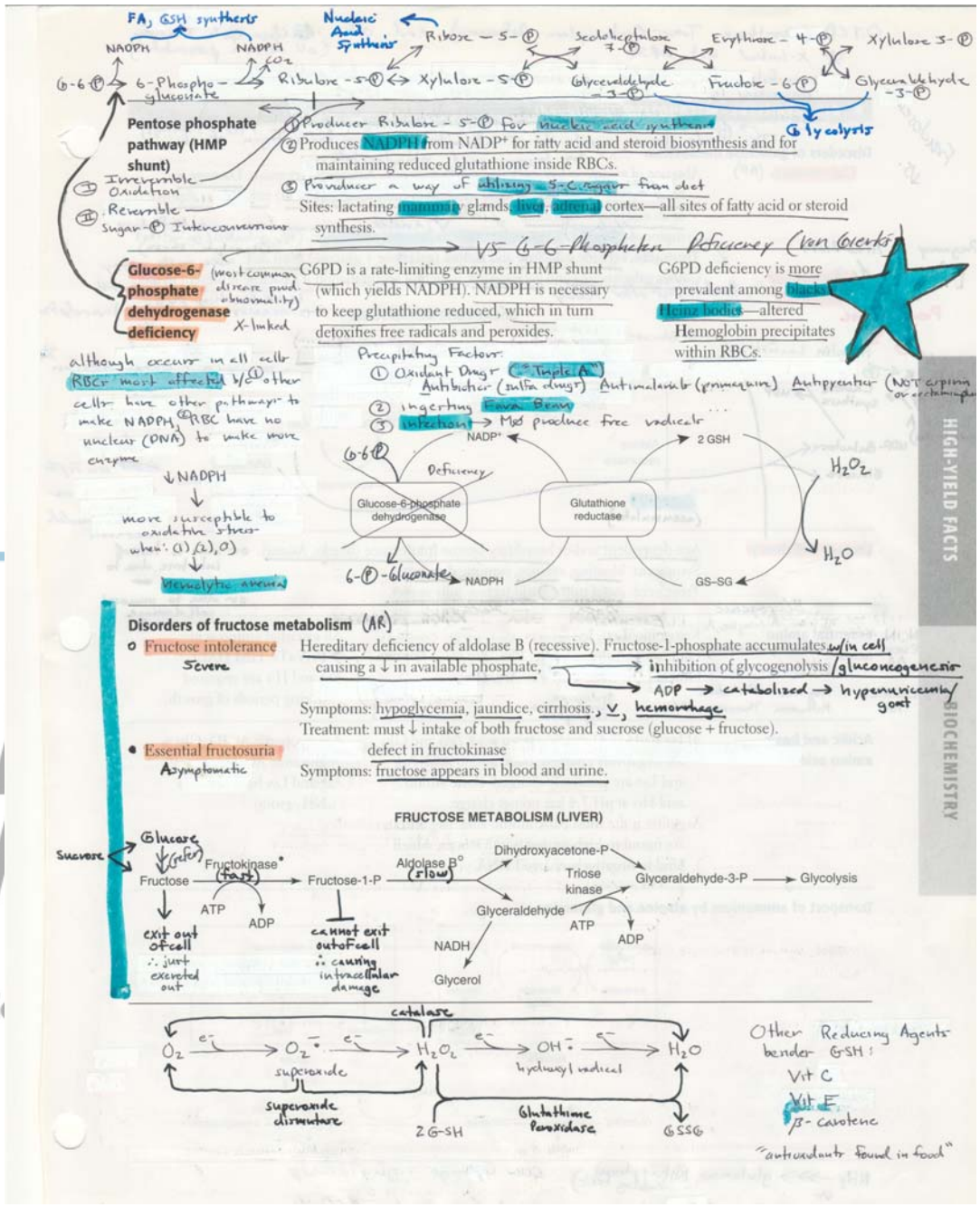
Progesterone ⊖ Prolactin ⊕ Lactose

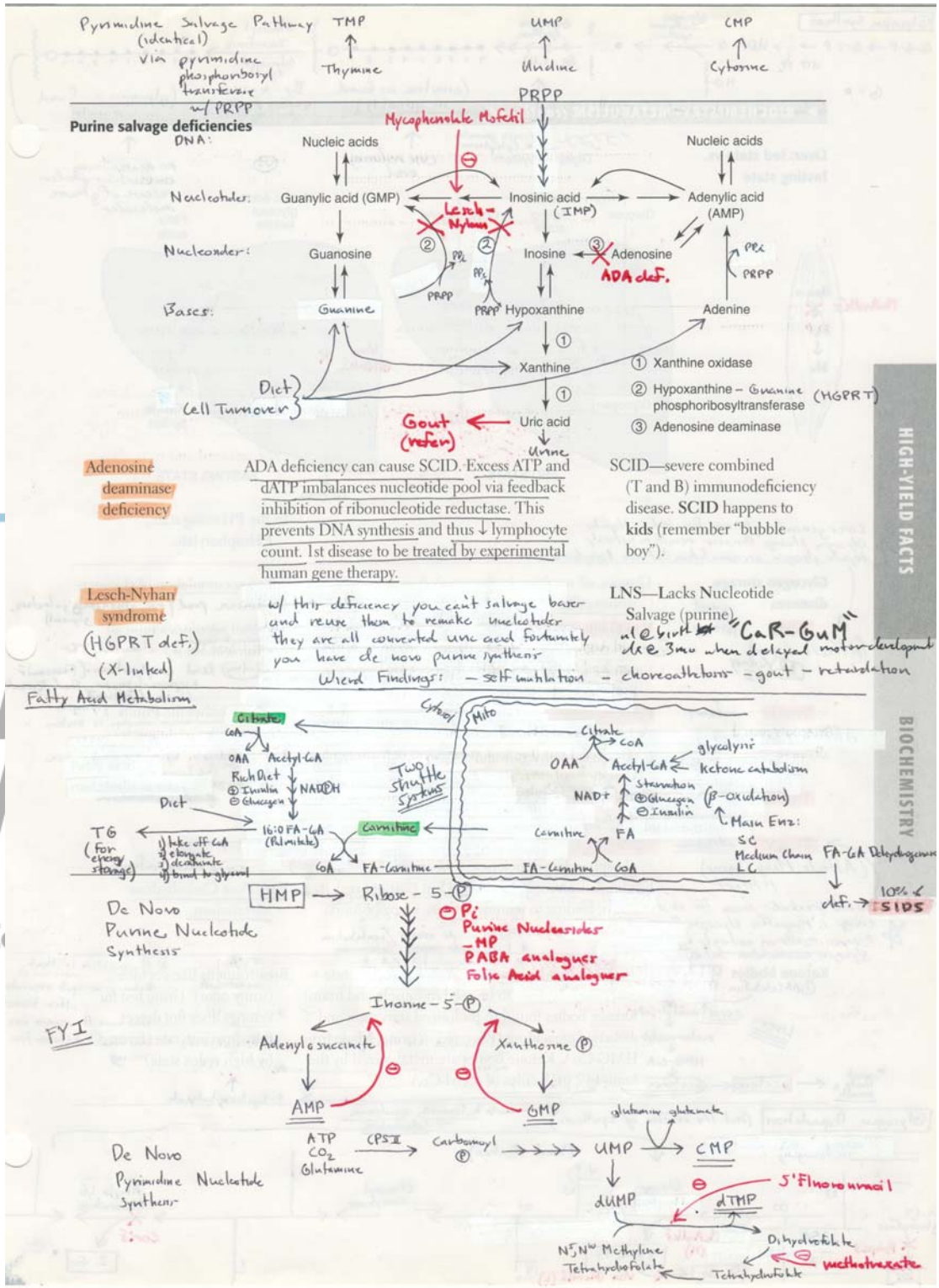
Protein B (only in mammary gland) + Lactose synthase → UDP
Protein A (all tissue)

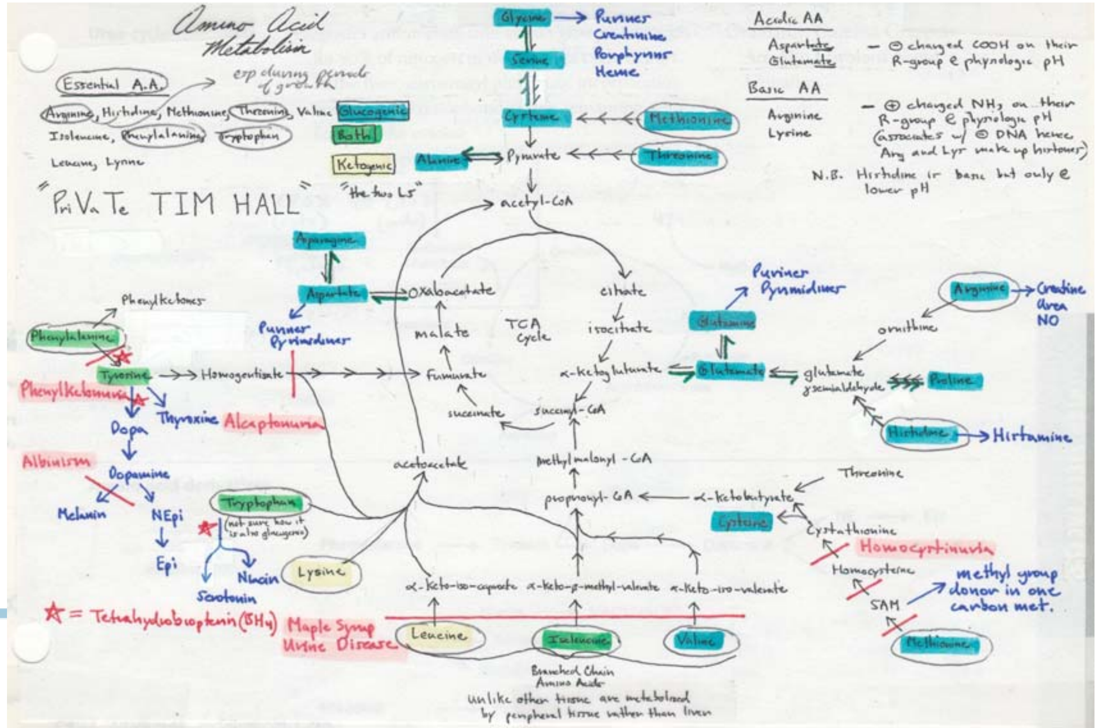
UDP-Galactose + Glucose



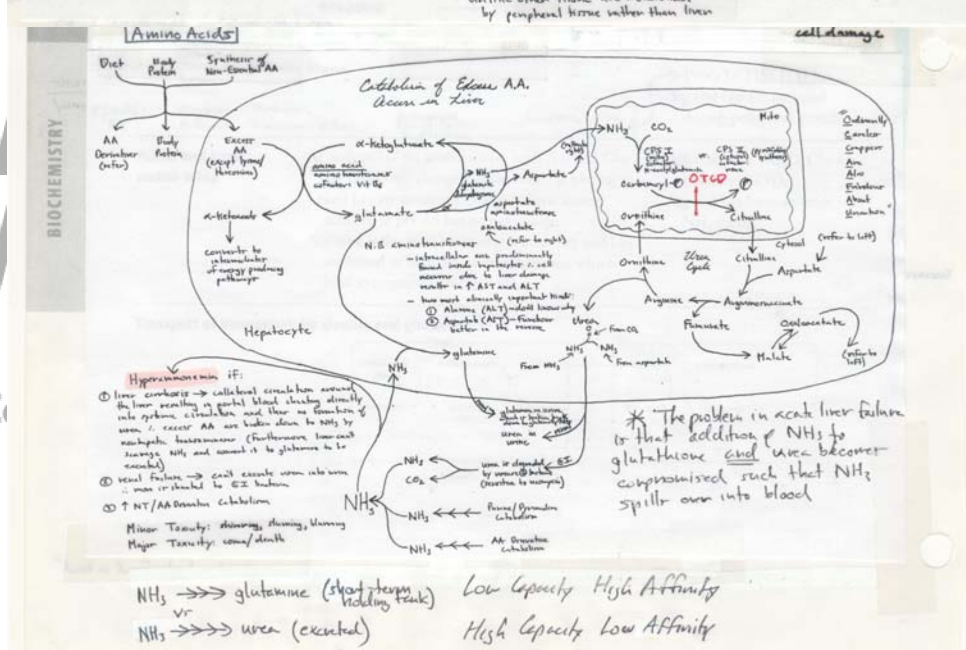
↓ and 1° overexpression in female.
∴ galactose is transformed to glucose
E. coli sepsis


FA, GSH synthesis
Nucleic Acid Synthesis
NADPH
NADPH
CO2
6-6-P
6-Phospho-gluconate
Ribulose-5-P
Ribose-5-P
Sedoheptulose-7-P
Erythrose-4-P
Xylulose-5-P
Xylulose-5-P
Glyceraldehyde-3-P
Fructose-6-P
Glyceraldehyde-3-P
Glycolysis
Pentose phosphate pathway (HMP shunt)
Irreversible Oxidation
Reversible Sugar-P Interconversion
① Produces Ribulose-5-P for nucleic acid synthesis
② Produces NADPH from NADP+ for fatty acid and steroid biosynthesis and for maintaining reduced glutathione inside RBCs.
③ Provides a way of utilizing 5-C sugars from diet
Sites: lactating mammary glands, liver, adrenal cortex—all sites of fatty acid or steroid synthesis.
Glucose-6-phosphate dehydrogenase deficiency
(most common disease pmd abnormality)
X-linked
G6PD is a rate-limiting enzyme in HMP shunt (which yields NADPH). NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides.
G6PD deficiency is more prevalent among blacks.
Heinz bodies—altered Hemoglobin precipitates within RBCs.
Precipitating Factors:
① Oxidant Drugs ("Triple A") Antibiotics (sulfa drugs) Antimalarials (primaquine) Aspirin (NOT ibuprofen or acetaminophen)
② Ingesting Fava Beans
③ Infections → Mϕ produce free radicals
although occurs in all cells RBCs most affected b/c other cells have other pathways to make NADPH, RBC have no nucleus (DNA) to make more enzyme
↓NADPH
more susceptible to oxidative stress when: (1), (2), (3)
Hemolytic anemia
NADP+
2 GSH
6-6-P
Deficiency
Glucose-6-phosphate dehydrogenase
Glutathione reductase
H2O2
H2O
6-P-Gluconate
NADPH
GS-SG
HIGH-YIELD FACTS
BIOCHEMISTRY
Disorders of fructose metabolism (AR)
• Fructose intolerance
Severe
Hereditary deficiency of aldolase B (recessive). Fructose-1-phosphate accumulates w/in cell causing a ↓ in available phosphate, → inhibition of glycogenolysis / gluconeogenesis
ADP → catabolized → hyperuricemia/gout
Symptoms: hypoglycemia, jaundice, cirrhosis, ↓, hemorrhage
Treatment: must ↓ intake of both fructose and sucrose (glucose + fructose).
• Essential fructosuria
Asymptomatic
defect in fructokinase
Symptoms: fructose appears in blood and urine.
FRUCTOSE METABOLISM (LIVER)
Sucrose
Glucose
(refer)
Fructose
Fructokinase* (fast)
ATP
ADP
Fructose-1-P
Aldolase B° (slow)
Dihydroxyacetone-P
Triose kinase
Glyceraldehyde-3-P
Glycolysis
Glyceraldehyde
ATP
ADP
NADH
Glycerol
exit out of cell
∴ just excreted out
cannot exit out of cell
∴ causing intracellular damage
catalase
O2
e-
O2-
superoxide
e-
H2O2
e-
OH·
hydroxyl radical
e-
H2O
superoxide dismutase
2 G-SH
Glutathione Peroxidase
G-SSG
Other Reducing Agents besides G-SH:
Vit C
Vit E
β-carotene
"antioxidants found in food"

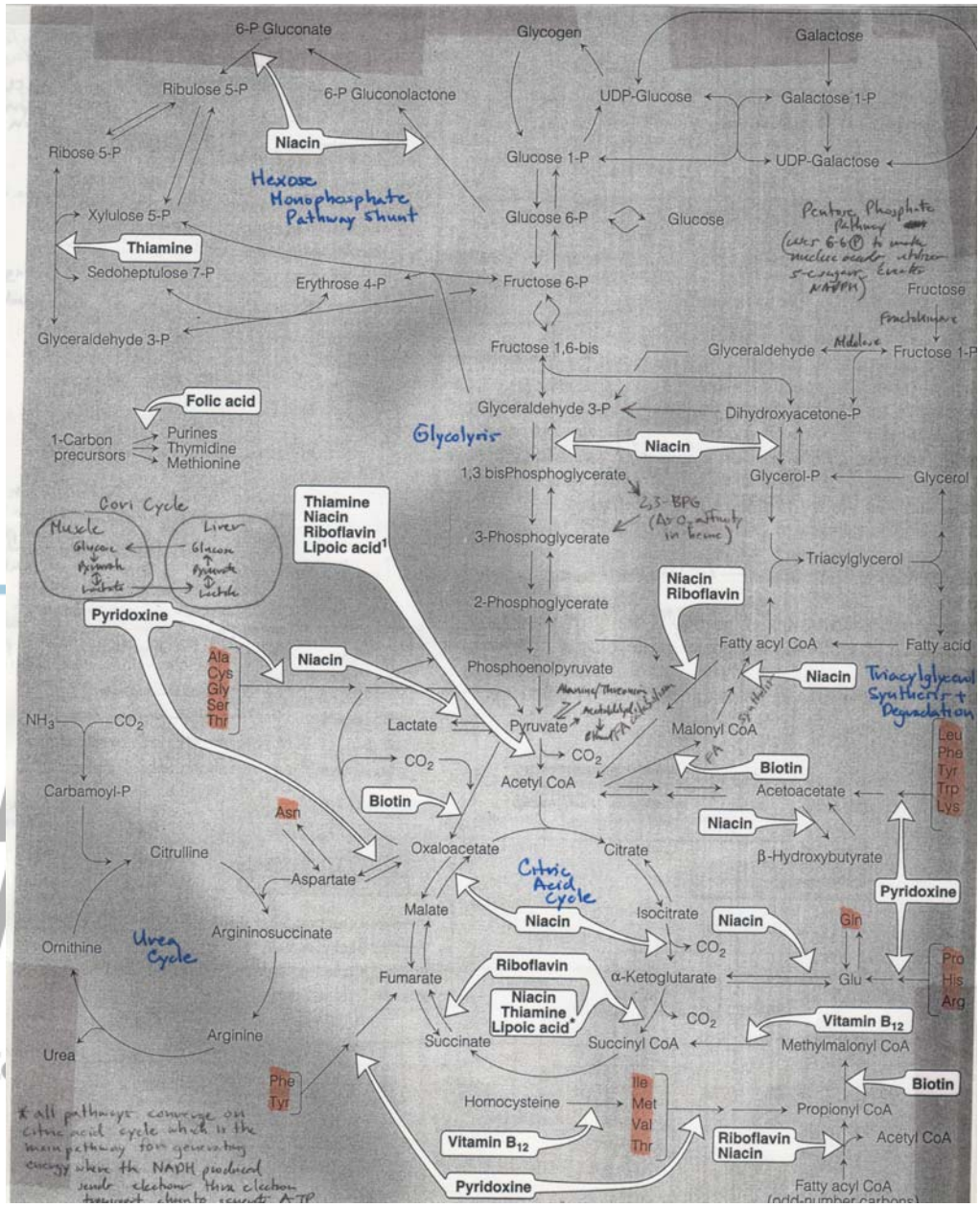

Pyrimidine Salvage Pathway (identical) via pyrimidine phosphoribosyl transferase w/ PRPP
TMP
Thymine
UMP
Uridine
CMP
Cytosine
PRPP
Purine salvage deficiencies
Mycophenolate Mofetil
DNA:
Nucleic acids
Nucleic acids
Nucleotides:
Guanylic acid (GMP)
Inosinic acid (IMP)
Adenylic acid (AMP)
Lesch-Nyhan
Nucleosides:
Guanosine
Inosine
Adenosine
ADA def.
PRPP
Bases:
Guanine
Hypoxanthine
Adenine
Xanthine
Diet
Cell Turnover
Gout (refer)
Uric acid
Urine
① Xanthine oxidase
② Hypoxanthine – Guanine phosphoribosyltransferase (HGPRT)
③ Adenosine deaminase
Adenosine deaminase deficiency
ADA deficiency can cause SCID. Excess ATP and dATP imbalances nucleotide pool via feedback inhibition of ribonucleotide reductase. This prevents DNA synthesis and thus ↓ lymphocyte count. 1st disease to be treated by experimental human gene therapy.
SCID—severe combined (T and B) immunodeficiency disease. SCID happens to kids (remember "bubble boy").
Lesch-Nyhan syndrome (HGPRT def.) (X-linked)
w/ this deficiency you can't salvage bases and reuse them to remake nucleotides they are all converted uric acid fortunately you have de novo purine synthesis
Weird Findings: – self mutilation – choreoathetosis – gout – retardation
LNS—Lacks Nucleotide Salvage (purine)
"CaR-GuM"
at birth
age 3mo when delayed motor development
Fatty Acid Metabolism
Cytosol
Mito
Citrate
CoA
OAA
Acetyl-CoA
Rich Diet
Insulin
Glucagon
NADPH
Two shuttle systems
Diet
TG (for energy storage)
1) take off CoA
2) elongate
3) desaturate
4) bind to glycerol
16:0 FA-CoA (Palmitate)
Carnitine
CoA
FA-carnitine
Citrate
CoA
OAA
Acetyl-CoA
glycolysis
ketone catabolism
Starvation
Glucagon
Insulin
NAD+
β-oxidation
Main Enz:
FA
Carnitine
SC
Medium Chain
LC
FA-CoA Dehydrogenase
def. → 10% of SIDS
HMP
Ribose – 5-P
De Novo Purine Nucleotide Synthesis
Pi
Purine Nucleosides
-MP
PABA analogues
Folic Acid analogues
FYI
Inosine – 5-P
Adenylosuccinate
Xanthosine P
AMP
GMP
glutamine glutamate
ATP
CO2
Glutamine
CPSII
Carbamoyl P
UMP
CMP
De Novo Pyrimidine Nucleotide Synthesis
5'Fluorouracil
dUMP
dTMP
N5,N10 Methylene Tetrahydrofolate
Dihydrofolate
Tetrahydrofolate
methotrexate



Amino Acid Metabolism
Essential A.A.
esp during period of growth
Arginine, Histidine, Methionine, Threonine, Valine
Isoleucine, Phenylalanine, Tryptophan
Leucine, Lysine
Glucogenic
Both
Ketogenic
"PriVaTe TIM HALL"
"the two Ls"
Glycine → Purines, Creatinine, Porphyrins, Heme
Serine
Cysteine
Methionine
Alanine
Pyruvate
Threonine
acetyl-CoA
Acidic AA
Aspartate
Glutamate
− ⊖ charged COOH on their R-group @ physiologic pH
Basic AA
Arginine
Lysine
− ⊕ charged NH3 on their R-group @ physiologic pH (associates w/ ⊖ DNA hence Arg and Lys make up histones)
N.B. Histidine is basic but only @ lower pH
Asparagine
Aspartate
Oxaloacetate
citrate
isocitrate
malate
TCA Cycle
Fumarate
α-ketoglutarate
succinate
succinyl-CoA
Purines
Pyrimidines
Glutamine
Glutamate
glutamate γ-semialdehyde
Proline
Arginine → Creatine, Urea, NO
ornithine
Histidine → Histamine
Phenylketones
Phenylalanine
Tyrosine → Homogentisate
Phenylketonuria
Thyroxine
Alcaptonuria
Dopa
Dopamine
Albinism
Melanin
NEpi
Epi
Tryptophan
(not sure how it is also glucogenic)
Niacin
Serotonin
Lysine
acetoacetate
methylmalonyl-CoA
propionyl-CoA
α-ketobutyrate
Threonine
Cysteine
Cystathionine
Homocystinuria
Homocysteine
methyl group donor in one carbon met.
SAM
Methionine
α-keto-iso-caproate
α-keto-β-methyl-valerate
α-keto-iso-valerate
★ = Tetrahydrobiopterin (BH4)
Maple Syrup Urine Disease
Leucine
Isoleucine
Valine
Branched Chain Amino Acids
unlike other tissue are metabolized by peripheral tissue rather than liver



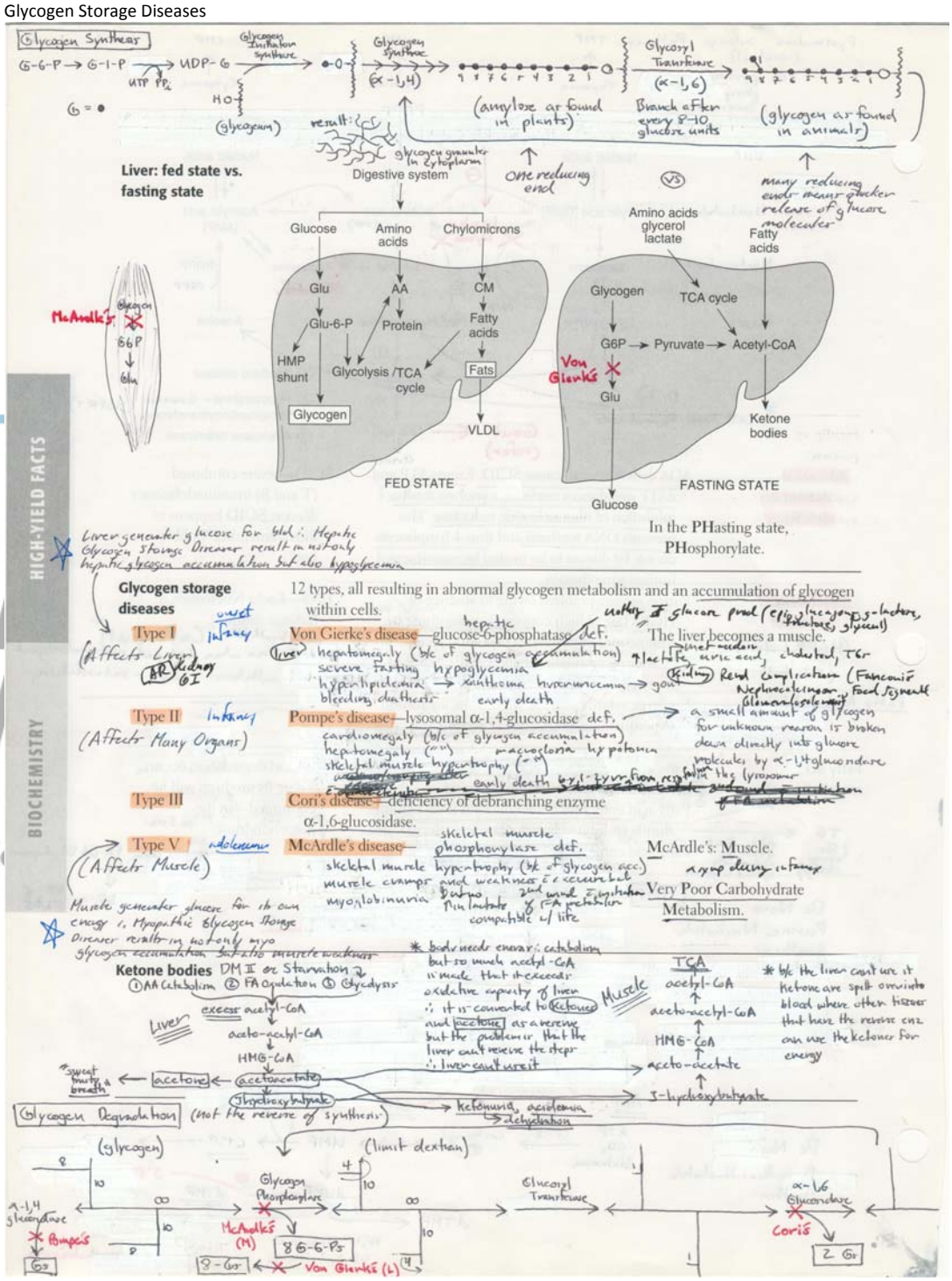
Amino Acids
cell damage
Diet
Body Protein
Synthesis of Non-Essential AA
AA Derivatives (other)
Body Protein
Excess AA (except lysine/threonine)
Catabolism of Excess A.A. Occurs in Liver
α-ketoglutarate
α-ketoacids
glutamate
Aspartate
aspartate aminotransferase
oxaloacetate
converts to intermediates of energy producing pathways
N.B. aminotransferases
Hepatocyte
glutamine
Mito
NH3
CO2
Carbamoyl-P
OTC
Ornithine
Citrulline
Urea Cycle
Cytosol
Aspartate
Arginase
Argininosuccinate
Fumarate
Oxaloacetate
Malate
Urea
Hyperammonemia if:
① liver cirrhosis → collateral circulation around the liver resulting in portal blood draining directly into systemic circulation
② renal failure → can't excrete urea into urine
③ ↑ NT/AA Derivative Catabolism
Minor Toxicity: shivering, slurring, blurring
Major Toxicity: coma/death
NH3
CO2
Purine/Pyrimidine Catabolism
AA Derivative Catabolism
* The problem in acute liver failure is that addition of NH3 to glutathione and urea becomes compromised such that NH3 spills over into blood
NH3 →→→ glutamine (short-term holding tank) Low Capacity High Affinity
vs
NH3 →→→→ urea (excreted) High Capacity Low Affinity



- **Teratogens**
  - Fetal Alcohol Syndrome
    - Facial Dysmorphisms: tipped up nose w/ crease, big space b/t nose and upper lip, smooth philtrum, small upper lip , small eyes w/ short palpebral fissures, ptosis, flat mid face
    - CNS: microcephaly, agenesis of corpus collosum, cerebral hypoplasia leading to MR, fine motor problems, sensorineural hearing loss, poor gait/coordination, poor hand/eye coordination, hyperactive
    - CV: Malformations
    - MS: Joint Contractures
    - Renal: Malformations
    - General: Growth Retardation
  - Phenytoin aka Fetal Hydantoin Syndrome (Facial Dysmorphisms, MR, IUGR, Hypoplasia of Nails and Distal Phalanges)
  - Tetracycline (tooth discoloration, inhibit bone formation)
  - Accutane (hydrcephalus, microtia, micrognathia, aortic arch abnormalities)
  - Warfarin (abnl cartilage development, MR, deafness, blindness)

- Narcotics (IUGR, SIDS, accelerated maturation of organs, “Narcotic Withdrawal Syndrome”: irritability, poor sleeping, high-pitched cry, diarrhea, sweating, sneezing, seizures, poor feeding, poor weight gain)
- Lead (ranges from mild learning disability to full MR, screen if RFs, Tx w/ stopping exposure and chelators (succimer/DMSA))

o Glycogen Storage Diseases



o Peroxisomal Disorders
- Abnormal oxidation of very long FAs, plasmalogens, bile acids, etc
- Most common one is X-linked Adrenaleukodystrophy
- S/S: ~6yo, behavior problems, spastic paraparesis, dysphagia, visual loss, Addison’s

o Lysosomal Storage Diseases

- Abnormal accumulation of normal substances and their catabolic products w/in lysosomes
- S/S: variable presentation from usually infancy to rarely adulthood, apathy, lack of visual interest, development delay, followed by seizures, hypotonia, loss of vision w/ unique PEx features like HSM, cherry red spot on retina, megalencephaly, choreoathetosis, skin/hair changes
- Dx: EM of skin Bx

① Carb ② AA ③ NH_3 ④ Mucopolysaccharides Metabolism

Can't Use It !!!	Can't Break It Down !!!
Disorders of Intermediary Metabolism	(vs) Disorders of Catabolism (Storage Diseases)
· Fast progression (wks)	· slow progression (yrs)
· not fatal (can still be excreted out)	· Fatal! (b/c can't go anywhere)
· treatable (dietary restriction)	· untreatable!
Eg. PKU, Galactosemia, etc.	Eg. Lysosomal Storage Diseases and Glycogen Storage Diseases

often nl at birth but can show met acidosis, poor feeding, V, lethargy, seizures, HR, organomegaly, odor, (AR) ē notable exceptions

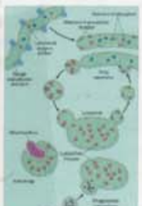
I-Cell Disease

Worst Lysosomal Storage Disease b/c here all lysosomal enzymes (interestingly which are glycoproteins) fail to have their mannose phosphorylated to M-6-Ⓟ as a result none of the enzymes are present unlike the other diseases which lack only one enzyme, these enzymes are found in plasma unlike the other diseases b/c it is not b/c the enzymes are being made rather they are not being tagged for the lysosome and thus end up in blood

↓

- skeletal problems
- restricted joint movement
- coarse facial features
- psychomotor problems

Synthesis and transport of lysosomal enzymes



lysosomal enzymes are unique in that function in an acid milieu and that even though they are secretory enzymes they remain intracellular in organelles rather than extracellularly (how? like secretory enzymes they are made in ER and Golgi but uniquely in the Golgi they are tagged with a mannose-6-phosphate which is a ligand for receptors found on the inner surface of Gogli therefore lysosomal enzymes bind and are thus segregated from those enzymes destined to be secreted; vesicles then pinch off and fuse with lysosomes and the vesicle with receptors recycles back to Golgi)

With an inherited defect in one of these lysosomal enzymes the lysosome enlarges as the partially degraded insoluble metabolite (normally the final metabolite is soluble) accumulates and interferes with normal cell function... **Lysosomal Storage Disorders**

NOTE the distribution of the stored material and hence the organisms affected is determined by the tissue where most of the material to be degraded is found (eg. brain is rich in ganglioside) and the location where most of the degradation normally occurs (eg. defective enzyme results in storage within neurons) (b/c mononuclear phagocytic system is rich in lysosomes and are involved in degradation of many substances they are often affected

Degradation of: "Sphingolipidoses"
① Glycolipids (most imp)
② GAGs
③ Glycoproteins (least imp) → "Mucopolysaccharidoses"

Glucosaminoglycans (GAGs) – repeating disaccharides attached to protein
6 Major Types:
1) Chondroitin (cartilage, tendon, ligament)
2) Keratan Sulfate (" ")
3) Hyaluronic Acid (lubricant, shock absorber in joints)
4) Dermatan Sulfate (skin, vessels)
5) Heparan (anticoagulant)
6) Heparan Sulfate (BM)

* properties of "resilience, sponginess, slipperiness" is attributed to the relationship b/t highly ⊖ GAGs and H_2O

Most Important **Lysosomal storage diseases** — Sphingolipidoses

Disease	Findings	Deficient enzyme	Accumulated substrate	Inheritance	Pathology
Farber's Disease 1	painful deformed joints, subcut nodules	ceramidase	ceramide		
Fabry's disease 1	Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular/renal disease (progressive renal failure)	α-galactosidase A	Ceramide trihexoside (found in urine)	XR	nl at birth ē Dx @ yrs nodules on joints, vocal cords (hoarseness)
Gaucher's disease 1 (Most Common)	Hypersplenism → pancytopenia, skeletal breakdown → pain/fracture/avascular necrosis, no CNS involvement	β-glucocerebrosidase	Glucocerebroside (Adult = nl lifespan; Infantile = rapid neuro deterioration)	AR	mø w/ "crumpled tissue" cytoplasm and eccentric nucleus (no vacuolization)
Niemann-Pick Dz 1 (Ashkenazies)	Progressive neurodegeneration, organomegaly (liver/spleen), cherry red spot/blindness	Sphingomyelinase	Sphingomyelin	AR	neurons distended w/ "onion shaped" lysosomes
Sandhoff's/Tay-Sachs disease 1 (Ashkenazies) (2nd Most Common)	death by 3yo ē Dx @ 3mo (same as above) + hyperacusis (exaggerated startle response), frog-like position, organomegaly only in Sandhoff not Tay-Sachs	Hexosaminidase A	GM_2 ganglioside	AR	(same as above)
Krabbe's disease 1	Peripheral neuropathy, → paralysis, developmental delay, deafness, optic atrophy → blindness	β-galactosidase	Galactocerebroside accumulates in white matter of brain	AR	"globoid cells" in areas of demyelination
Metachromatic leukodystrophy 1	Central and peripheral demyelination with ataxia, dementia	Arylsulfatase A	Cerebroside sulfate	AR	metachromatic nerves (stain yellow w/ cresyl violet stain)
Hurler's syndrome 2	Developmental delay, MR, gargoylism, airway obstruction, corneal clouding, coarse facial hair, joint/skeletal deformities (stiff), narrowed coronary arteries → CAD, cardiac valve lesions, enlarged tongue, organomegaly, hearing loss	α-L-iduronidase	Heparan sulfate, dermatan sulfate	AR	"Gargoyle Cells" cells ē engorged lysosomes ē mucopolysaccharides
Hunter's syndrome 2	Mild Hurler's + aggressive behavior, no corneal clouding, no CNS problems, no narrowed arteries, no valve lesions	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	XR	"Hunters are Males"

Mild Hurler's = Scheie's

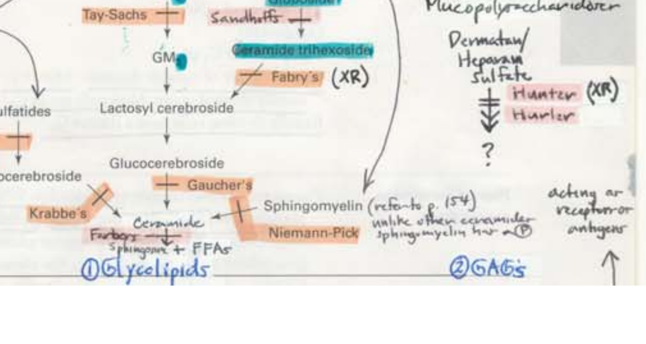
For all in general: HSM, skeletal problems

Dysostosis Multiplex
- large dolichocephalic skull
- thick calvarium
- ovoid vertebral bodies
- flared disc, longer
- shallow acetabulum
- irregular

* These are glycosphingolipids which are essential components of all membranes and this pathway is their degradation pathway (all esp found in CNS)

* all of these are ceramides w/ diff attached sugar residues

(occurs in RER not Golgi)



unlike other ceramides sphingomyelin has a Ⓟ

① Glycolipids

Mucopolysaccharidoses
Dermatan/Heparan Sulfate
Hunter (XR)
Hurler
?

acting as receptors or antigens

② GAGs

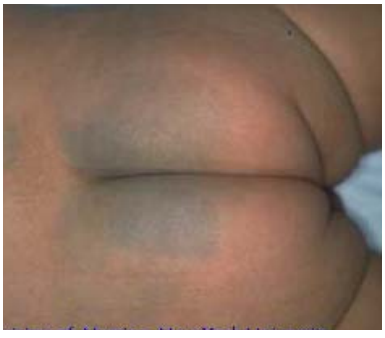
- Heme
  - Anemia Screening only if RFs (premature, LBW, use of Cow's Milk b/f 1yo, poor po intake)
  - HUS
- ID
  - **Immunodeficiencies** (refer)
  - **URTIs**: **Otitis Externa/Media, Mono/Strept/Diphtheria Pharyngitis, Mumps, Epiglottitis, Tracheititis, Croup, Pertussis Bronchitis, Bronchiolitis** (refer)
    - **Otitis Media** (so common that if infant is ill always check ears, if recurrent can cause hearing loss w/ language developmental delay therefore prophylactic abx, tympanostomy tubes, adenoidectomy, etc)
  - **UTI** (if <5yo and 1st male or 2nd female consider urinary tract malformation esp vesicoureteral reflux or posterior urethral valves, check w/ renal US and voiding cystourethrogram)
  - **Meningitis** (mainly only seen in infants <2yo, look for unusual Sx of lethargy, fever/hypothermia, poor muscle tone, bulging fontanelle, vomiting

	Prenatal (infections that cross placenta) • **TORCH** (Toxo, Other: varicella/syphilis, Rubella, CMV, Herpes) intrauterine infections cause **MR/microcephaly/hydrocephalus, HSM/jaundice, anemia, LBW/IUGR** AND other specific problems depending on the infection	**Perinatal** (infections acquired through fetal membranes, ascending infections after ROM, infections via birth canal, chorioamnionits, intrapartum maternal fever, premature)	**Postnatal** (nosocomial infections)
Bacteria	• **Listeria** (sepsis, meningitis) • **Syphilis** (unlike other STDs *T. pallidum* does not inoculate baby during birth but actually crosses placenta at any time during pregnancy, TORCH S/S + spontaneous abortion or still birth or alive at birth but dies quickly (baby looks **old** b/c of wrinkles, **pot-bellied** b/c of hepatomegaly, **bow-legged** b/c of ?, sick with a **cold** b/c of the chronic rhinitis and sniffles) or if lives past infancy and unTx (notched central incisors aka **Hutchinson's Teeth, blindness, deafness, saber shin, saddle nose**))	• Strep (all Strepts but esp S. agalactiae (Early aka right after birth: sepsis vs Late aka after 1wk: meningitis w/ bulging fontanelle, lethargy, irritability, V, seizures), Tx: penG all women should be screened with vaginal/rectal swabs at 36wks b/c 20% are colonized and if so should be given peripartum PenG) • E. coli (mother has UTI during last mo of pregnancy, sepsis, meningitis, UTI, pneumonia) • Klebsiella • Chlamydia (1wk: conjunctivitis, 2ks: pneumonia) • Gonorrhea Conjuctivitis	• All Staphs • E. coli • Klebsiella • Pseudomonas • Clostridia • Bacteroides • Enterococcus
Virus	• **Rubella** (always check maternal Ab at 1st prenatal visit, can only vaccinate b/f pregnancy b/c live vaccine, most doctors recommend abortion if mother contracted Rubella b/c there is no Tx, TORCH S/S + **CV defects esp PDA/VSD, deafness, cataracts, microophthalmia**) • **CMV** (TORCH S/S + **deafness, cerebral calcifications, microophthalmia, petechiae aka blueberry infant**) • **Herpes** (TORCH S/S + after 2 wks the fetus develops a **rash** of skin/eyes/mouth which can lead to sepsis followed by **encephalitis, pneumonitis, hepatic necrosis** followed by death 60% of time or survival but with significant M&M) • **Varicella** (TORCH S/S + **limb hypoplasia and skin scarring**) • **HIV** • **Parvo** (death)	• HepA/B • RSV • Herpes (same)	
Fungi	• **Toxoplasma** gondii (F→O cat feces therefore pregnant women should avoid cats, TORCH S/S + **intracranial calcifications and chorioretinitis**)		• Candida

- Derm

- **Vernix Caseosa**: formed in utero from shed epithelial cells, hair, and sebum and is designed to lubricate and provide a barrier to amniotic fluid, when exposed to air after delivery it thickens and looks like "cheese"
- **Parchment Skin**: cracking and peeling of skin seen in postterm newborns
- **Erythema Toxicum Neonatorum**: erythematous macule w/ a very small pustule ("flea bittern appearance"), unknown cause, can occur anywhere on body except palms/soles, onset after 1-2d of life, benign, and self-limited (2d), eosinophils on smear
- **Transient Neonatal Pustular Melanosis**: Three Phases (Large Pustule, Rupturing and Scaling, Hyperpigmented Macules that fade over months), unknown cause, occurs on dark skinned pts, present at birth, neutrophils on smear
- **Lanugo**: Dark hair
- **Cutis Marmorata (Mottling)**: Lacy reticulated appearance 2/2 cold and disappears when rewarming, Seen in premature infants, down syndrome, sepsis, shock, If permanent if is called: Cutis Marmorata Telengectica Congenita
- **Harlequin:** Dependent sided rubor and nondependent pallor, Lasts minutes, Normal reflecting immature brain
- **Subcutaneous Fat Necrosis**: Big red plaques w/ induration 2/2 calcification, 2/2 birth trauma
- **Sucking Blister/Erosion:** In utero and outside babies sometimes suck on body parts (eg. hand, legs, penis) creating what looks like a blister like one generated from wearing new shoes. Sometimes it breaks and appears as an erosion
- **Milia:** Obstructed Pilosebacceous Gland forming an Epidermal Cyst, Small pimples that often seen in face (called Epstein Pearl if b/t hard and soft palate or Bohn Nodules if on gums), Disappear after 1mo, Retention of keratin and sebaceous material
- **Miliaria:** Obstructed Eccrine Sweat Gland forming ?, Type I (Crystallina) sweat under skin forming numerous small vesicles, Type II (Rubra) reddish skin
- **Sebaceous Hyperplasia**: Little white dots on nose 2/2 maternal androgen stimulation, Disappear after 1wk
- **Seborrheic Dermatitis** (refer)
- **Diaper Rash**
  - Irritant Contact Dermatitis (spares folds, 2/2 chronic exposure to moisture, reaction to feces, urine, medications, creams, type of diaper), Tx: barrier creams (zinc oxide), more frequent diaper changes
  - Candida Dermatitis (includes folds + satellite lesions, 2/2 infection of irritant contact dermatitis), Tx: antifungal creams, keep dry
- **Mosaicism or Blaschko Line Anomalies** (reflect the migration of ectodermal precursors during embryogenesis manifesting in various patterns such as whorls, streaks, blocks, leafs, checkerboard, etc.)

- **Mongolian Spot** (flat benign purple marks w/ indistinct edges often at base of spine and buttocks but can occur anywhere on back, shoulders, and legs represent a dense collections of melanocytes more common in darker skinned people appear at birth and most fade considerably by 2yo but if they persist to puberty they are likely to last into adulthood often mistaken for bruises and thus child abuse)



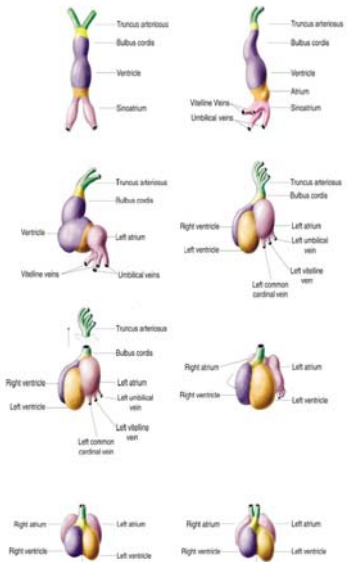
- **Vascular Anomalies** (refer)

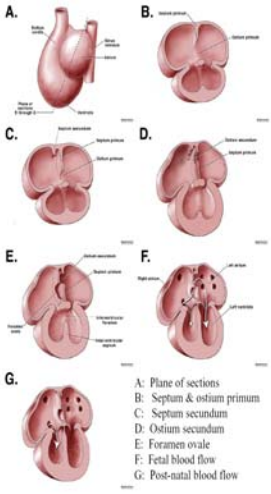
- Head
  - Hyrdocephalus (increase FOC, bulging fontanelle, scalp vain engorgement, paralysis of upward gaze, large ventricles on imaging, DDx: congenital malformation, tumor, s/p –itis or hemorrhage)
  - Fontanelles (assess size and tension either bulging/normal/depressed)
    - Anterior (Nl: 1-5cm, closes @2yr, Large (increased ICP, Rickets, hydrocephalus, subdural hematoma, brain tumor, meningitis, HypoTH) vs Small (Down Syndrome, HyperTH))

        - Posterior (Nl: finger tip, closes @2mo)
    - Craniosynostosis
    - Molding
    - Plagiocephaly (flattening of head/face, often occurs in infants w/ torticollis and thus lies w/ head in one position)
    - Cephalohematoma (subperiosteal collections of blood 2/2 ? that do NOT cross suture lines, Tx: evacuation of blood is contraindicated b/c of r/o infection and thus usually nothing is done unless you suspect it is 2/2 fracture) vs Caput Succedaneum (subcutaneous collections of fluid 2/2 scalp compression by cervix that do cross suture/mid lines, Tx: not necessary)
    - Subdural and Subarachnoid Hemorrhage (2/2 delivery trauma)
    - Craniotabes (skull feels like "plastic bottle" that you are squeezing b/c it is compressible, benign 2/2 poor calcification if isolated or syphilis if diffuse)
    - No Redundant Neck Skin
- Eyes
    - Vision Screening Q1-2yrs from 3-16yo w/ regular test
    - Red Reflex
        - Normal: Symmetric Red/Yellow
        - Abnormal: Asymmetry White aka "leukocoria"
            - Congenital Cataracts 2/2 Rubella, Inherited Metabolic Disorder esp Galactosemia, etc
            - Glaucoma 2/2 Hereditary, etc, S/S: conjuctival injection, excessive lacrimation, light sensitivity, blepharospasm, corneal clouding
            - Retinal Pathology (Retinoblastoma or Retinal Detachment/Hemorrhage seen in Shaken Baby Syndrome)
    - Conjuctivitis
        - Chemical: eye gtts use to prevent infections below may cause non-purulent inflammation 6-12hr after giving gtts and resolving in 48hr
        - Gonorrhea: +Sx in mother, severe purulent inflammation 2-5d after birth, Tx w/ topical erythromycin + IV ceftriaxone, usually infants are given prophylactic erythromycin eye gtts
        - Chlamydia: -Sx in mother, mild purulent inflammation 5-14d after birth, Tx w/ PO erythromycin, no prophylaxis available
        - Usual adult causes including infectious (bacteria/viral)
    - Strabismus aka "Lazy Eye" usually deviating inward, nl 0-3mo but after 3mo you need to Tx b/c if not then it will cause amblyopia aka blindness and neural tissue linked with bad eye will not develop
    - Retinopathy of Prematurity (ROP) RFs: prematurity, Mech: HYPERoxia induced vasospasm and endothelial damage in retinal vessels
    - Other: Anirida 2/2 Wilms Tumor, Eye Width > Width b/t Eyes 2/2 Congenital Syndromes, Scleral Hemorrhage 2/2 abuse, Blue Sclerea 2/2 Osteogenesis Imperfecta, Sun-Setting Sign 2/2 Hydrocephalus
- Ears
    - Hearing Screen at birth w/ Brainstem Auditory Evoked Response Test and then Q1-2yrs from 4-16yo w/ regular test
    - Acquired Hearing Loss 2/2 Meningitis or Chronic Otitis Media
    - Malformed
    - Low Set Ears (superior attachment of auricle to scalp must be higher than eyelid)
    - Canal Patency by pulling ear down (NOT up and back as in adults)
    - Skin Tags, Dimpling, Pits
- Nose
    - Babies are often nose breathers therefore assess patency of each nostril by covering and seeing if other steams up your pen
    - Nasopharyngeal Angiofibroma (unprovoked epistaxis in adolescent boys)
    - Choanal Atresia
        - Definition: uni or bi separation of nose and pharynx by a membrane or bony septum
        - Sx: variable respiratory distress depending on how well baby can mouth breath but most babies are nose breathers (dyspnea/cyanosis improves while crying but worsens while feeding) can be life threatening
        - Dx: inability to pass catheter through nostril, CT
        - Tx: temporary trach or intubation followed by surgery
        - NB: 50% of choanal atresia babies have the CHARGE Syndrome (C = Coloboma, H = Heart Defects, A = Atresia of Chonae, R = Retarded Growth, G = Genital Anomalies, E = Ear Defects)
- Mouth
    - Teeth: 1° 8mo-2yo, 2° 7-8yo w/ Dentist Appt Q1yr >3yo, Fluoride found in tap water
    - Epstein's Pearls (b/t soft/hard palate)
    - Bohn's Nodules (on gumline)
    - Epulis
    - Cleft Lip with/without Cleft Palate (2M:1F, Asian, more than 50 syndromes)
    - Large Tongue (HypoTH, Down's, Beckwith-Wiedmann)
    - Isolated Cleft Palate (1M:2F)

        - Pierre-Robin Sequence (micrognathia causes cleft palate)
        - Stickler Syndrome
        - Deletion 22q11
        - Treacher Collins Syndrome
- Neck
    - Micrognathia
    - Goiter
    - Cystic Hygroma
    - Brachial Cleft Cyst
    - Thyroglossal Duct Cyst
    - Webbing
    - Sinuses
    - Torticollis (shortening of SCM 2/2 (1) delivery trauma, (2) mass, (3) rotatory subluxation of upper cervical spine resulting in mandible turned to opposite side and tilted up (Tx: PT, warm soaks, analgesics, NSAIDs, cervical collar)
    - Opisthotonis (extension of neck/back 2/2 kernicterus, meningitis, cerebral palsy, fetal alcohol syndrome)
- Pulmonary
    - **Respiratory Distress Syndrome (RDS) aka Hyaline Membrane Disease**
        - Etiology: preterm infants who have not made enough surfactant (<32wks gestation)
        - Mechanism: resp distress → high oxygen (toxic) and mechanical ventilation (barotrauma) given → in preterm infants capillaries are destroyed b/c the lungs are not mature enough to handle the insult → hyaline membrane formation (composed of protein and sloughed off epithelium) → pt worsens over the first 2d → type II alveolar cells repopulate → surfactant production increases → pt gets better
        - CXR: groundglass appearance w/ air bronchograms
        - Tx: oxygen, unique types of mechanical ventilation, exogenous surfactant therapy
        - Prophylaxis: steroids given 48hrs before delivery if preterm delivery can be delayed
    - **Bronchopulmonary Dysplasia aka Wilson-Mikity Syndrome**
        - Etiology: occurs when oxygen is needed for >28d (therefore is often seen in RDS pts which require oxygen or any infant that has lung injury therefore NOT JUST RDS)
        - Mechanism: smooth muscle hypertrophy and squamous metaplasia of small airways resulting in atelectasis and emphysema ("necrotizing bronchiolitis")
        - CXR: acute (total opacification) late (thickened fibrotic markings and cystic changes)
        - Tx: oxygen, steroids, bronchodilators, diuretics
        - Prognosis: usually require therapy for 6-12mos but usually normal lung fxn by 5yo
    - **Meconium Aspiration Syndrome**
        - Mechanism: postterm infants or SGA infants 2/2 IUGR → placental insufficiency → fetal hypoxia → vagal reflex → passage meconium into amniotic fluid → fluid is swallowed normally during gestation → at birth the infant initiates breathing → intake contaminated amniotic fluid → asphyxia → lung damage
        - CXR: diffuse infiltrates w/ hyperinflation
        - Tx: remove fluid before infant takes first breath by suctioning before delivery of thorax and again when infant is on bed warmer
    - **Laryngomalacia** (most common cause of stridor in infants, begins with first month of life, accentuated with increased ventilation from for example crying, etc. or URTI, resolved by 1yr, Larynx is disproportionally small and supporting structures are abnormally soft, Tx: No tx necessary except if FTT then laser therapy or tracheostomy, DDx: bronchomalacia, subglottic stenosis, vocal cord paralysis, bronchogenic cysts, vascular rings)
    - **Vascular Rings** (stridor, opisthotonic position to decrease airway collapse, congenital anomalies of aortic arch or branches creating a ring around airway, Tx: surgery)
    - **Apnea** (Central (premature, medications, infections, anemia, arrhythmias, seizures, GER, hypoglycemia) vs Obstructive (macroglossia, enlarged tonsils, laryngospams, cleft lip, achondroplasia))
    - **Pneumonia** 2/2 aspiration of infected amniotic fluid or maternal bacteremia which crosses placenta and spreads to lung
    - **Pneumothorax** 2/2 sporadic or iatrogenic from mechanical ventilation
    - **Pulmonary Hypoplasia** 2/2 oligohydramnios (dysfunctional kidneys) or intrathoracic space-occupying lesion (diaphragmatic hernia, tumor, etc) w/ CXR showing bilateral small lungs, pneumothorax, pleural effusion
    - **Diaphragmatic Hernia**
    - **Congenital Lobar Emphysema** (CXR: early (dense, opaque overinflated area of lung) late (hyperlucency))
    - **Persistence of Fetal Circulation** (infant experienced hypoxia in utero resulting in failure of pulmonary vascular resistance to fall after postnatal lung expansion and oxygenation, normal CXR, Tx: oxygen, ventilation, bicarb, NO (pulmonary vasodilator), eventually ECMO (b/c mortality is very high)
    - **Transient Tachypnea of the Newborn** (2/2 decreased lymphatic absorption of fetal lung fluid from alveoli and interstitium, RFs: CS (the normal labor and vaginal delivery process triggers reabsorption of lung fluid

therefore during periods of no labor aka scheduled deliveries and abnormal deliveries aka CS the trigger for reabsorption is not there), CXR: Bilateral Perihilar Streaky Infiltrates w/ Pleural Effusions, Tx: supportive)
    - **Supranumery Nipples** (ranges from a flat pigmented mark to a full nipple, along mammary line from axilla to groin, not concerning unless large and in females and thus could develop into a noticeable breast during puberty)
    - **Cystic Fibrosis**
- Cardiovascular
    - **Epidemiology**: General risk is 1% (not including MVP and bicuspid AV with a prevalence of 5% and 3% respectively because they do not become clinically significant until 30-60 years old), increases to 4% if prior child had CHD, 85% of infants born with CHD reach adulthood esp ASD, PFO, VSD, PDA, and Coarctation, Proportion: **30% VSD, 10% ASD, 10% PDA, 7% Coarctation of Aorta, 7% Pulmonic Stenosis, (rest are <5%)** In most cases the etiology of CHDs cannot be determined and thus are considered sporadic but some environmental insults, genetic defects, and maternal RFs are known (TORCH infection, radiation, fetal alcohol syndrome, various chemicals, various genetic syndromes)
    - **Normal Developmental Anatomy & Physiology**: During the <u>first month</u> of gestation, the **primitive, straight cardiac tube** is formed. It develops constrictions that divide it into several segments consisting of the (a) **sinuatrium (pink)**, (b) **primitive ventricle (bottom purple/orange)**, (c) **bulbus cordis (top purple/yellow)**, and (d) **truncus arteriosus (green)**. In the <u>second month</u> of gestation, the tube elongates. Because it is fixed at both ends, it bends on itself as it elongates, forming an **"S" shape**. The bulbus cordis and the primitive ventricle are displaced anteriorly and to the right, whereas the sinuatrium is displaced posteriorly to lie behind the ventricles. The **two atria** develop from the sinuatrium. The bulbus cordis expands to become the **right ventricle** while the primitive ventricle expands to become the **left ventricle**. Simultaneously, cephalic growth of the main ventricular septum occurs. The truncus arteriosus is partitioned into **aortic and pulmonary artery**. The primitive sinuatrium is separated into right and left atria by the caudal growth of tissue from its roof (the **septum primum**) toward the **endocardial cushions**. The hole that exists before the septum primum and endocardial cushion fuse is called the **ostium primum**. Several perforations develop in the superior portion of the septum primum as it fuses with the endocardial cushion. These perforations coalesce to form the **ostium secundum.** After the septum primum fuses with endocardial cushions, another septum (**septum secundum**) arises from the superior wall of the right atrium and grows down toward the endocardial cushions. It never reaches the endocardial cushions to fuse with them, but it usually extends far enough caudally to cover the ostium secundum. Its lower margin with the endocardial cushions form the **foramen ovale**. Gas exchange occurs at the placenta with oxygenated blood passing into a single umbilical vein that then feeds into the ductus venosus and finally into the IVC. When oxygenated blood from IVC enters the R atrium its vector directs it into the L atrium through the foramen ovale it then travels through the aorta supplying the coronary, R brachiocephalic, L carotid, and L subclavian arteries supplying the upper body with oxygen rich blood. When deoxygenated blood from the SVC enters the R atrium its vector directs it into the R ventricle through the tricuspid valve it then travels through the pulmonary arteries and ductus arteriosus (distal to the three branches off the arch of the aorta) mixing with the remaining oxygenated blood supplying arteries of the lower body while also feeding into two umbilical arteries which reach the placenta. Blood does not perfuse the lungs b/c pulmonary vascular resistance is higher than systemic vascular resistance in the fetus. This is due to the fact that vessels in the lung behave differently than any other vessels in the body. In the presence of low oxygen content in the alveoli the pulmonary vessels constrict. At birth, the placenta is eliminated from the circulation thereby doubling the systemic vascular resistance by virtue of loss of vessels. In addition, when the neonate initiates respiration, the lungs expand increasing oxygen content and thus decreasing pulmonary vascular resistance (quickly during the first 24hrs and then slowly to adult levels after 6wks) resulting in an increase in pulmonary blood flow. With the large increase in pulmonary blood flow, the volume of blood returning from the pulmonary veins to the left atrium is increased, displacing the septum primum against the septum secundum to close the foramen ovale forming the fossa ovalis. Finally, increased arterial oxygenation and decreasing PGE_2 stimulates functional closure of the patent ductus arteriosus by 18-24 hours after birth with complete anatomic closure 2/2 fibrosis forming the ligamentum arteriosum in 2-10 weeks.





- **Malrotations**
- **Malrotations**
  - Situs Solitus (L-cardia = all chambers of heart are in normal position with apex of heart to left (normal) and ab organs in correct orientation (normal))
  - Situs Inversus (D-cardia = all chambers of heart are in mirror image orientation with apex of heart to right (abnormal) and ab organs in mirror image orientation with liver on L side (abnormal))
  - Situs Ambiguous (unknown-cardia = unable to determine which chamber is which (abnormal) and ab organs in unknown orientation aka heterotaxia (liver is midline w/o a dominant lobe while the two sides of the body are both right aka asplenia syndrome or both left aka polysplenia syndrome) (abnormal))
- **Obstructions**
  - Coarctation of Aorta (refer)
- **Shunts**
  - **<u>R-to-L Shunt</u> ("The Five T's") occurs when blood from the right heart enters the systemic circulation without being oxygenated by the lungs** resulting in an abnormal decrease in oxygen content or saturation of blood in the chamber into which shunting occurs thus **resulting in central cyanosis and digital clubbing of the patient.** These pts interestingly also get scoliosis, arthropathy/arthritis, gallstones, pulmonary hemorrhage, renal insufficiency, hyperviscosity syndrome, etc
    - **T**etralogy of Fallot (TOF)
      - Epidemiology: **most common cyanotic CHD in children who survive infancy period (2-6mo)**
      - Four Anomalies: **RVOTO + RVH + VSD + Overriding Aortic** (not clinically significant)
      - S/S: balance b/t **FTT** (b/c of ? overall CO is decreased) and **cyanosis** (b/c of RVOTO blood shunts across VSD to LV hence cyanosis)
      - NB common presentation if cyanotic is the "**Tet Spell**": pt has a precipitating event (anger, stress, hot bath, fever, exercise, etc) which leads to increased sympathetic state and increase in CO but instead of increased blood going through a fixed RVOTO it goes thru VSD resulting in cyanosis, eventually, the child realizes this and increases systemic resistance by squatting so as to prevent this R-to-L shunt.
      - Murmur: systolic (LUSB)
      - CXR: **"boot shaped heart", decreased pulmonary markings, enlarged right aortic arch (b/c it is overriding**)
      - Tx: **VSD closure** and **shunt b/t RV and pulmonary arteries to bypass RVOTO**
    - **T**ransposition of the Great Vessels
      - Epidemiology: **most common cyanotic CHD in children who survive neonatal period (0-2mo)**
      - Anomaly: primitive heart loops to L instead of R resulting in an anterior aorta originating from RV and a posterior pulmonary artery originating from LV resulting in two **PARALLEL circulation systems**
      - S/S: it all depends on the degree of **mixing via VSD, ASD, or PDA** (each subsequent one has less mixing) therefore pts w/ VSDs have late mild cyanosis while those w/ PDAs only have early severe cyanosis
      - Murmur: ?

- CXR: **"egg on a string"**
- Tx: if pt has good mixing then go straight to **non-emergent vessel switch operation** but if mixing is poor then temporarily g**ive PGE1 to keep PDA patent** and perform emergent Balloon Atrial Septostomy (BAS) to increase mixing until vessel switch operation can be performed

- **T**runcus Arteriosus
  - Epidemiology: **second most common cyanotic CHD in children who survive neonatal period (0-2mo)**
  - Anomaly: a **single arterial trunk emerges from BOTH ventricles** overridding a VSD and supplying the coronary, pulmonary, systemic circulations
  - S/S: balance b/t **FTT** (when pulmonary vasculature resistance < systemic vasculature resistance) and **cyanosis** (when pulmonary vasculature resistance > systemic vasculature resistance)
  - Murmur: ?
  - CXR: CM and **increased pulmonary vascular markings**
  - Tx: VSD is closed leaving valve on LV side and pulmonary arteries are freed from trunk and connected to RV
- **T**ricuspid Atresia
  - Epidemiology: **cyanosis immediately at birth**
  - Anomaly: **essentially the RA does not connect w/ RV**
  - S/S: ?
  - Murmur: ?
  - CXR: ?
  - Tx: ?
- **T**otal Anomalous Pulmonary Venous Connection
  - Epidemiology:
  - Anomaly: **no connection b/t pulmonary veins and LA rather they drain into SVC (50%), IVC (20%), RA (20%), other (10%) and thus ASD is needed for blood to enter systemic circulation**
  - S/S: mild FTT, recurrent LRTIs, tachypnea but if the ASD is small the cyanosis can occur
  - Murmur: ?
  - CXR: "snowman or figure "
  - Tx: ?
- Hypoplastic Left Heart Syndrome (HLHS)
  - Epidemiology: cyanosis immediately at birth
  - Anomaly: **essentially the left side of the heart is non-functional therefore the only way for blood to enter the systemic circulation is thru the PDA, when blood leaves lungs and enters in LA it crosses over ASD to RA**
  - S/S: FTT
  - Murmur: ?
  - CXR: CM and increased pulmonary vascular markings
  - Tx: surgical correction is almost impossible so this becomes an ethical issue when surgery is attempted, transplant is the only reasonable option

- **<u>L-to-R Shunt</u>** ("The Four D's") **occurs when blood from the left heart enters the pulmonary circulation** resulting in an abnormal increase in the oxygen content or saturation of blood in the chamber into which shunting occurs
- NB However later on **shunt reversal occurs turning the L-to-R Shunt to a R-to-L Shunt resulting in <u>late cyanosis</u> --- a phenomenon known as the <u>Eisenmenger Reaction</u>**. If the defect is large and the left-to-right shunting is sustained over months to years, exposure of the pulmonary vasculature to systemic arterial pressure and/or increased blood flow leads to progressive pulmonary HTN eventually followed by obliteration of pulmonary arterioles and capillaries and increased pulmonary vascular resistance. Finally, pulmonary vascular resistance approaches systemic vascular resistance, reversal of the shunt occurs and late cyanosis occurs. In the patient with a moderate or large left-to-right intracardiac shunt, surgery to correct the intracardiac defect should be performed prior to the development of the Eisenmenger reaction, as this condition is permanent and irreversible. The only therapeutic approach is total lung and heart transplant. In the patient with congenital heart disease and Eisenmenger syndrome, a number of other complications may arise. The ratio of the flows in the pulmonary to systemic circulations (Qp/Qs) is calculated; if the flow is > 1.5:1, the defect should be closed b/c of high risk of Eisenmenger Reaction.
  - A**SD**
    - Epidemiology: 50% of all CHDs have also ASDs as one of the defects, the most common CHD in adults
    - Anomaly: Primum Defect, Secundum Defect (most common), Sinus Venosus Defect, Patent Foramen Ovale (PFO) normally closes when increased LA pressures causes the septum to press against each other, in some pts there is

not enough tissue to cover foramen and it remains patent which is seen in 25% of the adult population!!!, usually asymptomatic except when at allows paradoxic embolization resulting in cryptogenic strokes and if this occurs then Tx is similar to ASD
    - S/S: usually asymptomatic until adulthood, there is flow of **blood from LA to RA** 2/2 pressure gradient thus there is increased pulmonary blood flow resulting in RVH and **sometimes Eisenmenger's**, in adults S/S of R-CHF, AFib and pulmonary HTN results
    - Murmur: usually **NO murmur** just a **widely split S2** but sometimes diastolic murmur from TR or systolic murmur from increased pulmonary flow
    - CXR: RVH, **increased pulmonary vascular markings**
    - EKG: **R**AE, RVH, RAD, RBBB
    - Tx: 90**% will close (esp if <3mm) vs 10% will NOT close (esp if >8mm) and will persist into adulthood at which point if found then catheter closure w/ an umbrella device should be attempted if pt is symptomatic or there is significant L-to-R shunt and R sided volume overload**
- VS**D**
    - Epidemiology: the **most common** CHD in children, especially seen in Fetal Alcohol Syndrome, TORCH, Down's Syndrome, Cri-du-Chat, Trisomy 13/18, Apert's Syndrome
    - Anomaly: Membranous or Muscular
    - S/S: asymptomatic if small vs **FTT & pulmonary HTN if large**
    - Murmur: **holosystolic @ LLSB (the smaller the defect the louder the murmur)**
    - CXR: CM, increased pulmonary vascular markings
    - Tx: **50% will close on own (esp if muscular) vs 50% will NOT close (esp if membranous) and will require Tx (diuretics, digitalis, surgical closure) if Sx**
- P**D**A
    - Epidemiology: **usually disappears during the first 12hrs of life, stays open in Rubella or high altitude**
    - Anomaly: patency of ductus arteriosus
    - S/S: **asymptomatic if small vs wide pulse pressure, bounding peripheral pulses, CHF, lower extremity clubbing, and IE if large**
    - Murmur: **continuous "machine-like" murmur @ ULSB**
    - CXR:
    - Tx: **close w/ indomethacin (PGE2 antagonist) in infants and if fails or child then coil and if fails or adult then surgery**
- AVS**D** (Subendocardial Cushion Defect w/ **no true separation of A/V and L/R**)
- Ebstein's Anomaly
    - Anomaly: **TV is displaced into the RV, TV leaflets are redundant and plastered against RV wall causing physiologic pulmonary stenosis, RA is gigantic**
    - S/S: variable
    - Murmur: systolic murmur at LLSB w/ quadruple gallop
    - CXR: "balloon shaped wall-to-wall heart"
    - Tx: Glenn Procedure (TVR and RA reduction)

- Renal
    - Masses: **Wilm's/Neuroblastoma**
    - **Fetal Olig-/An-uria → Oligohydramnios → Pulmonary Hypoplasia**
    - **Renal Hypoplasia** (too little normal parenchyma) or **Dysplasia** (disorganized parenchyma containing nonrenal tissue 2/2 urinary tract obstruction) usually progress to ESRD in mid childhood
    - **Horseshoe Kidney** (1:400, M>F, midline fusion of lower kidney poles, this kidney is caught by the inferior mesenteric artery during development, 7% are associated with Turner's, pt are 4x more likely to develop Wilm's)
    - **Alport's Syndrome aka Hereditary Nephritis (AR) / Thin BM Disease aka Benign Familial Hematuria (AR)** (refer)
    - **Thin Basement Membrane Dz aka Benign Familial Hematuria (AR)** (refer)
    - **Fanconi's/Cystinosis/Hartnup's/Bartter's/Gitelman's Syndrome (AR)** (refer)
    - **Nephrogenic DI (X-linked)** (refer)
    - **Fabry's (X-linked)** (refer)
    - **Infantile Polycystic Kidney Disease** (refer)
- EndoGU
    - Male (circumcision, testicle = size of green pea, cryptochordism, hypo/epispadias, micropenis (<2cm), indirect inguinal hernia)

- Female (Vaginal Tags, Bleeding 2/2 maternal estrogen withdrawal and resolves w/in a few days, vaginitis is usually non-specific and resolves on own but look for foreign objects or sexual abuse or Candida w/ undx T1DM)
- Ambiguous Genitalia (refer to gyn notes)
- Sex Chromosomal Abnormalities (refer to gyn notes)
- Premature/Delayed Puberty (refer to gyn notes)

- MS/Rheum
  - CTD (refer)
    - Seropositive**: Juvenile Rheumatoid Arthritis**
    - Seronegative**: Ankylosing Spondylitis, Reactive Arthritis**
    - Vasculitis**: Henoch-Schonlein Purpura, Kawasaki's, Beurger's, Behcet's**
    - Other: **Ehlers Danlos Syndrome, Marfan's Syndrome**
  - Muscle (refer)
    - **Duchenne/Becker Muscular Dystrophy**
    - **Mitochondrial Myopathy**
    - **Myoclonic Myopathy**
  - Bone (refer)
    - Organic: **Scurvy, Osteogenesis Imperfecta**
    - Inorganic: **Ricket's, Osteopetrosis**
    - NB Pediatric Fractures
      - Growth Plate Fracture (Salter-Harris Classification)
      - Greenstick Fracture (b/c the bone is not brittle like in adult the bone does not fracture with energy but bows/bends with only incomplete fracture of cortex)
  - Back
    - **Scoliosis** >10° curvature usually R thoracic, 80% idiopathic (prepubertal female), usually asymptomatic unless >90° where cardio-pulmonary dysfxn can occur, Dx: see curvature when pt stands and touches toes, Tx: <40° Milwaukee/Boston Brace vs >40° rod fixation surgery
  - Hip
    - **Congenital Hip Dysplasia (CHD) at birth**
      - Definition: abnormal growth and development of hip resulting in abnl relationship b/t proximal femur and acetabulum
      - RFs (general risk 1/1000): 1° Female, Breech Presentation, First Born, 2° FHx, Foot Deformities, Congenital Torticollis, Down Syndrome
      - Dx
        - Newborn: 1st Barlow Maneuver (flex hip and knee of both legs, stabilize one hip, cup hand around hip of other leg, adduct, push posteriorly to see if you can dislocate hip, if it does you should feel it on your hand) 2nd Ortalani Maneuver (after Barlow Maneuver if you suspect that hip is dislocated, abduct, pull anteriorly to see if you can relocate hip, if it does you should feel it on your hand or hear a "clunk" vs. "click" which is a normal sound) 3rd Repeat on Other Leg, 4th Asymmetric Thigh Creases
        - 3-6mo: Galeazzi Sign (when hip and knee flexed the knee of the affected leg is lower), Allis Sign (when legs are extended the leg of then affected hip is shorter b/c it is posterior and superior)
        - 12mo: Trendelenburg Sign (painless limp and lurch to the affected side with ambulation, when the child stands on the affected leg there is a dip of the pelvis on the opposite side due to a weakness of the gluteus medius muscle, if bilateral the pt has a waddling gait)
      - Tx: 0-6mo: Pavlik Harness (flexes and abducts hip), 6mo-3yrs: closed or open reduction, >3yrs: surgery
    - **Legg-Calve-Perthes (LCP) at 5-10yo**
      - Definition: idiopathic AVN of femoral head
      - RFs: white, male, hypoTH, bleeding diathesis
      - S/S: decreased hip ROM, painless limp, often complain of knee pain but pain reproduced w/ passive internal rotation and extension of hip
      - Tx: orthoses
    - **Slipped Capital Femoral Epiphysis (SCFE) at 10-15yo**
      - Definition: fx of femoral growth plate
      - RFs: AA, male, overweight, hypogonadism
      - S/S: similar to LCP
      - Tx: surgical pinning
  - Anterior Knee
    - **Patellar Subluxation** (seen in teenage girls)

        - **Sindig-Larsen-Johansson Syndrome aka Jumper's Knee aka Patellar Tendonitis** (seen in teenage boys who have recently gone through a growth spurt, pain at distal pole of patella where the patellar tendon originates, Tx: conservative)
        - **Osgood-Schlatter Disease aka Tibial Apophysitis** (seen in teenage boys who have recently gone through a growth spurt, self-limiting micro fractures to bilateral tibial tubersity 2/2 quadricep overuse 2/2 jumping resulting in chronic pain esp w/ squatting, walking up/down stairs, jumping, etc, PEx: inflamed tibial tuberosity, Tx: conservative)
        - **Osteochondritis Dissecans** (degeneration and recalcification of articular cartilage and underlying bone esp of the medial femoral condyle, chronic pain w/ morning stiffness and recurrent effusions, Xray: osteochondritis and loose bodies in knee joint)
        - NB always consider hip pathology as it can be referred down to the knee
    - Hand/Feet
        - **Polydactyly**
        - **Flexion Contractures**
        - **Club Feet** 2/2 Intrauterine Problems
        - **Unusual Creases**: Palmer (Many vs. One ("Simian Crease")) vs Planter (Creases across 1/4,1/3,1/2 or whole plantar surface)
- Oncology
    - Ectoderm Derived Tumors
        - **Posterior Fossa Brain Tumors**
        - **Retinoblastoma** (unilateral leukoria or exophthalmos)
        - **NF**
    - Endoderm Derived Tumors (rare)
    - Mesoderm Derived Tumors
        - **Germ Cell Tumors**
        - **ALL/HL**
        - **Sarcomas**
        - **Wilm's vs Neuroblastoma**
- Pysch
    - MR: Down's, FAS, Fragile-X
    - Autism
    - Learning Disorder: ADHD
    - Conduct Disorder: Conduct, Oppositional-Defiant, Tourette
    - Eating Disorder: Anorexia/Bulemia
    - Encopresis/Enuresis
- Neuro
    - **Interventricular Hemorrhage (IVH)** RFs: prematurity, Sx: most asymp, lethargy, poor suck, high pitched cry, bulging fontanelle, Dx: cranial US thru ant fontanelle, Tx: VP shunt
    - **Cerebral Palsy** ("white matter damage") aka Static Encephalopathy
        - Non progressive static spasticity w/ NO cognitive impairment or epilepsy
        - Usually lower > upper extremities affected
        - DOE
        - Etiology unknown (very few 2/2 hypoxic insult)
        - RFs: maternal MR, breech, LBW
    - Neural Tube Defects b/c low folate
        - **Spina Bifida Occulta** (pilonidal dimple w/ tuft of triangular patch of hair over lumbar region)
        - **Spina Bifida w/ meningocele or myelomeningocele**
    - Floppy Baby
        - **Werdnig-Hoffman Syndrome** (AR degeneration of anterior horn cells in spinal cord, hypotonic at birth, Tx supportive)
        - **Infant Botulism** (acquired sudden onset of hypotonia after exposure to honey or canned foods)
    - Plexopathy
        - Upper Brachial Plexopathy (**Erb-Duchenne's**) "Erb the Waiter"
            - 5^{th} and 6^{th} cervical nerves = adducted and internally rotated arm "tip the waiter"
            - more common in normal presentation b/c shoulders pulled down
            - 80% resolve
        - Lower Brachial Plexopathy (**Klumpke's**) "The Klumpke Krab"
            - 7^{th} and 8^{th} cervical and 1^{st} thoracic nerves = paralyzed hand into grasping position "claw"
            - often also have Horner's Syndrome also
            - more common in breech presentation b/c shoulders pulled up
            - 80% resolve
    - Neurocutanous Syndromes
        - Neurofibromatosis
            - Etiology: AD, two types

- S/S: café au lait spots, neurofibromas, CNS tumors (optic gliomas, meningiomas), axillary/inguinal freckling, Lisch nodules aka iris hamartomas, sphenoid dysplasia, thinning of long bone cortices, renal artery stenosis, pheo

- Tuberous Sclerosis
  - Etiology: AD mutation of TSC1/2 genes
  - Mech: proliferation of atypical astrocytes
  - S/S: seizures + mental retardation + skin lesions (facial angiomas, shagreen patch, ash leaf spot) + other (renal angiomyolipomas, heart rhabdomyomas
- Sturge-Weber Syndrome (refer)
- Von Hippel Lindau Syndrome (refer)

o Seizures

- Other: Infection, Pregnancy Complications, Birth Complications, Congenital Malformations (cortical dysgenesis), Neurocutaneous Syndromes, Congenital Metabolic Disorder (eg. PKU, VitB6 deficiency), FHx
- **Infantile Spasm (West Syndrome)**
  - Pt: <1yo male, +FHx
  - Sx: flexion of neck/head w/ extension of arms, arrest of psychomotor development at age of seizure onset, mental retardation
  - EEG: "Hypsarrhythmia" (chaotic high voltage bilateral asynchronous slow wave activity)
  - Prognosis: poor w/ severe MR
  - Tx: ACTH (b/c seizures are 2/2 to increased CRH and thus if you give ACTH it feedback inhibits) and generalized AEDs
  - Etiology: 50% cryptogenic vs 50% clear etiology (esp Tuberous Sclerosis)
- **Febrile Seizure**
  - Pt: 1-3yo, +FHx
  - Sx: single brief tonic clonic seizure, correlate with rate of increase in temperature and thus occurs during the first 24hrs, no effect on intelligence
  - EEG: nothing specific
  - Prognosis: 3% of all children get febrile seizures w/ recurrence of 30% but risk of developing epilepsy is low (2%)
  - Tx: no AED needed, antipyretics not that effective but often given, just look for source of fever specifically infection (usually Roseola, Shigella, AOM, meningitis) or hypoNa, if long seizure begin status Tx, LP always if <1yo but variable if >1yo
- **Lennox-Gastaut**
  - Pt: 3-4yo
  - Sx: tonic-clonic seizures, mental dysfxn
  - EEG: 1-2Hz Spike & Slow Wave Complex
  - Prognosis:
  - Tx: ketotic diet, vagal stimulation
- **Benign Focal Epilepsy of Childhood (BFEC) aka Benign Rolandic Epilepsy**
  - Pt: 4-10yo
  - Sx: occur during sleep, includes face/pharynx/arms, drool
  - EEG: "Rolandic Spikes"
  - Prognosis: almost all resolve by 16yo
  - Tx:
- **Absence (Petit Mal) Idiopathic or AR**
  - Pt: 4-10yo girls
  - Sx: must differentiate from complex partial and day dreaming, many (~75x/d) short (~3sec) episodes where pt looks like she is day dreaming, staring, etc w/ no motor/sensory changes, b/c LOC they do not remember a thing, precipitated by hyperventilation
  - EEG: 3Hz Spike & Slow-Wave Complexes
  - NB consider if child is having school problems, 60% resolve by adolescence
- **Mesial Temporal Sclerosis (MTS)**
  - Pt: young adults
  - Sx: sclerosis at hippocampus results in complex partial seizures (consider in a pt with intractable complex partial seizures b/c you can surgically intervene)
  - EEG:
  - Prognosis:
  - Tx: temporal lobectomy
  - Complication: superior quadrant-anopsia (obviously)
- **Benign Juvenile Myoclonic Epilepsy (BJME)**
  - Pt: teenager

- Sx: any type of seizure but 1/2 of pts also have tonic-clonic seizures, often triggered by flashing lights or loud sounds
- EEG: Polyspike & Slow Wave Complex
- Prognosis:
- Tx:

o Reflexes

Reflex	Test	Response	Timing
Moro	Support head and shoulders 30 above horizontal then allow head to drop to horizontal	Arms extend up	Onset: 28wks GA Lasts: 6mo
Asymmetric Tonic Neck	Lay infant supine and rotate to left or right	Arms and leg extend up on face side while arms and legs flex down on occipital side	Onset: 37wks GA Lasts: 6mo
Parachute	Support infant in vertical position and then tip upper body downward	Arms extend out	Onset: 8mos Lasts: forever
Sucking	Place finger in mouth	Sucking	Onset: 37wksGA Lasts: NA
Rooting	Draw finger across side of mouth	Head turns to finger	Onset: 37wks Lasts: 3mo
Grasping	Place finger in palm/sole	Hand/Foot grasps finger	Onset: 20wks Lasts: 4-5mo
Placing	Support infant in vertical position and then touch dorsum of foot	Foot moves down and touches surface	Onset: 37wks Lasts: NA
Babinski	Stimulating plantar aspect by drawing reflex hammer edge along lateral side and then across ball of feet	Positive/Nl Newborn/Abnl Adult: big toe extends up and small toes fan out Negative: all toes flex down	

Genetics

General Genetics

- Definitions
  - **Genomics**: all genes and their interactions vs **Proteomics** – study of proteins and protein expression
  - **Congenital**: means "born with"; Can be non-genetic (congenital syphilis) or genetic (Fragile X Syndrome) vs **Hereditary** – derived from one's parents and transmitted through the germ line and therefore familial
  - **Dysmorphisms**: an abnormality in structure
    - **Malformations**: poor tissue formation
    - **Deformations**: tissue formed well but is abnormal because of outside mechanical forces
    - **Disruptions**: tissue destroyed
  - **Mutations**
    - **Missense**: that alters the meaning of the genetic code by changing an aa
      - **Conservative**: aa substitution causes little change in the protein function
      - **Non-Conservative**: substitution replaced the normal aa w/ a very different one, eg. SCD
    - **Frameshift**: alterations in the reading frame (deletion or insertions), eg ABO locus, Tay-Sachs
    - **Nonsense**: change of the a.a. to a chain terminator (stop codon), eg B-thalessemia
    - NOTE the above mutations concern exons but mutations of introns also have deleterious effects because they include promoters, enhancer sequences, etc. therefore affect TF binding; introns themselves can also influence splicing
- Prenatal Diagnosis
  - **Maternal Serum Triple Screen** (AFP, Estriol, bHCG) @ 15-17wks, High AFP: neural tube defect vs Low AFP: Down Syndrome
  - **Fetal US**: @ ?, offered when there is a r/o structural fetal anomalies or growth abnormalities
  - **Amniocentesis** @ 16wks, offered to high risk pts, needle inserted into amniotic cavity and ~30mL of amniotic fluid is removed and sloughed cells from fetus are examined for fetal chromosome anomalies, mutations, biochemical abnormalities, AFP, Complications: spontaneous labor, amniotic fluid leakage leading to labor or oligo, puncture of fetus, infection
  - **Chorionic Villus Sampling**: @ 10-12wks, catheter is placed thru cervix under US guidance or a needle is inserted transabdominally into the developing placenta where chorionic villus cells of the placenta are aspirated for chromosomal, DNA, or biochemical studies, complications: fetal loss, infection (greater than amniocentesis), advantages: performed earlier, allows mother to terminate pregnancy, less psychologically traumatic
  - **Percutaneous Umbilical Blood Sampling**: @ ?, fetal blood is obtained from umbilical cord under US guidance for chromosome analysis and biochemical study
  - **Fetoscopy**: @ ?, fiberoptic tube inserted transabdominally under US guidance into uterine cavity where the fetus is visualized and skin Bx obtained, Complications: bleeding, pregnancy loss, infection, amniotic fluid leakage
- Types of Markers/Polymorphisms
  - ***Site Polymorphisms*** **(aka Restriction Fragment Length Polymorphisms (RFLPs))**
    - if you examine DNA from two people there is a different NT every 200-500 BP; these variations can occur in non-coding regions and are phenotypically silent however these variations can also abolish or create enzyme restriction sites therefore if you digest DNA from these two people upon electrophoresis you will have slightly different bands THESE POLYMORPHISMS ARE NOT MUTATIONS JUST VARIATIONS however if a person is a carrier of mutation that person also has unique polymorphisms THEREFORE THE CHROMOSOME THAT HAS THE MUTATION CAN BE TRACKED BY THE POLYMORPHISMS ALSO ASSOCIATED WITH IT, Use in detecting autosomal recessive diseases → separate normal, carrier, and affected
  - ***Length Polymorphisms***
    - For some reason noncoding regions contain repetitive sequences that vary in the number of repeats b/t people hence length polymorphisms; there are two kinds of repetitive sequences:
      - **Microsatellites:** 2-6bp repeats that vary in number creating fragments, 0-1kb in size
      - **Minisatellites:** 15-70bp repeats that vary in number creating fragments, 1-3kb in size
    - If a person is a carrier of a mutation that person also has unique length polymorphisms THEREFORE THE CHROMOSOME THAT HAS THE MUTATION CAN BE TRACKED BY THE SATELLITES ALSO ASSOCIATED WITH IT
    - Used to track autosomal dominant disorders
- <u>MENDELIAN DISORDERS</u>
  - **Autosomal Dominant Disorders** (Vertical Transmission) – Manifested in the heterozygous state; at least one parent affected (if not then new mutation and occurs more often in germ cells of older father); both males and females equally affected and can transmit; more common is loss of function (if enzyme and heterozygote zero penetrance b/c other gene can produce sufficient amounts --- most enzymes however follow recessive inheritance) (however nonenzyme proteins are affected eg. those involved in the regulation of metabolic pathways such as LDL-R or those involved in structure such as collagen via dominant negative effect), less common is gain of function (eg. Huntington's results from an abnormal gene product that is toxic to neurons)
  - **Autosomal Recessive Disorders (Horizontal Appearance)** – Manifested in the homozygous state; trait usually does not affect parents rather siblings may show the disease w/ a 25% recurrence risk in other siblings; the mutation occurs in low frequency thus suggesting consanguinity; phenotype is uniform, complete penetrance,

onset early in life; as stated above enzyme loss of function mutations have no effect when heterozygote but when homozygote there is a problem and thus recessive; thus inborn errors of metabolism are all recessive
    - **X-linked Recessive Disorders** – affected male does not transmit to his sons but all daughters are carriers; sons of heterozygous women have a 50% risk of being affected, b/c of Lyon Hypothesis since one female X-chromosome is inactivated during embryogenesis a female could be mosaic for the X-linked recessive disorder however the severity of the disorder is always less in women than in men
    - **X-linked Dominant Disorder (rare)** – dominant disease allele on the X chromosome; affected heterozygous females transmit to half her sons and half her daughters; affected male transmits to all daughters and none of his sons
- <u>CYTOGENIC DISORDERS</u>
    - Aneuploid (a chromosome compliment that is not an exact multiple of a haploid 23) NOTE not 46 (caused non-disjunction or lag anaphase)
    - Monosomy (2n-1) usually *incompatible* with life if it involves an autosome, viable if sex chromosome
    - Trisomy (2n+1) there are many autosomal trisomies that are compatible w/life (21), viable if sex chromosome
    - Non-Disjunction – a homologous pair that fails to disjoin at the first meiotic division or two chromatids that fail to separate either at the second meiotic division or in somatic divisions
    - Anaphase Lag – one homologous chromosome in meiosis or one chromatid in mitosis lags behind and is left out of the nucleus resulting in one cell that is monosomy and the other is normal
    - Mosaicism – two or more cell lines in the same individual that arise from mitotic errors in *early development* (common in sex chromosomes i.e. 46,XX/45,X/47,XXX Turner Females)
    - Deletion – loss of a terminal (1 break) (46,XY,del(16)(p11.2)) or interstitial (2 breaks) (46,XY,del(16)(p11.2,p24.4)) segment of a chromosome *the material that is deleted out is lost*
    - Ring Chromosome - involves terminal deletions at both ends and fusion of the damaged ends (46,XY,r(14)) because it is a ring it does not behave normally during mitosis thus serious consequences
    - Inversion - rearrangement involving two breaks in the chromosome followed by inverted reincorporation; this can happen in a segment that includes centromere (pericentric) or not (paracentric) *i = include centromere*
    - Isochromosome - occurs when one arm of a chromosome is lost and the other arm is duplicated resulting in a chromosome that is 2p or 2q resulting in a trisomy and monosomy; the most common form of this is i(Xq), involving the long arm of an X resulting in trisomy of the long arm of the X and monosomy of the short arm (occurs during mitosis or meiosis II when the centromeres dissociate in the wrong direction)
    - Translocation - involves switching a segment of one chromosome with a segment from another chromosome (46,XX,t(2;5)(q31;p14)) note the semicolons in this notation
        - *Balanced Reciprocal* - exchange of chromosomal material between two chromosomes with no net gain or loss of genetic material. Phenotypically normal person, but will cause generational defects, i.e. individual who is a carrier of a balanced translocation has an increased chance of producing abnormal gametes
        - *Robertsonian (Centric) Fusion* – unbalanced reciprocal translocation between two acrocentric chromosomes involving the short arm of one (w/o centromere) and the long arm of the other (w/ centromere); transfer of segment leads to formation of one abnormally long chromosome and one short one (usually lost), but has little genetic info and not catastrophic. Phenotypically normal person, but abnormal progeny will likely result.
- <u>Sex Chromosomal Disorders (refer)</u>
- <u>Autosomal Chromosomal Disorders</u>

(1) Trisomy 21 (Down Syndrome)

a. General
    i. Most common chromosomal abnormality and retardation w/ an incidence of 1/700 such that 6000 children born in US have Down Syndrome
    ii. RFs: advanced maternal age (35yo 1/400, 40yo 1/100, 45yo 1/30) but b/c by far most infants are born to young mothers, most down syndrome infants are born to young mothers!!!
    iii. Mortality: 75% die in embryonic or fetal life, 85% survive to 1yr, 50% can be expected to live longer than 50yrs w/ congenital heart disease being the most important factor that determines survival (other: GI problems and leukemia)
    iv. Morbidity: 2/2 impaired immune system
    v. Dx: elevated AFP on Triple Screen then confirm w/ Amniocentesis Cytology

b. Type of Defect
    i. 95% have trisomy 47,XX,+21 b/c of a maternal meiotic nondisjunction
        1. Nondisjunction increases with maternal age esp when >35yo
        2. Extra 21 comes from mother rarely from father
        3. Risk of Recurrence: 1%
    ii. 4% are euoploid but have a maternal Robertsoninan translocation of the long arm of 21 with another acrocentric chromosome 13,1415,21,22 thus 46,XX,t(#q,21q)
        1. 3/4 are de novo not familial w/ Risk of Recurrence of 2%
        2. 1/4 are familial w/ Risk of Recurrence varying from 15% to 100% depending on the acrocrentric chromosome
        3. Maternal age is not an issue

iii. 1% are mosaics w/46,XX/47,XX,+21 b/c fetal mitotic nondisjunction
    1. Maternal age is not an issue
    2. Phenotype varies depending on the proportion of trisomy cells (could be just one cell line and thus affecting one system)

c. Clinical Features (*Chr21 encodes two of the three proteins needed to assemble the triple helix of collagen VI which is important in scaffolding during embryologic development of nervous tissue (thus explaining the neurologic manifestations) and connective tissue (thus explaining the multitude of dysmorphic physical features)*
    i. Growth
        1. Short Stature
        2. Obesity
        3. Premature Aging (decreased skin tone, graying/loss of hair, hypogonadism, cataracts, hearing loss, hypoTH, neoplasms, dementia)
    ii. Head
        1. Microcephaly
        2. Bradycephaly
        3. Flat Occiput
        4. Balding Scalp Hair Pattern
        5. Large Fontanels w/ Late Closure
        6. Sinus Hypoplasia
    iii. Face
        1. Flat Facial Profile
        2. Short Upslanting Palpebral Fissures, Epicanthal Folds, Brushfield Spots on Iris, Refractive Errors, Strabismus, Nystagmus, Cataracts, Conjuctivitis
        3. Flat Nasal Bridge
        4. Small Mouth w/ Prominent Protruding Tongue, Mouth Breathing w/ Drooling, Chapped Lower Lip, Angular Cheilitis, Malformed Teeth
        5. Small Retroplaced Mandible
        6. Small Ears w/ Overfolded Helix
    iv. Neck
        1. Excess Posterior Skin
    v. Cardiac *(primary cause of mortality)*
        1. AV Canal Defect
        2. Endocardial Cushion Defect
        3. A/VSD, TOF, PDA
        4. Lesions resulting in arrhythmia
    vi. GI
        1. Diastasis Recti, Umbilical Hernia
        2. Duodenal Atresia/Stenosis
        3. Hirchsprung Disease
        4. TE Fistula
        5. Omphalocele
        6. Meckel Diverticulum
        7. Imperforate Anus
    vii. Extremities
        1. Short Hands and Fingers (Brachydactyly)
        2. Incurved 5th Finger (Clinodactyly)
        3. Single Transverse Palmar Crease (Simian Crease)
        4. Wide Gap b/t 1st and 2nd Toes
    viii. GU
        1. Renal Malformations
        2. Hypospadias, Micropenis, Cryptorchidism
    ix. Neurologic
        1. Variable MR w/ Mean IQ of 50 and Range 20-85
        2. Developmental Delay
        3. Generalized Hypotonia that improves w/ age
        4. Alzheimer-like Dementia in 3rd and 4th Decade
        5. Hearing Loss
        6. Sleep Apnea
        7. Unique Personality (natural spontaneity, genuine warmth, cheerful, gentleness, patience, tolerance, stubbornness, anxiety)
        8. Psychiatric Disorders (ADHD, autism, conduct disorder, OCD, Tourettes, Depression)
        9. Seizure Disorder
    x. Skeletal
        1. Atlanto-Axial Instability resulting in variable Spinal Cord Injury (every Down pt must have a cervical spine X-ray so as to be cleared for sports)

xi. Endocrine
    1. Hypothyroidism
    2. Diabetes
    3. Infertility (only 20% of pts are fertile, no affected male is known to have fathered a child, 50% risk of having an affected child)
xii. Heme *(primary cause of morbidity)*
    1. Myeloproliferative Disorder aka "Preleukemia"
    2. Leukemia (ALL and AML)
    3. Immunodeficiency

d. Immediate Concerns (Thyroid, CV) vs. Long Term Concerns (Oncology/Immunodeficiency)
e. Management
    i. Labs: TSH, Ig, CBC, O2 Sat
    ii. Studies: X-Ray, EKG, Echo, BAER (Brainstem Auditory Evoked Response), Ophthalmic Examination
    iii. Parental Genetic Counseling (refer above)

(2) Trisomy 18 (Edward's Syndrome) very similar to Trisomy 21 w/ noted exceptions below

a. Mortality: very poor prognosis w/ 90% die w/in 1yr of birth from apnea
b. Clinical Features: similar to Down Syndrome +
    i. Micrognathia
    ii. Low Set Ears
    iii. Overlapping of 2nd finger on 3rd, 4th, and 5th finger
    iv. Fixed Finger Contractures (Camptodactyly)
    v. Lack of Interphalangeal Flexion Creases
    vi. Rocker Bottom Feat
    vii. Hypertonia
    viii. Severe MR

(3) Trisomy 13 (Patau Syndrome) very similar to Trisomy 21 w/ noted exceptions below

a. Mortality: very poor prognosis w/ 90% die w/in 1yr of birth from apnea
b. Clinical Features: similar to Down Syndrome +
    i. Failure of Telencephalon to divide into two hemispheres (Holoprosencephaly)
    ii. Open Scalp Lesion (Cutis Aplasia)
    iii. Cleft Lip and Palate
    iv. Microphthalmia
    v. Colobomata of the Eye
    vi. Polydactyly
    vii. Rocker Bottom Feet
    viii. Cystic Kidneys
    ix. Genital Malformations

(4) 22q11.2 Deletion Syndrome

a. Incidence of 1/4000 births which is quite common but often missed because clinically variable
b. Clinical Features
    i. Short Stature
    ii. Cleft Palate
    iii. Small Ears
    iv. "Squared Off" Nose Tip
    v. Malar Hypoplasia
    vi. Velocardiofacial Syndrome and Conotruncal Heart Anomaly-Face Syndrome
    vii. Long Tapering Fingers
    viii. Mild MR
    ix. Learning Disabilities, ADHD, Difficulty w/ Social Interaction, Bipolar, Psychotic
    x. DiGeorge Syndrome
        1. HypoPTH = HypoCa
        2. Thymic Aplasia = T-Cell Deficiency

(5) Cri du Chat Syndrome aka 5p Deletion Syndrome

a. Clinical Features
    i. Cat-Like Cry
    ii. MR
    iii. Congenital Heart Diseases
    iv. Ocular Malformations

<u>NON-CLASSICAL / NON-MENDELIAN INHERITANCE DISORDERS</u>

<u>Triplet Repeat Mutations</u>

- mutations characterized by amplification of a repeating sequence of three nucleotides (with the specific nucleotides varying from disorder to disorder but usually are Cs and Gs)
- normally the number of copies is small and with each meiosis there is expansion of the trinucleotide
    - mild expansion aka permutation: the expansion is not enough to cause a disorder
    - severe expansion: the expansion has surpassed a threshold causing a disorder
- expansion depends on sex of parent occurring during spermatogenesis or oogenesis
- mutations can be divided into two groups based on mechanism:
    - expansion occurs in NONCODING regions (introns) thereby suppressing protein synthesis around it (*thus loss of function*)
    - expansion occurs in CODING regions (exons) usually they are CAG repeats resulting in proteins that have polyglutamines which unfortunately give the proteins new, different functions particularly neurodegeneration (*thus gain of function*)

Disease	Gene	Locus	Protein	Repeat	Normal	Disease
Expansions Affecting Noncoding Regions						
Fragile-X syndrome	*FMR1(FRAXA)*	Xq27.3	FMR-1 protein (FMRP)	CGG	6–53	00–200 (pre) >230 (full)
Friedreich ataxia	*X25*	9q13–21.1	Frataxin	GAA	7–34	34–80 (pre) >100 (full)
Myotonic dystrophy	*DMPK*	19q13	Myotonic dystrophy protein kinase (DMPK)	CTG	5–37	50–thousands
Expansions Affecting Coding Regions						
Spinobulbar muscular atrophy (Kennedy disease)	*AR*	Xq13–21	Androgen receptor (AR)	CAG	9–36	38–62
Huntington disease	*HD*	4p16.3	Huntingtin	CAG	6–35	36–121
Dentatorubral-pallidoluysian atrophy (Haw River syndrome)	*DRPLA*	12p13.31	Atrophin-1	CAG	6–35	49–88
Spinocerebellar ataxia type 1	*SCA1*	6p23	Ataxin-1	CAG	6–44	39–82
Spinocerebellar ataxia type 2	*SCA2*	12q24.1	Ataxin 2	CAG	15 31	36 63
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	*SCA3 (MJD1)*	14q32.1	Ataxin-3	CAG	12–40	55–84
Spinocerebellar ataxia type 6	*SCA6*	19p13	α_{1A}-Voltage-dependent calcium channel subunit	CAG	4–18	21–33
Spinocerebellar ataxia type 7	*SCA7*	3p12–13	Ataxin-7	CAG	4–35	37–306

(1) Fragile-X-Syndrome

a. General
    i. Incidence of 1/1550 males and 1/8000 females
    ii. 2nd most common cause of retardation

b. Type of Defect
    i. cytogenic abnormality seen as a discontinuity of staining or as a **constriction** ("broken or fragile site") in the long arm (q28) when cells are cultured in **folate** deficient medium ("it literally looks like a random piece that just hangs off the x-chromosome)
    ii. **Familial Mental Retardation-1** (FMR-1) which has multiple tandem repeats of **CGG**
        1. **Normal: 10-55**
        2. **Premutation: 55-200 = transmitting males and carrier females**
        3. **Full Mutation: 200-4000 = affected males and females**
    iii. How? when transmitting males w/ pre-mutations pass on their X to their sons and daughters there is little expansion of the repeat BUT when carrier females w/ pre-mutations pass on their X to their sons and daughters the repeat expands primarily affecting sons (and daughters if unfavorable lionization) Why? expansion occurs during oogenesis NOT spermatogenesis

c. Clinical Features
    i. LGA w/ Macrocephaly leading to a Long Face w/ Protuberant Forehead, Large Mandible, and Protruding Everted Ears
    ii. Large Testicles
    iii. MR, Shyness, Autism, Avoidance of Eye Contact

<u>Mutations in Mitochondrial Genes</u>

- Mitochondrial genes entirely obey maternal inheritance b/c zygote receives all of its cytoplasm and organelles from the ovum NOT the sperm. Therefore in a pedigree if you see a generation that has a mitochondrial gene mutation the affected individuals are related to each other through the maternal line and transmission from affected males to their offspring is not seen.
- Organs (CNS, muscle, GI) that are highly energy dependent are affected
- *Heterosomy* (the relative population of mutant mitochondria can vary within different tissues in an individual, this suggests that a minimum number of cells with mutant mtDNA must be present in a tissue before dysfunction arises this is called the threshold effect)

<u>Genomic Imprinting</u>

- Process that results in differential expression of maternal allele or paternal allele of a specific gene, if allele is imprinted via methylation it is turned off during gametogenesis, for example, when a sperm is being made a particular gene has a maternal and paternal allele and one allele say for example the maternal allele is imprinted when a particular sperm is formed it can get the imprinted maternal allele or the normal paternal allele; if it gets the imprinted allele and the other parent unfortunately provides a deleted gene then you get the following syndromes:

(1) Prader-Willi Syndrome

a. Type of Defect
   i. 75% Paternal 15q12 Deletion
      1. maternal gene at 15q12 is imprinted while paternal gene at 15q12 is deleted therefore there are no genes that are active (normally maternal gene at 15q12 is imprinted while paternal gene at 15q12 is intact therefore one gene is active)
      2. Recurrence Risk of 1/100
   ii. 25% Maternal Uniparental Disomy
      1. both of the chromosomes are from mom and both are imprinted

b. Clinical Features
   i. Infantile Hypotonia, Failure to Thrive
   ii. Central Obesity 2/2 Appetite Disorder (they eat large amounts of food without feeling of satiety), Decreased Movement, and OCD that focuses on food
   iii. Short
   iv. Small Feet and Hands
   v. Lighter Pigmentation than other family members (sometimes perceived as very attractive children w/ blonde hair and blue eyes)
   vi. Downturned Mouth, Almond-Shaped Palpebral Fissures
   vii. Hypogonadism, Micropenis
   viii. Mild MR, Difficult Behavior (Temper Tantrums, Stubborn, Manipulative, Aggressive, Difficulty w/ Change in Routine, Sleep Disturbances)

(2) Angelman Syndrome

a. Type of Defect
   i. 75% Maternal 15q12 Deletion
      1. paternal gene on 15 at q12 is imprinted and while the maternal gene is mutated therefore both are inactive
   ii. 25% Paternal Uniparental Disomy
      1. both of the chromosomes are from dad and neither are imprinted

b. Clinical Features
   i. Microcephaly
   ii. Happy, Laughing Disposition, Stereotyped Flapping Hands aka “Happy Puppet Syndrome” or “Marionette Joyeuse Syndrome”
   iii. Lighter Pigmentation
   iv. Large Mandible and Open-Mouthed Expression revealing Tongue
   v. Complete Absence of Speech
   vi. Ataxic Gait
   vii. Seizures
   viii. MR