Amino Acids and Amino Acidopathies: Phenylketonuria, Tyrosinemias, and Homocystinuria

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Some slides adapted from:

Thank you, Jean Marie Saudubrey, Mark Korson,
Jerry Vockley and many others

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Learning Objectives:

How to recognise different types of trees from quite a long way away.

No. 1 The Larch.

9al

Also see:
https://www.youtube.com/watch?v=mBcTXBhYzfM

Learning Objectives:

How to recognise different types of trees from quite a long way away.

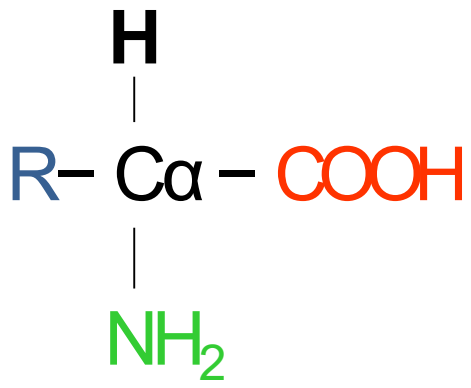
And

After participation in this session, the attendee will:

- Understand the metabolic fate of different amino acids in humans
- Recognize the variety of therapeutic approaches available for phenylketonuria and other amino acidopathies
- Identify at least multiple causes of hyperhomocysteinemia

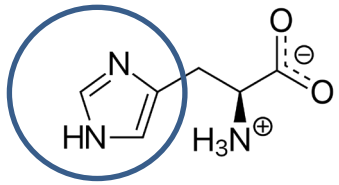
No. 1 The Larch.

Amino acid metabolism

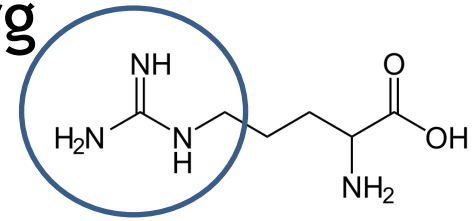


Amino Acid Structures

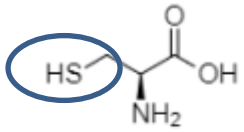
- Lateral chain R:
  - Carboxyl: Asp (β), Glu (γ)
  - Amine: Lys (ε), Orn (δ)
  - Hydroxyl: Thr, Ser, Tyr
  - Imidazole: His



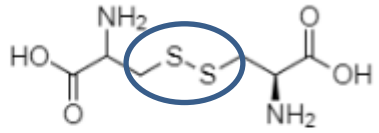
  - Guanidinium: Arg



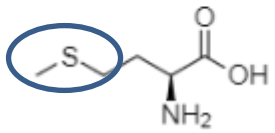
  - Thiol: Cys, Hcy



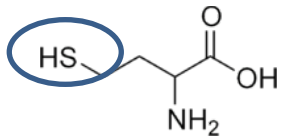
cysteine



cystine



methionine



homocysteine

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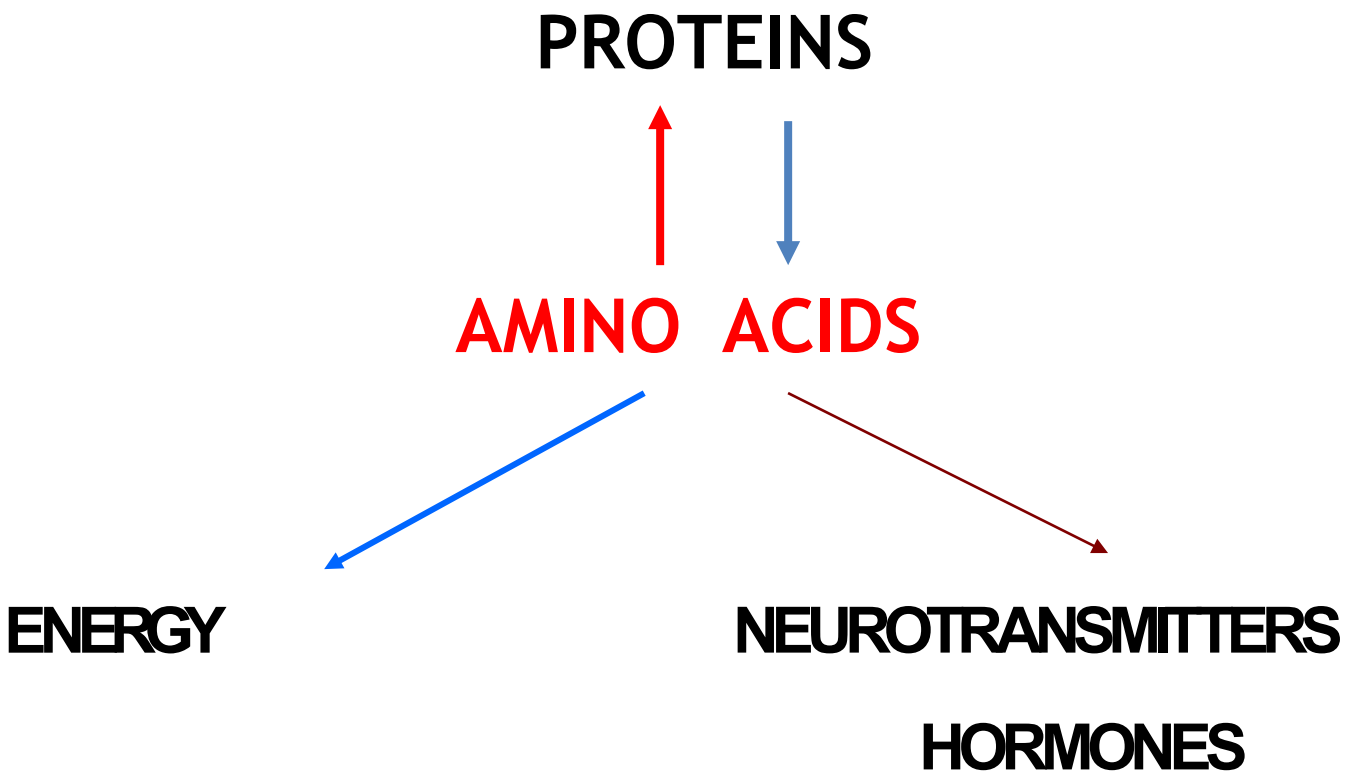
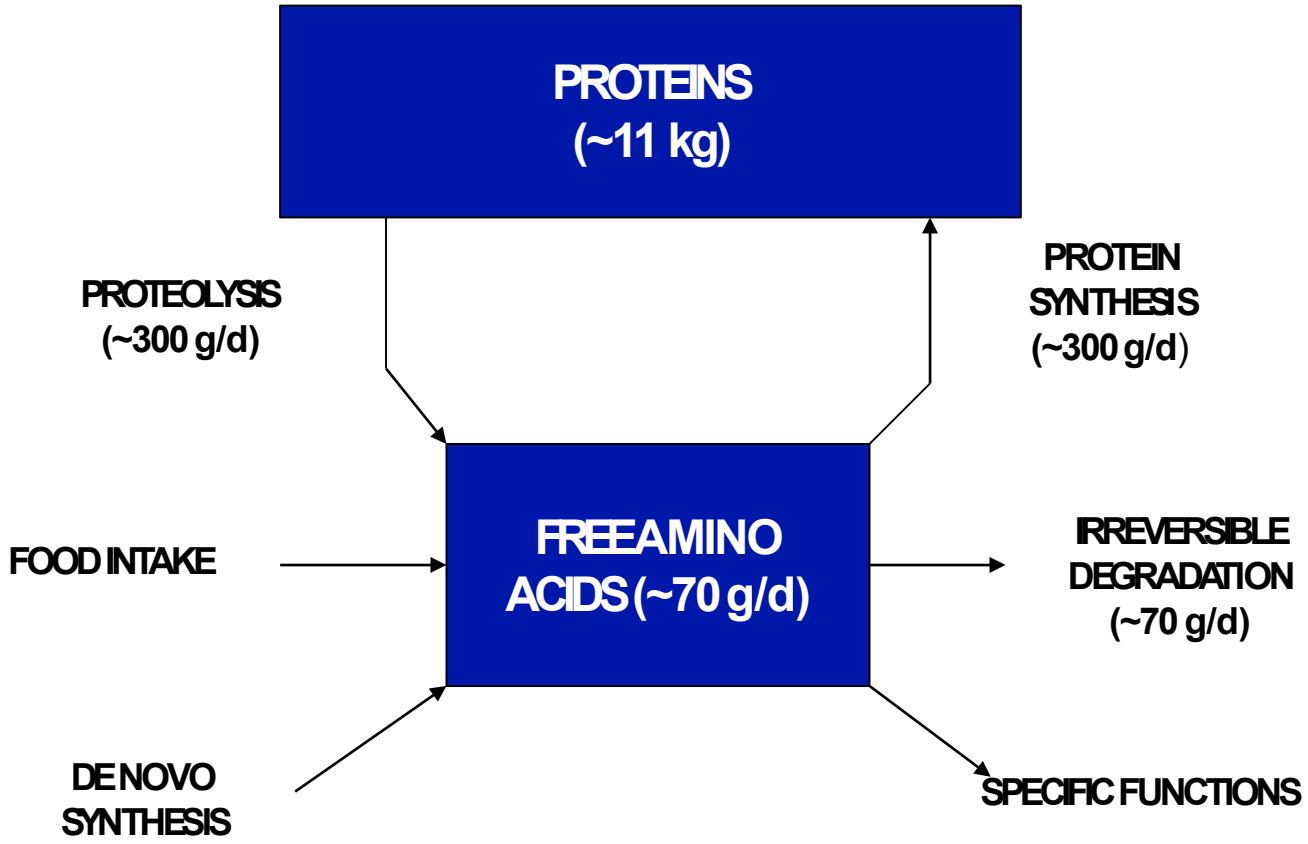
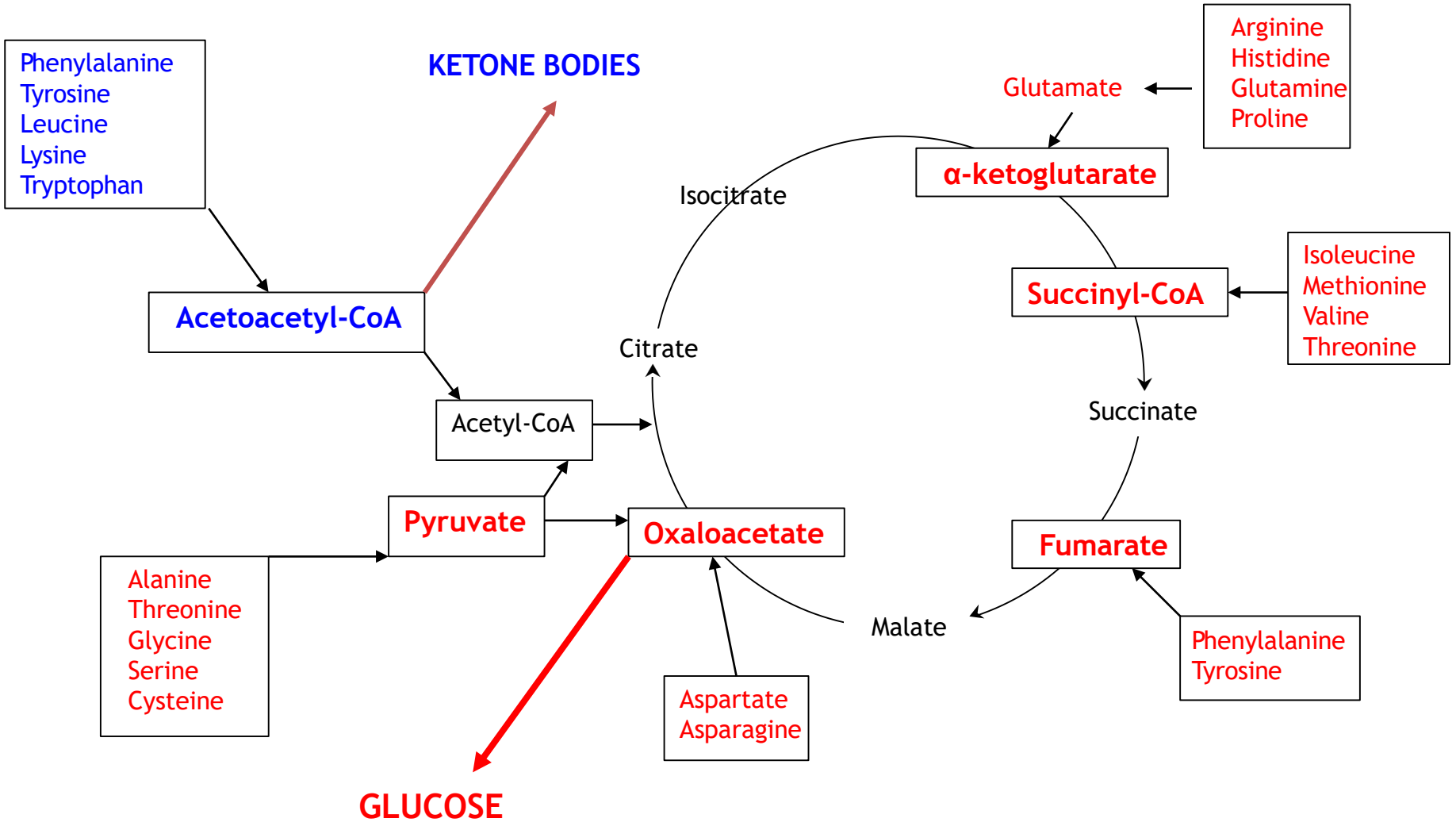


Protein metabolism (Adult 70 kg)



Irreversible degradation



KETOGENIC and **GLUCONEOGENIC** amino acids

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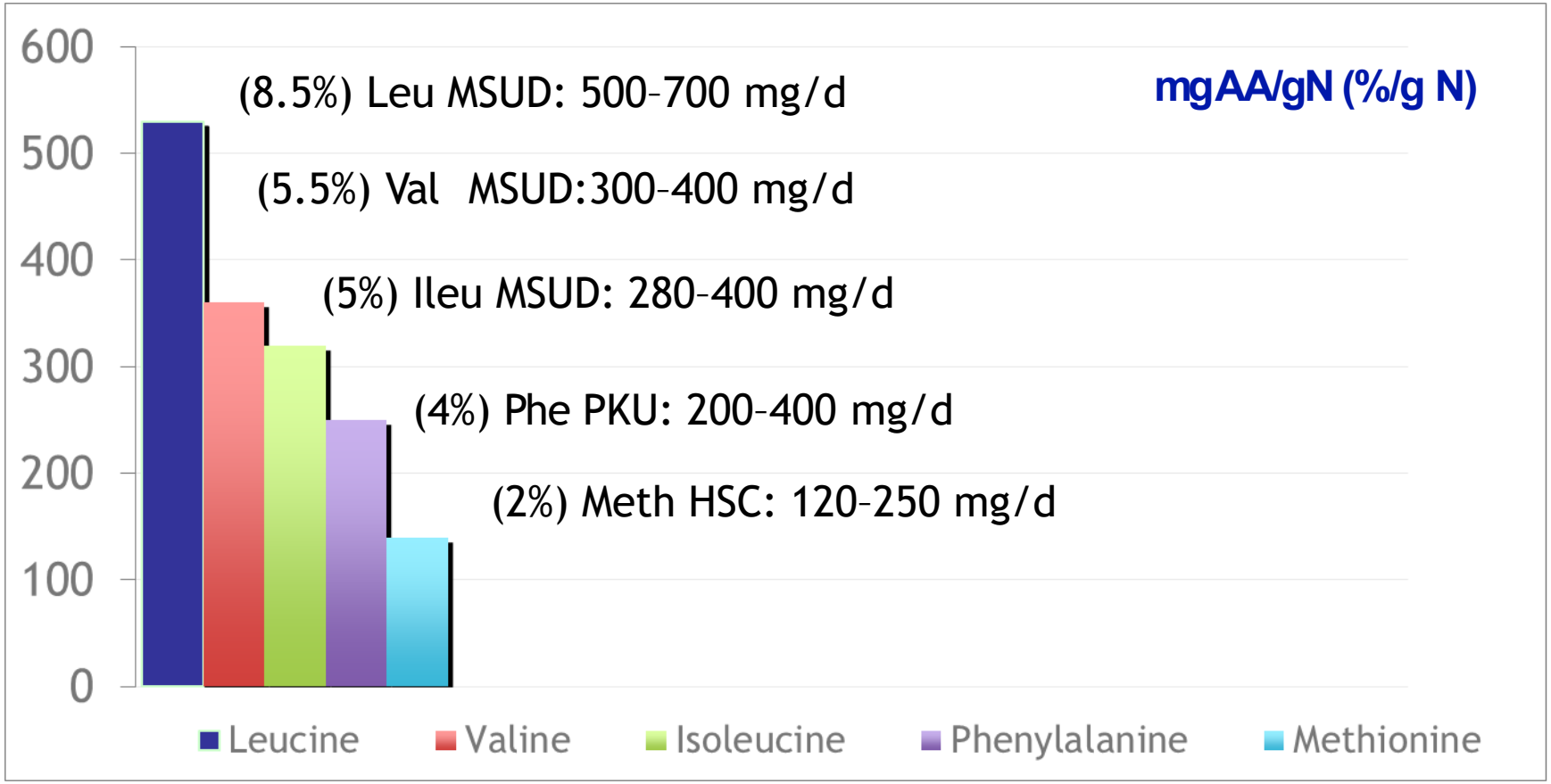
Muscle amino acids

1 g N = 6.25 g protein = 30 g muscle



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De novo amino acid synthesis

- Essential and non-essential amino acids
- Essential AA: Inborn errors of AAcatabolism
  - Cannot be synthesized by humans
  - Must come from food
- Non-essential AA: Inborn errors of AAsynthesis
  - Can be synthesized by humans
  - Carbon skeletal comes from glucose and other amino acids
  - Nitrogen comes from other amino acids

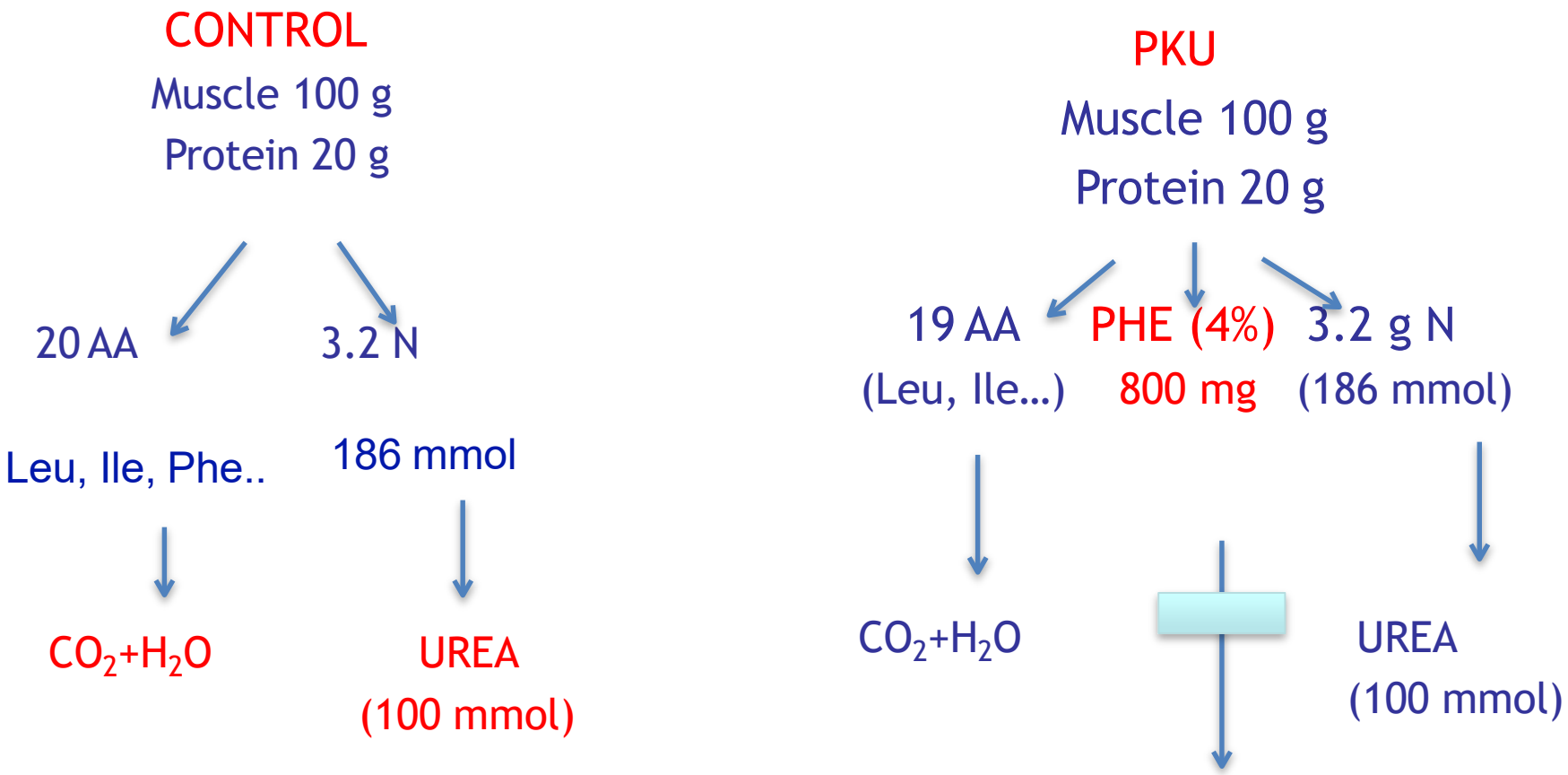
Amino acid classification

Essential	Non-essential
Threonine	Alanine
Valine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Methionine	Glutamate
(Cysteine)	Glutamine
Phenylalanine	Glycine
(Tyrosine)	Hydroxyproline
Lysine	Hydroxylysine
Tryptophan	Proline
Histidine	Serine
Arginine	Tyrosine

Protein catabolism

- Muscle protein content is 20 g%
- Nitrogen protein content is 16%
- 1 g nitrogen = 6.25 g protein = 30 g muscle
- Amino acid composition of proteins is genetically determined (doesn’t depend on the diet)
- In catabolic situations amino acids released from muscles circulate for use in protein synthesis or oxidized (for energy or gluconeogenesis) and nitrogen is converted to urea

Catabolism in control and PKU



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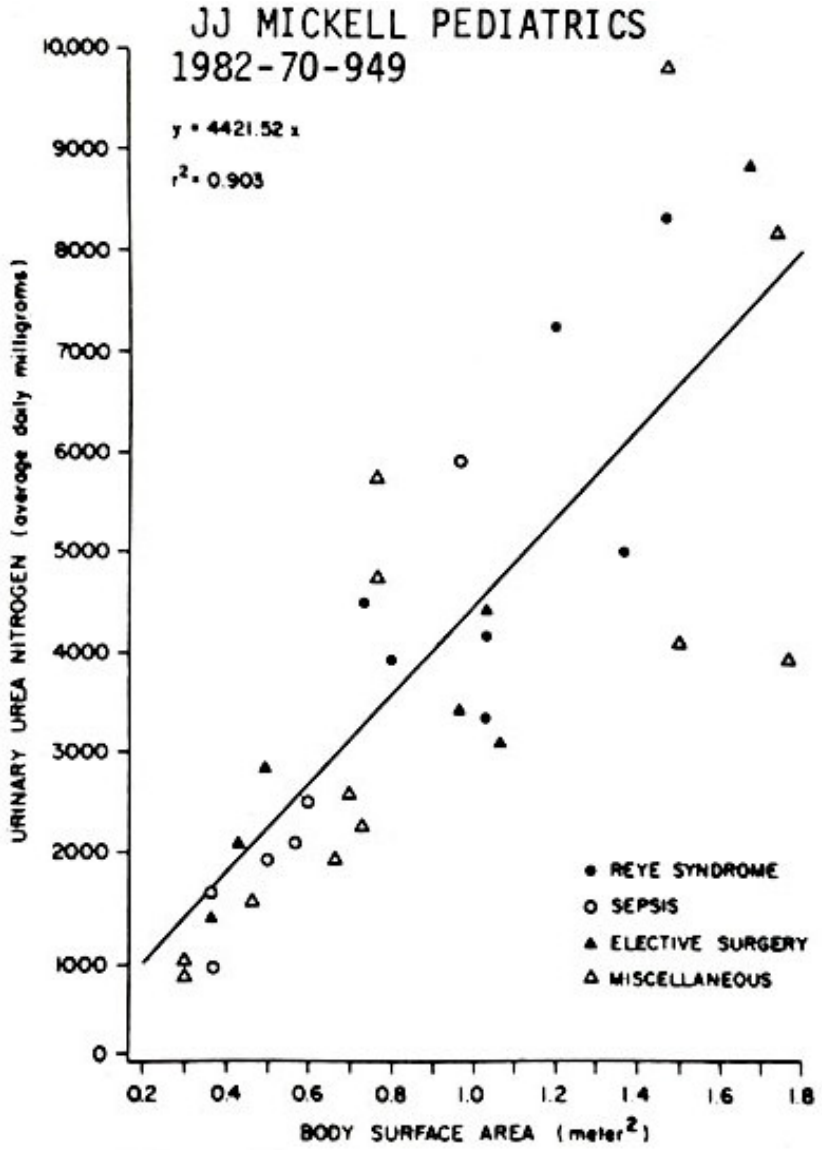
Nitrogen excretion



- Relationship between urinary urea nitrogen excretion and body surface area

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Food intake

- Feeding → exogenous proteins
  - –Digestion → free amino acids and peptides (di- and tri-)
  - –Essential and non-essential amino acids
  - –Allows endogenous protein synthesis
- Defective intake
  - – Kwashiorkor: protein-only deficit
  - – Marasmus: combined deficit of protein and calories

Amino acidopathies

Majority can be identified by newborn screening

Phenylalanine

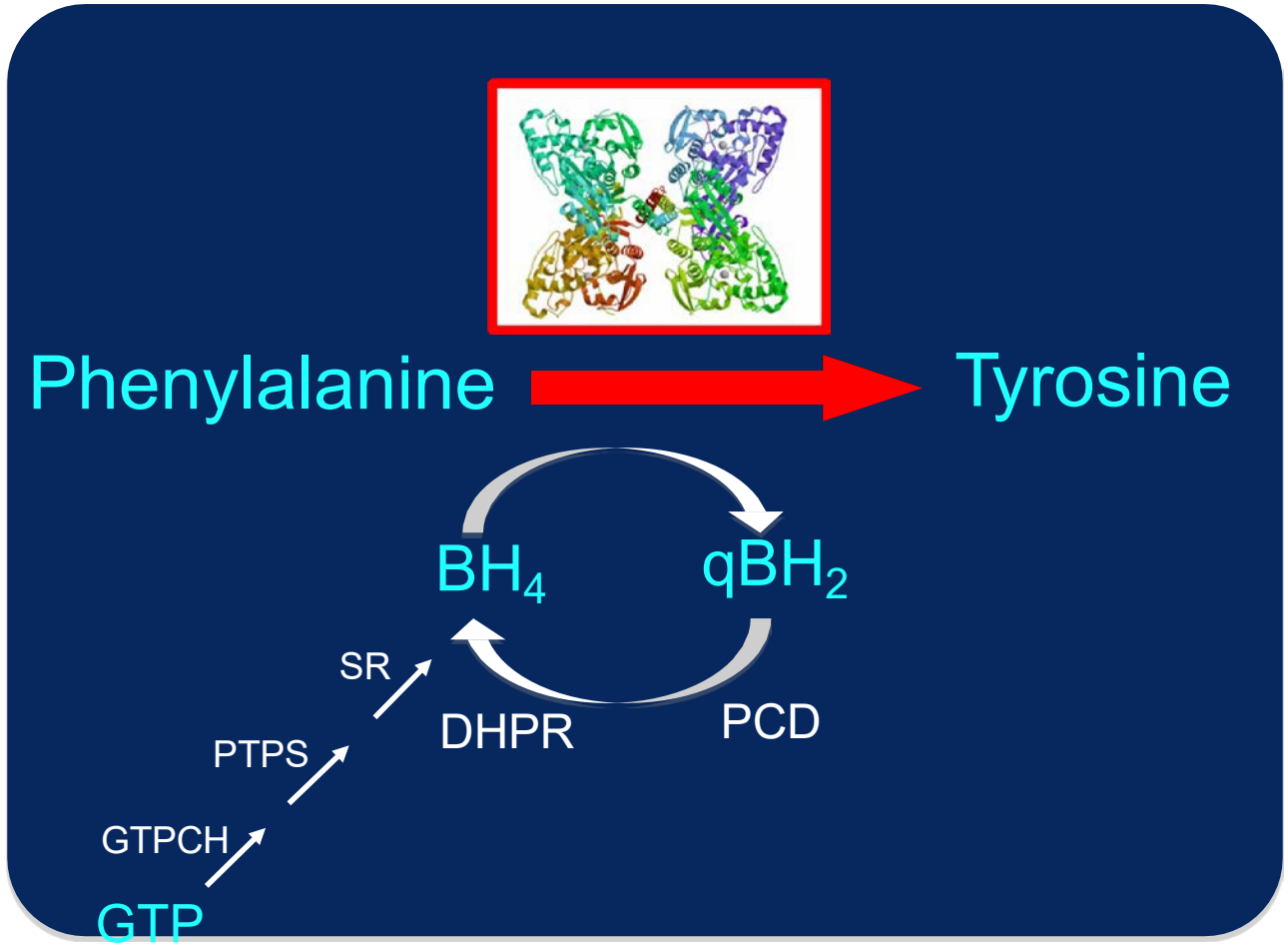
- Essential amino acid
- Required for synthesis of proteins
- Precursor to
  - Tyrosine
  - Catecholamines (including dopamine)
  - Seratonin
  - Melanin

Hyperphenylalaninemias

Phenotypic classification

- "Classic" phenylketonuria
  - –untreated phe >1200 µmol/L
- "mild PKU"
  - –untreated phe 600-1200 µmol/L
- Hyperphenylalaninemia
  - –untreated phe < 600 µmol/L when well

Phenylalanine hydroxylase (PAH)



BH_4 is also a cofactor for tyrosine hydroxylase (dopamine synthesis) and tryptophan hydroxylase (seratonin synthesis)

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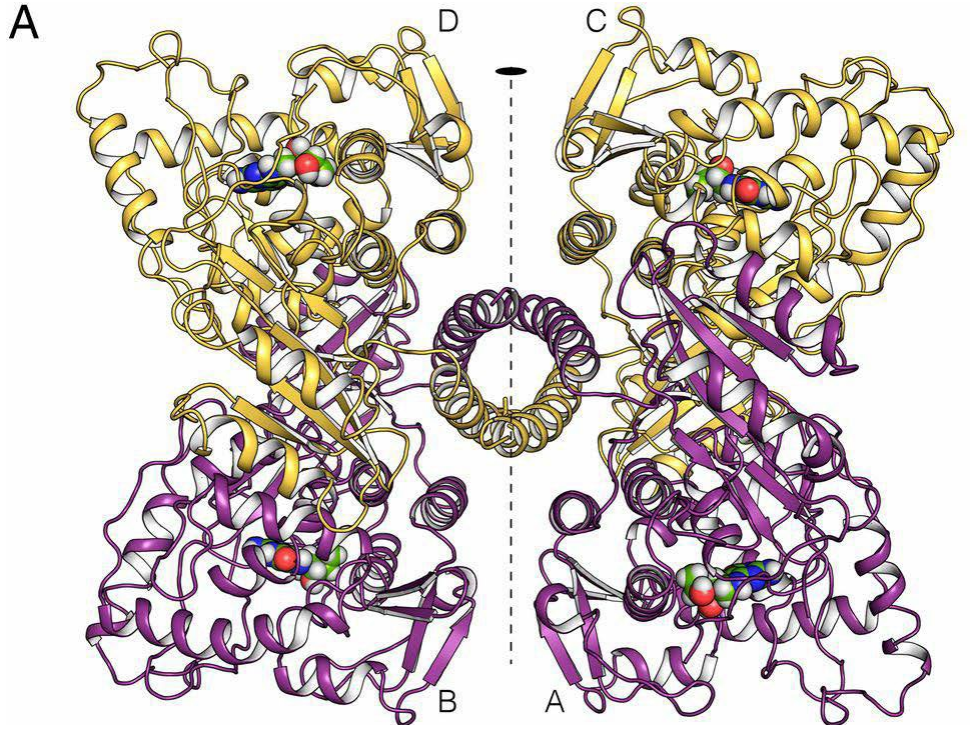
Phenylketonuria (PKU)

- Liver phenylalanine hydroxylase (PAH) deficiency
- Autosomal recessive inheritance
- Incidence ~1:16,000 live births in the US



PNAS v116 p11229 2019

- Homotetramer ("dimer of dimers")
- Allosteric activation
  - confirmation determines enzyme activity
  - Phe activates enzymatically favorable conformation
  - BH4 stabilizes tetramer, but supports lower activity confirmation

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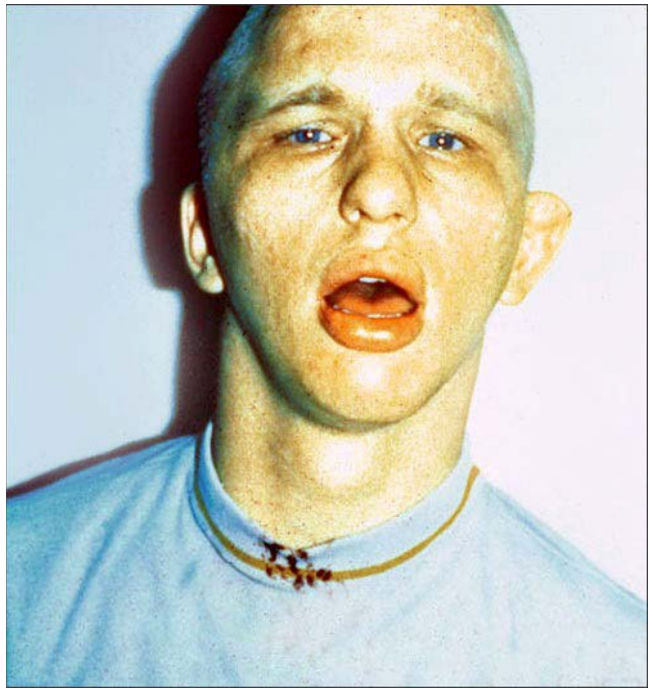
Other causes of hyperphe

- Rare variants of biopterin synthesis or recycling (about 1% of severe hyperphe)
  - GTP cyclohydrolase
  - Dihydropteridine reductase
  - 6-pyruvoyl-tetrahydropterin synthase
    - All 3 generally more difficult to treat, require BH4 and usually dopa
  - Pterin-alpha-carbinolamine dehydratase
    - Generally mild, excrete 7-biopterin
- Hyperphe, not BH4 deficient
  - *DNAJC12* – molecular chaperone for the hydroxylases – PAH, TH and TPH

Untreated PKU



- “Normal” development for 6–9 months, feeds well
- 9–12 months signs of slowing in developmental progress, head growth slows
- About 1 year clearly developmentally delayed, light hair, eczema, musty odor of “mouse urine”, may have seizures

- Severe intellectual disability with behavior problems — eventual institutionalization
- White matter hyperintensities – “pseudoleukodystrophy”

Pathophysiology

- Elevated total body phenylalanine
- Excessive phe in the brain
- Reduced large neutral amino acid transport into the brain (including tyrosine and tryptophan)
- Reduced synthesis of key neurotransmitters (e.g., dopamine, serotonin), especially during development
  - Mouse data suggests inhibition by CNS Phe of TH and TPH2 activity
- No direct pathologic effect on the liver known

Goals of Treatment

- Normal neurocognitive development
- Normal growth
- Normal social interactions
- Normal micronutrient concentrations
- Normal bone calcium content

- Targets
  - Plasma phe 120-360 micromol/L
  - Plasma tyrosine normal

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Therapy

- Dietary phe reduction
- Competitive – large neutral amino acids supplements
- Chaperone therapy – sapropterin
- Enzyme substitution therapy – pegvaliase

Experimental

- Gut biome manipulation of absorption
- Gene correction or replacement therapy

Diet therapy

- Restrict dietary protein
- Phenylalanine intake: ~250-350 mg/day in classical form
  - Breastfeeding often manageable
- Supplement with phenylalanine-free medical food to guarantee the daily requirements
  - Non-offending amino acids
  - Glycomacropeptide – low phe casein product
  - Vitamins and minerals
  - Distribute through the day
- "Diet for life"

1 g dietary protein ≈ 50 mg phe

Strategies for breastfeeding

- Alternate feedings
- Mix in a bottle (breast milk provides intact protein in a traditional formula recipe
- Bottle first with metabolic formula with each feed, followed by nursing (one breast for at least 10 min to access hindmilk)

Table 3
Guidelines for PHE, TYR, and protein intake for individuals with PKU.

AGE	PHE[a] (mg/day)	TYR[a] (mg/day)	Protein[b] (g/kg/day)
Infants to <4 years[a]			
0 to <3 months[c]	130–430	1100–1300	2.5–3.0
3 to <6 months	135–400	1400–2100	2.0–3.0
6 to <9 months	145–370	2500–3000	2.0–2.5
9 to <12 months	135–330	2500–3000	2.0–2.5
1 to <4 years[d]	200–320	2800–3500	1.5–2.1
After early childhood[e]			
>4 years to adult	200–1100	4000–6000	120–140% DRI for age[f]
Pregnancy and lactation[g]			
Trimester 1	265–770	6000–7600	≥70
Trimester 2	400–1650	6000–7600	≥70
Trimester 3	700–2275	6000–7600	≥70
Lactation[h]	700–2275	6000–7600	≥70

[a] Adapted from Acosta [118], recommendations for PHE and TYR intake for infants and children <4 years with more severe PKU and treated with PHE-restricted diet alone. TYR intake recommendations may require adjustment based on blood TYR monitoring.

Monitoring diet therapy

- Provide adequate calories
- Provide adequate protein, vitamins, minerals
- Maintain normal growth and development
- Monitor blood Phe and Tyr
- Monitor other parameters (development, psychological status, bone density)
  - –Consider monitoring iron and Vitamin D from time to time

Collaboration with a knowledgeable IEM Dietician is critical!

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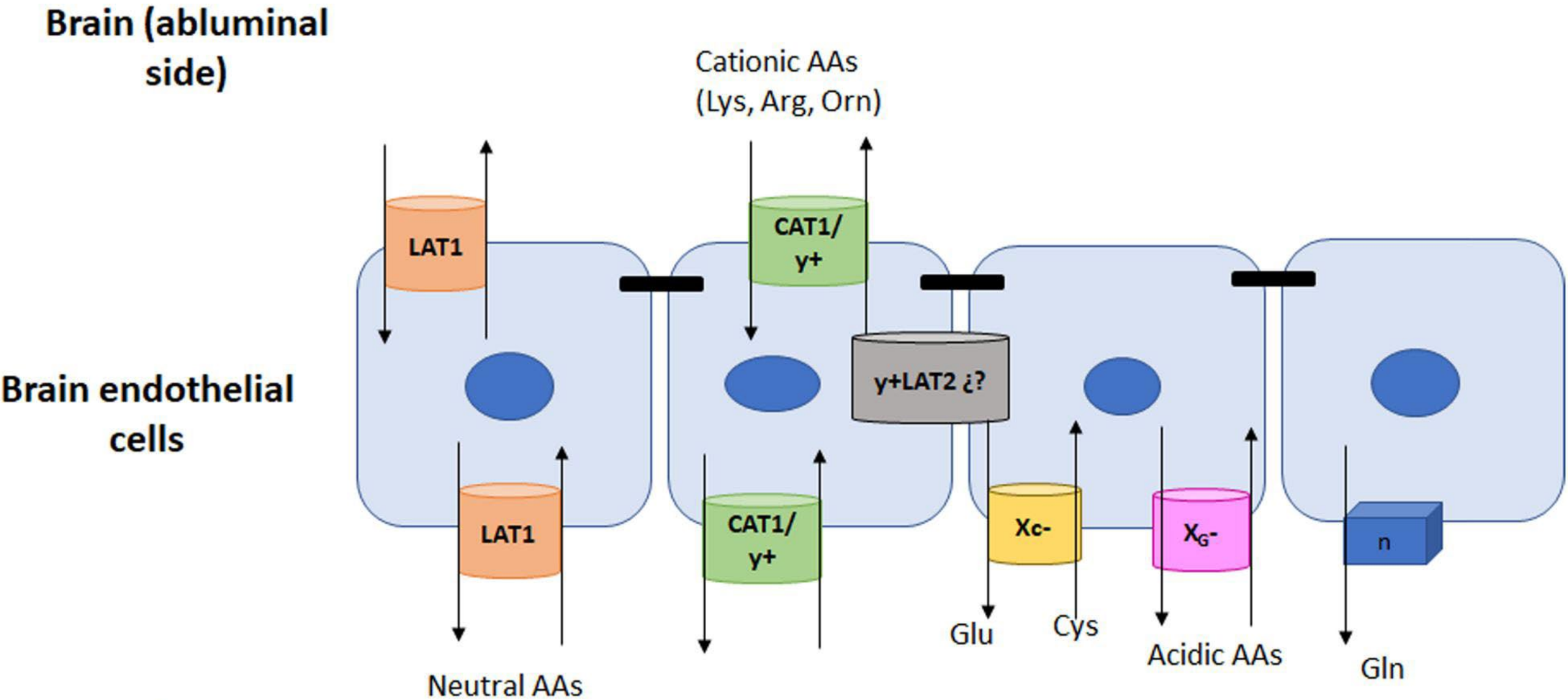
Monitoring diet therapy

- Frequency of monitoring Phe/tyr (recommended – rarely followed)
    - At diagnosis (newborn) – daily or QOD until at goal
    - Weekly for first year
    - Monthly or twice monthly age 1-12 years
    - Adolescents and adults – monthly
    - IF poorly controlled may need more frequent
    - Phe will go up during illness
- Other nutritional factors
    - Protein adequacy – growth, amino acids, transthyretin
    - Micronutrients – vitamin D, ferritin, others

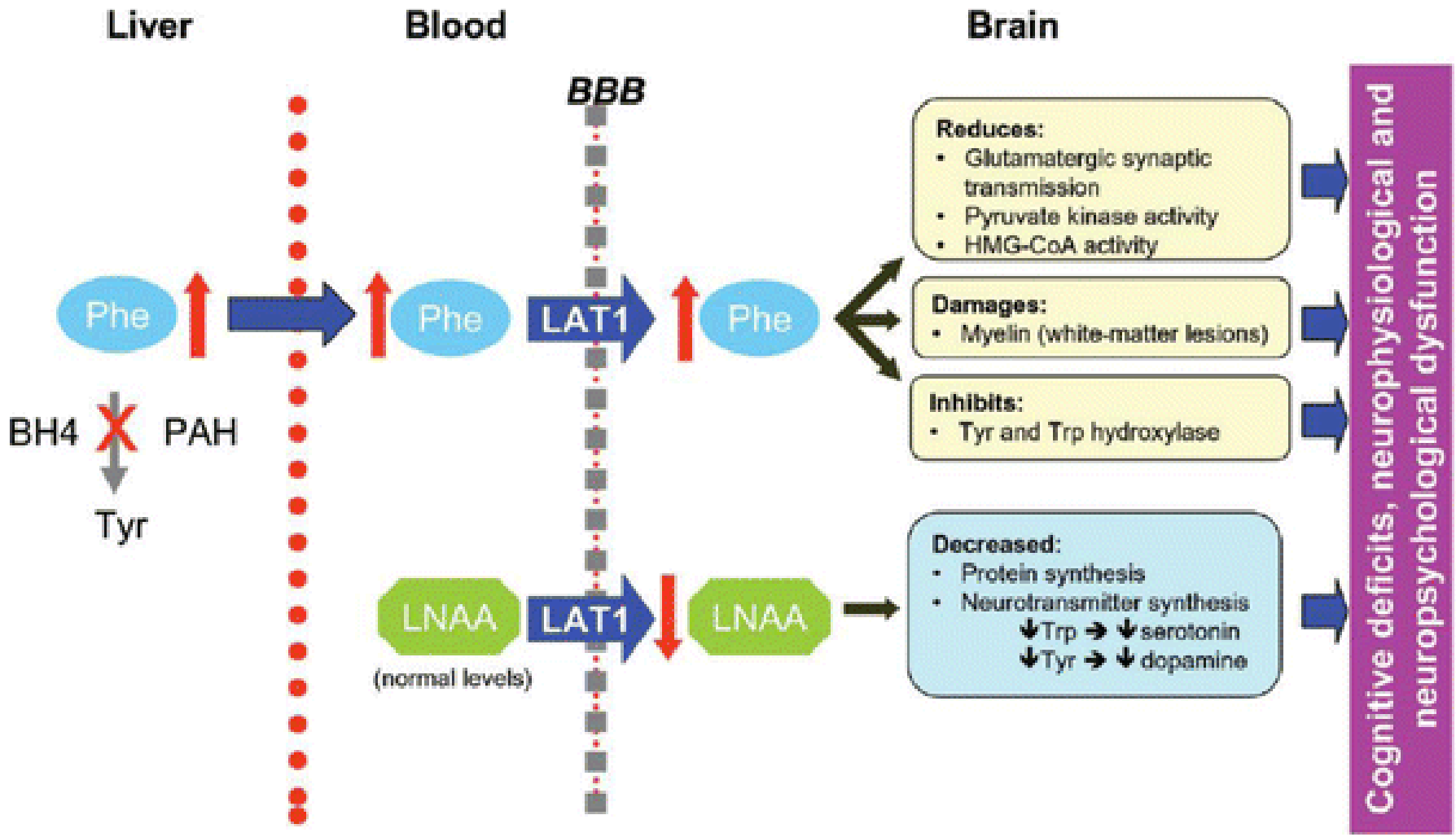
Other therapies - Large neutral amino acids

Goal to increase plasma tyr and reduce CNS phe

- 20-30% of medical food protein each day
- Does not require PAH protein to work
- Data are mixed on efficacy
  - possible modest reduction in plasma phe
  - improved plasma tyr
  - Possible improved CNS tyr
  - Some evidence of effect on neuropsych measures



https://www.frontiersin.org/files/Articles/570922/fphys-11-00973-HTML/image_m/fphys-11-00973-g001.jpg



https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0685-2/figures/2

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Other therapies - Sapropterin

Goal to enhance phe tolerance and normalize diet

– 20 mg/kg/day

–Infant – 24 hour trial >30% reduction in phe (with stable or no diet treatment)

–Older 48 hours to 30 days trial

–May have gradual onset

–Requires some PAH protein to work (null alleles unaffected)

Some sapropterin responsive mutations

cDNA	Protein	Cases in PAHdb	Responsive to Sapropterin
c.1222C>T	p.Arg408Trp	6.7%	<10%
c.1066-11G>A (IVS10-11G>A)		5.3%	<10%
c.194T>C	p.Ile65Thr	4.1%	89%
c.782G>A	p.Arg261Gln	3.6%	78%
c.842C>T	p.Pro281Leu	2.9%	None [Leuders et al 2014, biopku.org]
c.1315+1G>A (IVS12+1G>A)		2.8%	12.5% [biopku.org] None [Leuders et al 2014]
c.473G>A	p.Arg158Gln	2.7%	<10%

Data obtained from: PAHdb accessed 5/8/2016 (biopku.org); and Leuders et al [2014]. All changes with >2.5% frequency in the PAHdb database were included. In database searches, homozygosity was assumed for calculations; however, this is a rare finding in consanguineous individuals. It is recommended that all affected individuals be tested for personal responsiveness. Genetic changes shown affect >2.5% of the database population. See biopku.org for the most up-to-date information and additional references.

Genereviews
https://www.ncbi.nlm.nih.gov/books/NBK1504/

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Other therapies - Pegvaliase

Goal to enhance phe tolerance and normalize diet

- Enzyme replacement therapy
- Plant enzyme – phenylalanine ammonia lyase
- Does not reduce need for tyrosine
- Immunologic reactions must be managed
- Not recommended during pregnancy
- FDA approval for 16 years and up

Guidelines for use: *GIM* 21:1851 2019

Other therapies - Pegvaliase

- Pegvaliase – subcutaneous injection
  - Typical dose is 20 mg/day
    - Some may need less
    - Some may need up to 40 mg/day
  - Titration – see package insert
  - Response = at least 20% reduction in baseline plasma phe
  - Stop if no response after 16 weeks on 60 mg/day
  - May take more than one year to achieve response

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761079s000lbl.pdf

Table 1: Recommended Dosing Regimen

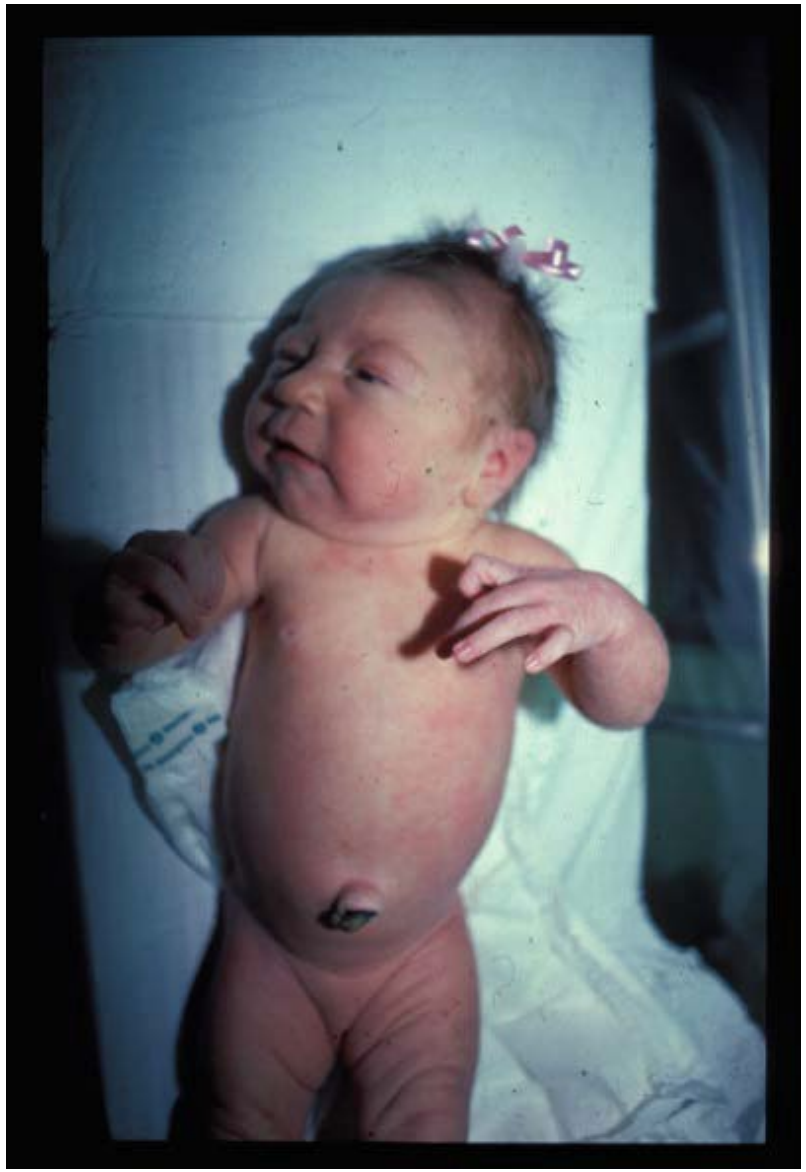
Treatment	Palynziq Dosage	Duration*
Induction	2.5 mg once weekly	4 weeks
Titration	2.5 mg twice weekly	1 week
	10 mg once weekly	1 week
	10 mg twice weekly	1 week
	10 mg four times per week	1 week
	10 mg once daily	1 week
Maintenance†	20 mg once daily	24 weeks
	40 mg once daily	16 weeks
Maximum‡	60 mg once daily	16 weeks

* Additional time may be required prior to each dosage escalation based on patient tolerability.

† Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to 40 mg once daily in patients who have not achieved a response with 20 mg once daily continuous treatment for at least 24 weeks. Consider increasing to a maximum of 60 mg once daily in patients who have not achieved a response with 40 mg once daily continuous treatment for at least 16 weeks *[see Clinical Studies (14)]*.

‡ Discontinue Palynziq in patients who have not achieved an adequate response after 16 weeks of continuous treatment at the maximum dosage of 60 mg once daily.

“Maternal” PKU



- Phenylalanine teratogenicity
- microcephaly,
- congenital cardiac lesion
- Intellectual disability

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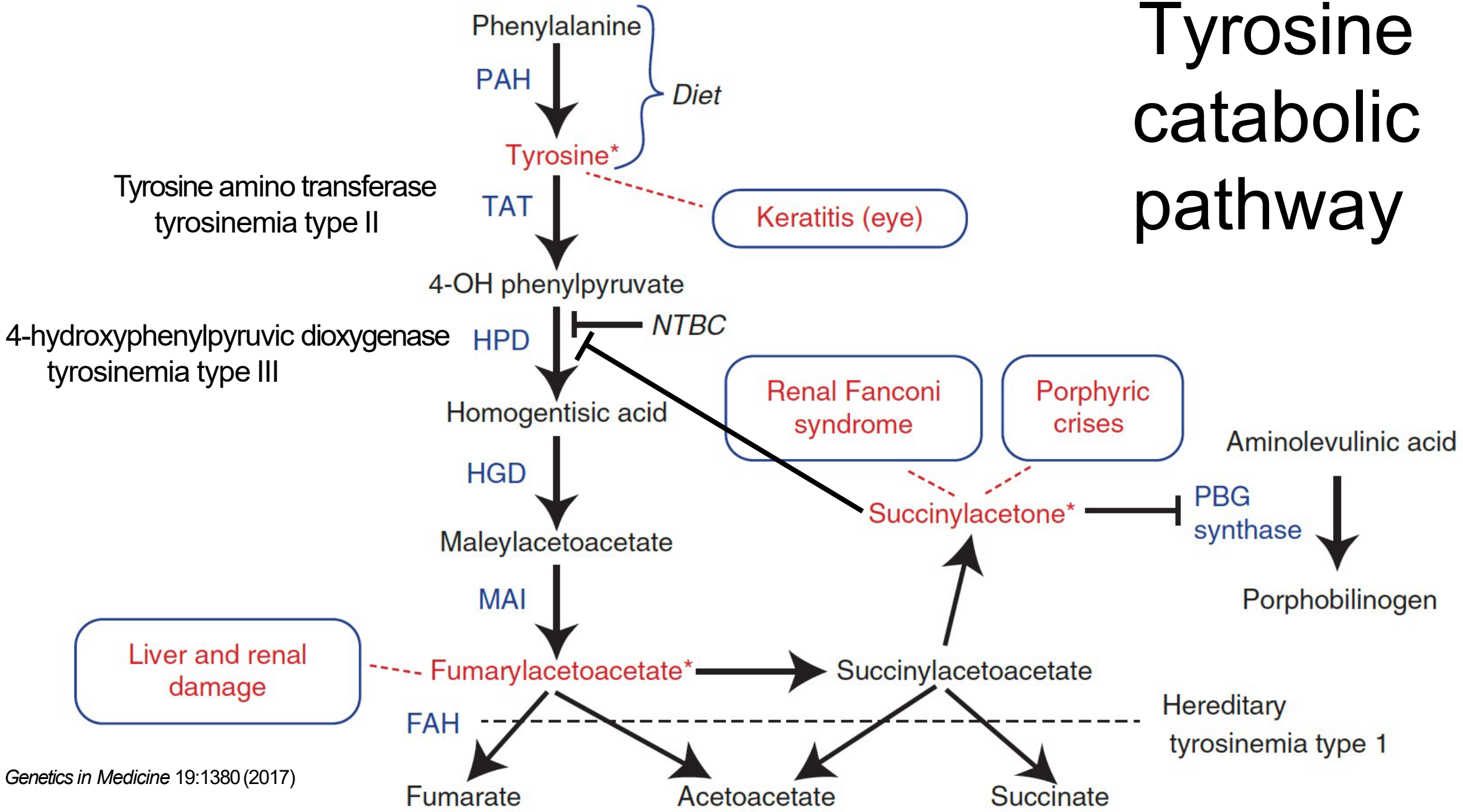
“Maternal” PKU Management

- Ideally start aggressive therapy before pregnancy
- Phe in target range as early as possible for unplanned pregnancy
- Often need aggressive Tyr supplements, especially 3rd trimester
- Sapropterin seems safe
- Risk of high phe likely outweighs potential risk for use of sapropterin and consideration for pegvaliase

Universal lessons from PKU

- Screening and treatment can be effective
- NBS can uncover milder forms for which the need to treat may not be obvious
- Unanticipated future consequences, for example maternal PKU, may occur or be revealed
- Treatment/intervention creates a new “natural history”
- The pathogenesis is more complicated than you think
- Alternative therapies may be developed over time

Tyrosine catabolic pathway



Genetics in Medicine 19:1380 (2017)

Tyrosinemia type 1

- Fumarylacetoacetate hydrolase deficiency
- Autosomal recessive inheritance
- Founder effect
  - Quebec, Canada
  - Finland
- 3 presenting forms:
  - Early in infancy (1 to 6 months): Liver disease (hepatic failure or cholestatic jaundice or cirrhosis with renal tubulopathy)
  - Late infancy: Rickets due to renal tubulopathy (Fanconi syndrome) with no obvious liver failure
  - Porphyria-like attack at any age (can be presenting sign)

Cellular effects tyrosinemia 1

- Toxic compounds (don’t cause ”intoxication” symptoms)
  - –Fumarylacetoacetate, maleylacetoacetate
  - –Succinylacetone
- Hepatocellular damage
  - –Cirrhosis
  - –Hepatocellular carcinoma
  - –High alpha fetoprotein
- Renal tubule damage
  - –Renal Fanconi syndrome
  - –Hypophosphatemic rickets

Succinylacetone

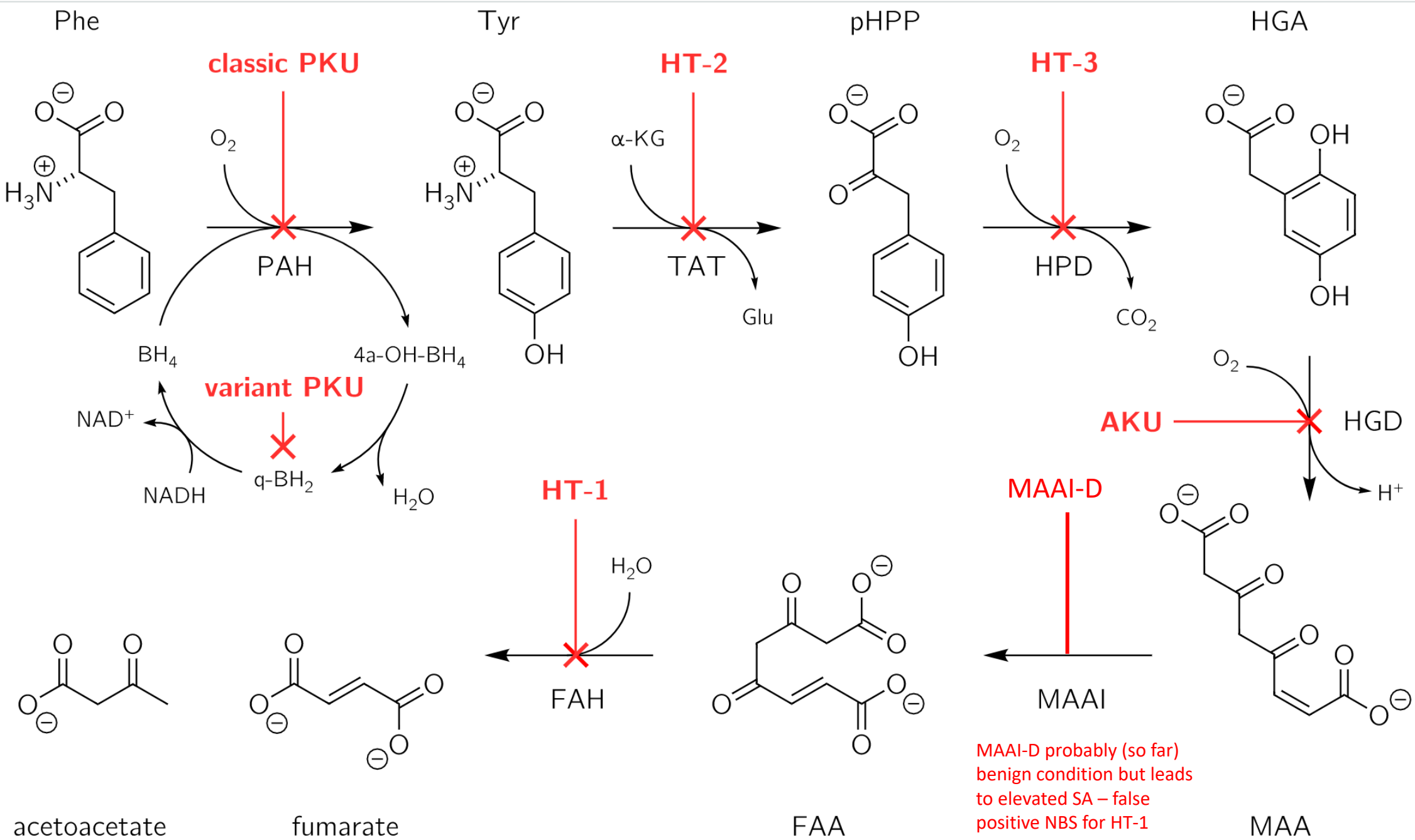
- Succinylacetone inhibits
  - –Δ-aminolevulinic acid dehydratase activity
    - Porphyria-like abdominal pain crises
    - Peripheral neuropathy
  - –4-hydroxyphenylpyruvic dioxygenase
    - Tyr II enzyme defect, target of NTBC

Treatment

- 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexane-dione (NTBC)
  - –Inhibits 4-hydroxyphenylpyruvic acid dioxygenase
  - –Further increases plasma tyrosine
  - –Decreased production of FAA and succinylacetone
  - –Markedly reduces, but may not eliminate, hepatocellular carcinoma
- Phenylalanine and tyrosine restriction to avoid excessive hypertyrosinemia (risk of keratitis as in TYR II)
- Liver transplant if hepatocellular carcinoma develops

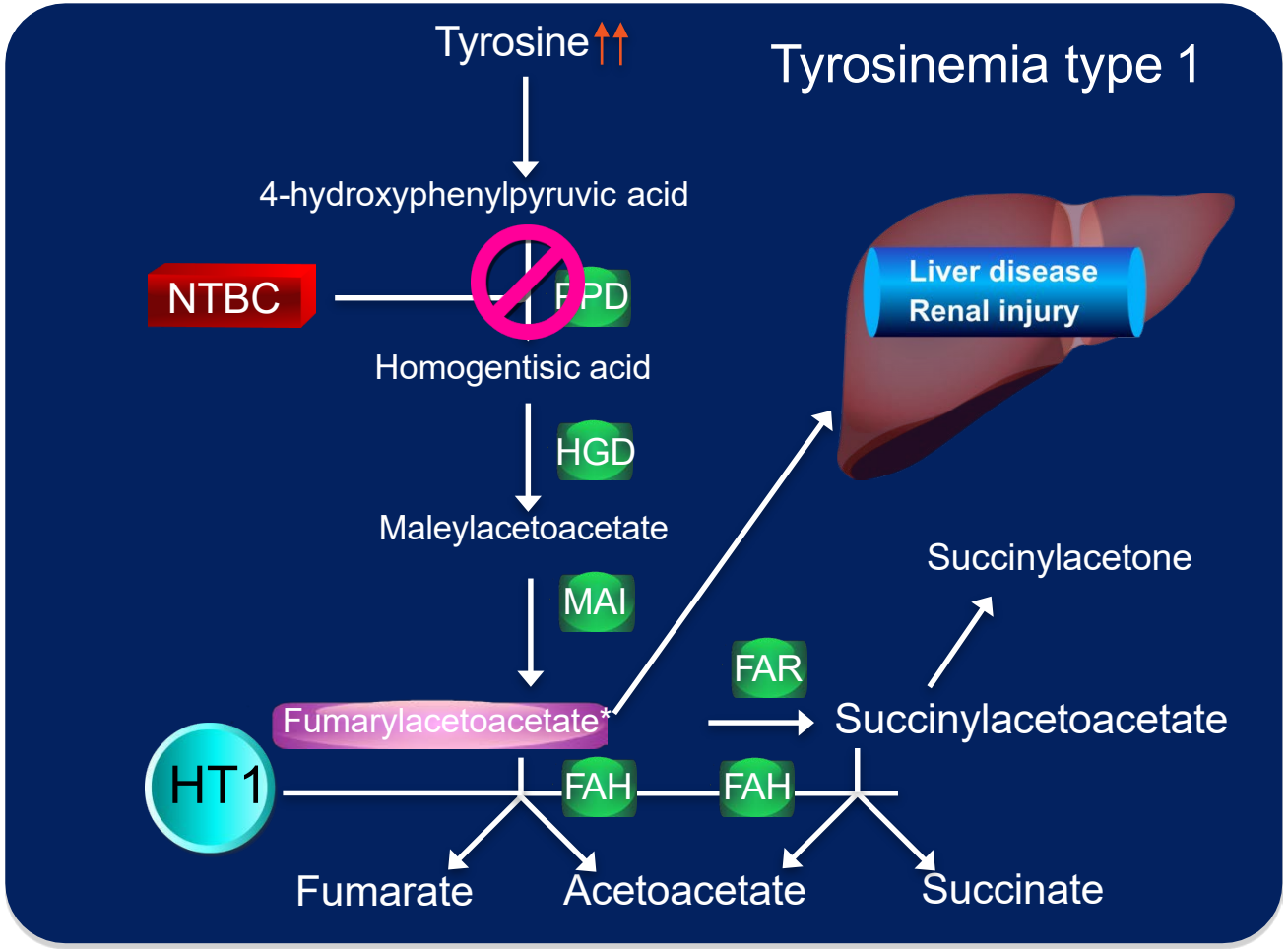
Monitoring

- Therapeutic response to nitisinone
  - –Plasma drug concentrations >35 µmol/L inhibit enzyme 99.9%
  - –Some also monitor plasma succinylacetone to see complete suppression (plasma SA normal)
  - –Start nitisinone at 1 mg/kg/day (usually divided BID for first year)
  - – Titrate dose to desired plasma concentration and/or suppression of SA
- Dietary restriction of Phe and Tyr to keep plasma tyr <600 µmol/L
- Dried blood spot testing including SA, nitisone concentration, tyr and phe is available but drug concentrations may not correlate well with plasma



Bradford Morris https://en.wikipedia.org/wiki/Tyrosinemia_type_II

Other defects in the tyrosine catabolic pathway



Plasma metabolites (amino acids)

- Tyrosine
- Phenylalanine

Urine metabolites (organic acids)

- 4-hydroxyphenylpyruvate,
- 4-hydroxyphenyllactate
- 4-hydroxyphenylacetate

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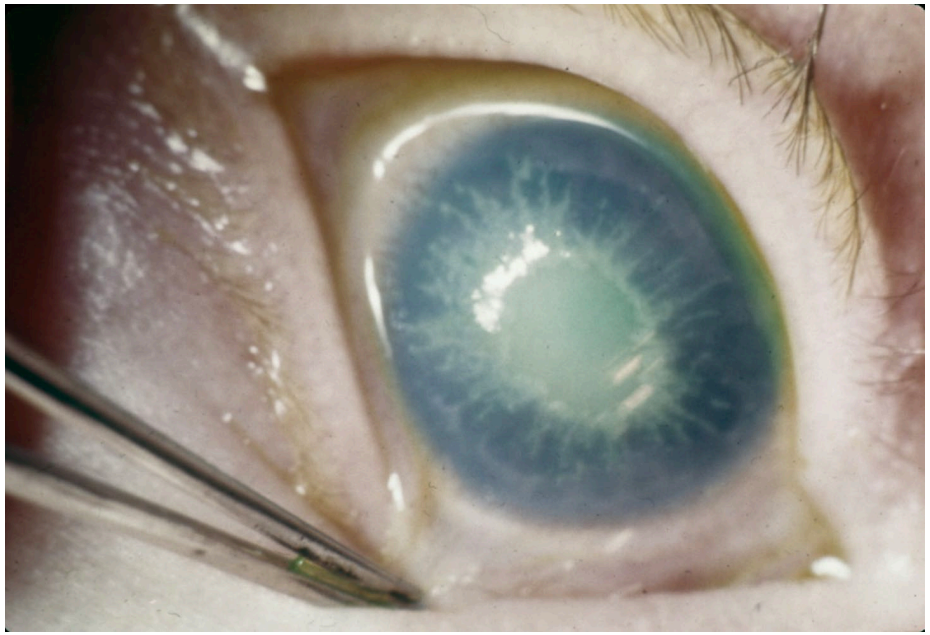
Other tyrosinemias

Type II – tyrosine aminotransferase

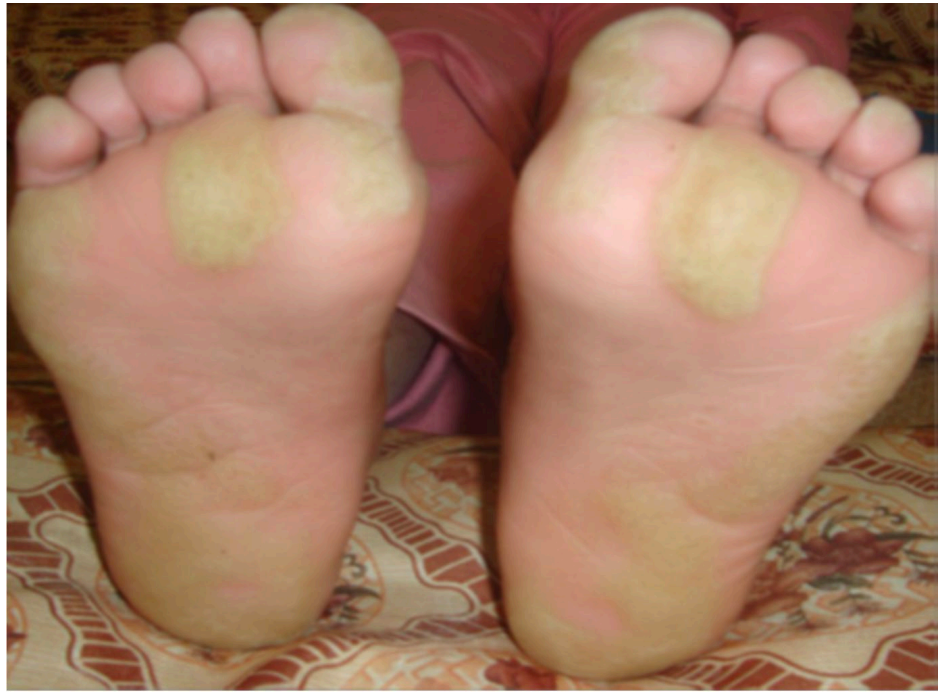
- AKA Richner Hanhart syndrome
- Incidence estimate <1:1X10^6
- Clinical findings
  - Corneal crystals (~75%) – typically develop in first year of life, but may occur later
    - Photophobia
    - Pain
    - Tearing
    - Erythema/injection of sclera
  - Eventually leads to corneal clouding
  - Can be mistaken for herpetic or other viral infection early on, but does not respond to anti-viral therapy



https://disorders.eyes.arizona.edu/disorders/tyrosinemia-type-ii

Type II – tyrosine aminotransferase

- Clinical findings
  - Plantarpalmar hyperkeratosis (~80%)
    - Begin in first year to adult life
    - Can have pits
    - Often painful
    - Non-specific histology
  - Intellectual disability
    - Up to 60% of untreated
    - Typically, apparent between 1-5 years of age
    - Treatment by 1 year of life appears to prevent intellectual decline



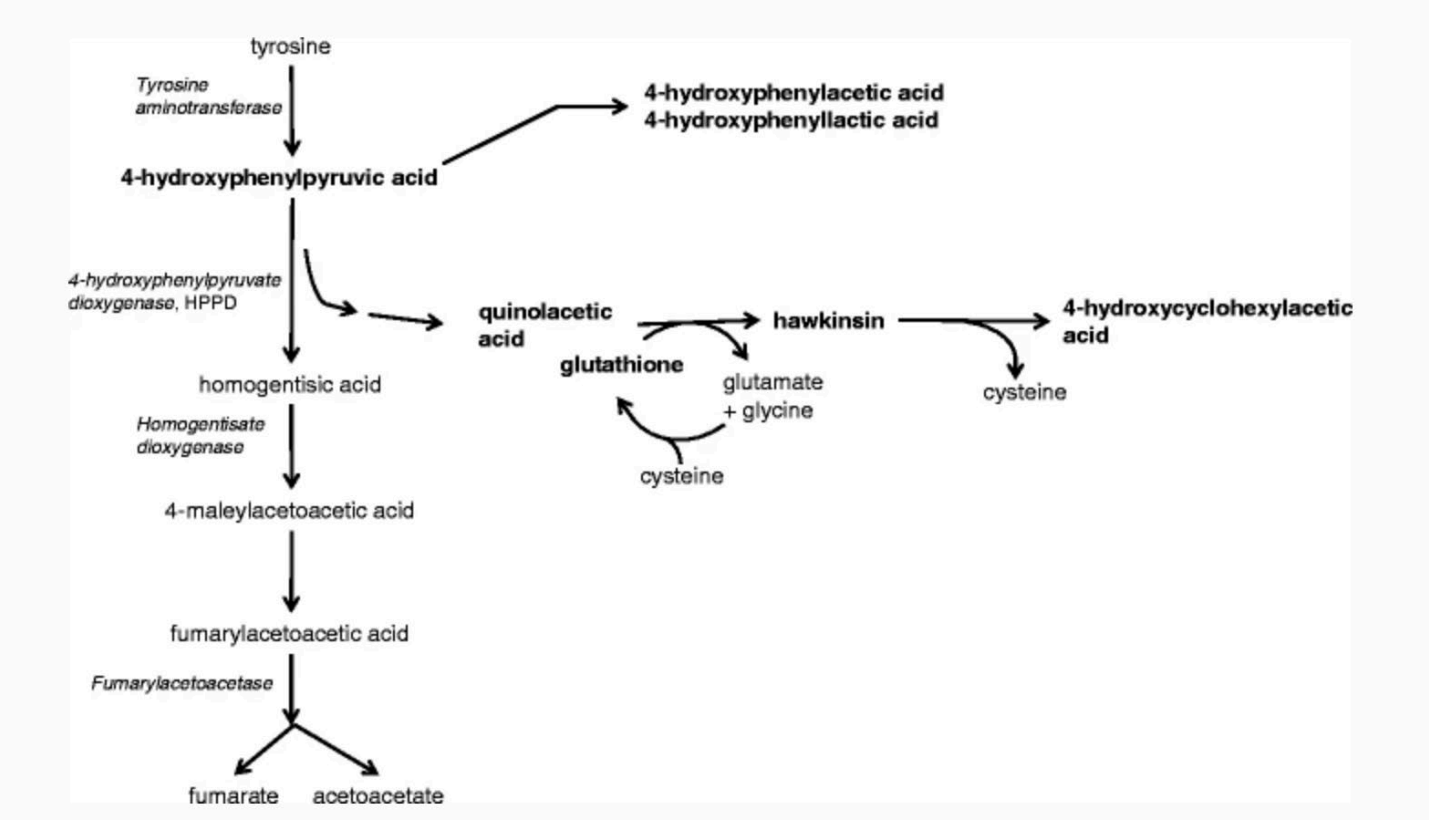
https://www.imagejournals.org/articles/tyrosinemia-type-presented-as-food-allergy-137.html

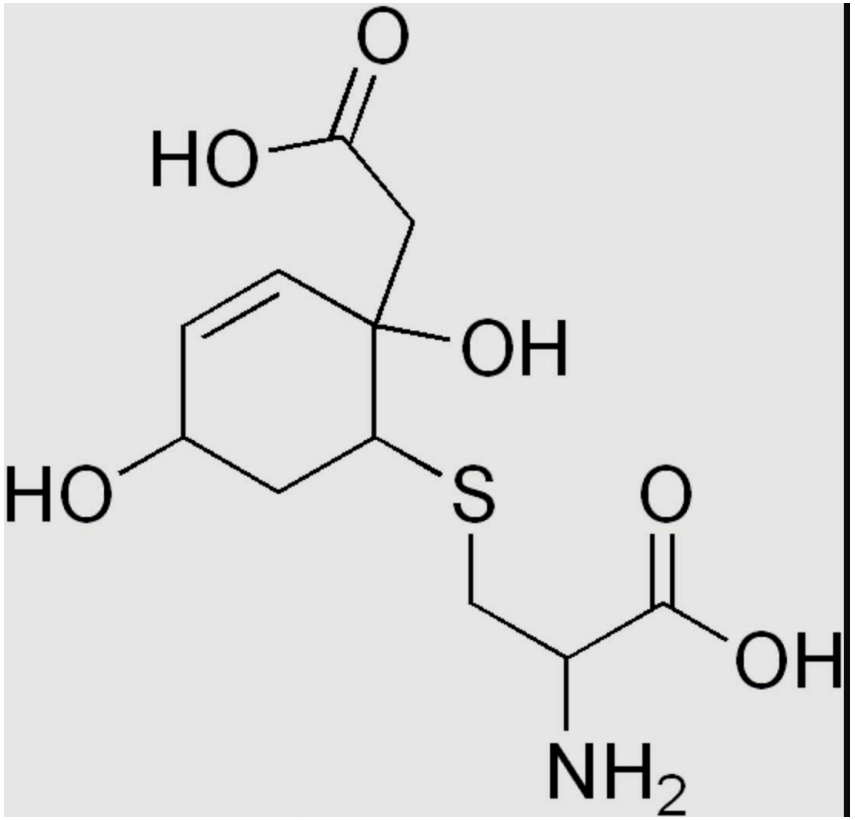
Type III – 4-hydroxyphenylpyruvic acid dioxygenase deficiency (enzyme inhibited by NTBC)

- Incidence estimate <1:1X10^6
- Ocular findings not reported
  - But have been reported in patients with HPPD deficiency due to NTBC
- Skin findings not reported as in type II

Type III – 4-hydroxyphenylpyruvic acid dioxygenase deficiency (enzyme inhibited by NTBC)

- Autosomal dominant form called Hawkinsinuria -- benign





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Type III – 4-hydroxyphenylpyruvic acid dioxygenase deficiency (enzyme inhibited by NTBC)

- Intellectual disability reported in late diagnosed patients
  - Question of several treated patients also having mild developmental abnormalities?
  - Seizures reported (but several case reports from consanguineous relationships, so relationship not entirely clear
  - Anecdotal reports of untreated adults with “normal” development
  - Some developmental abnormalities reported in patients identified by NBS who had less than recommended tyrosine control
    - Is there a role of CNS down-stream metabolites
    - Are there toxicities of phenolic metabolites

Other tyrosinemias

Treatment

- Restriction of dietary tyrosine and phenylalanine
- Goals based on empiric observation and practical issues (i.e., no data)
  - Plasma tyr <600
  - Plasma phe near normal range
- Regular eye exams and skin checks
- Monitor neurodevelopment

Transient tyrosinemia of the newborn

- Cause – purported to be due “immature” enzymes, particularly HPPD, the product of which may also inactivate the enzyme

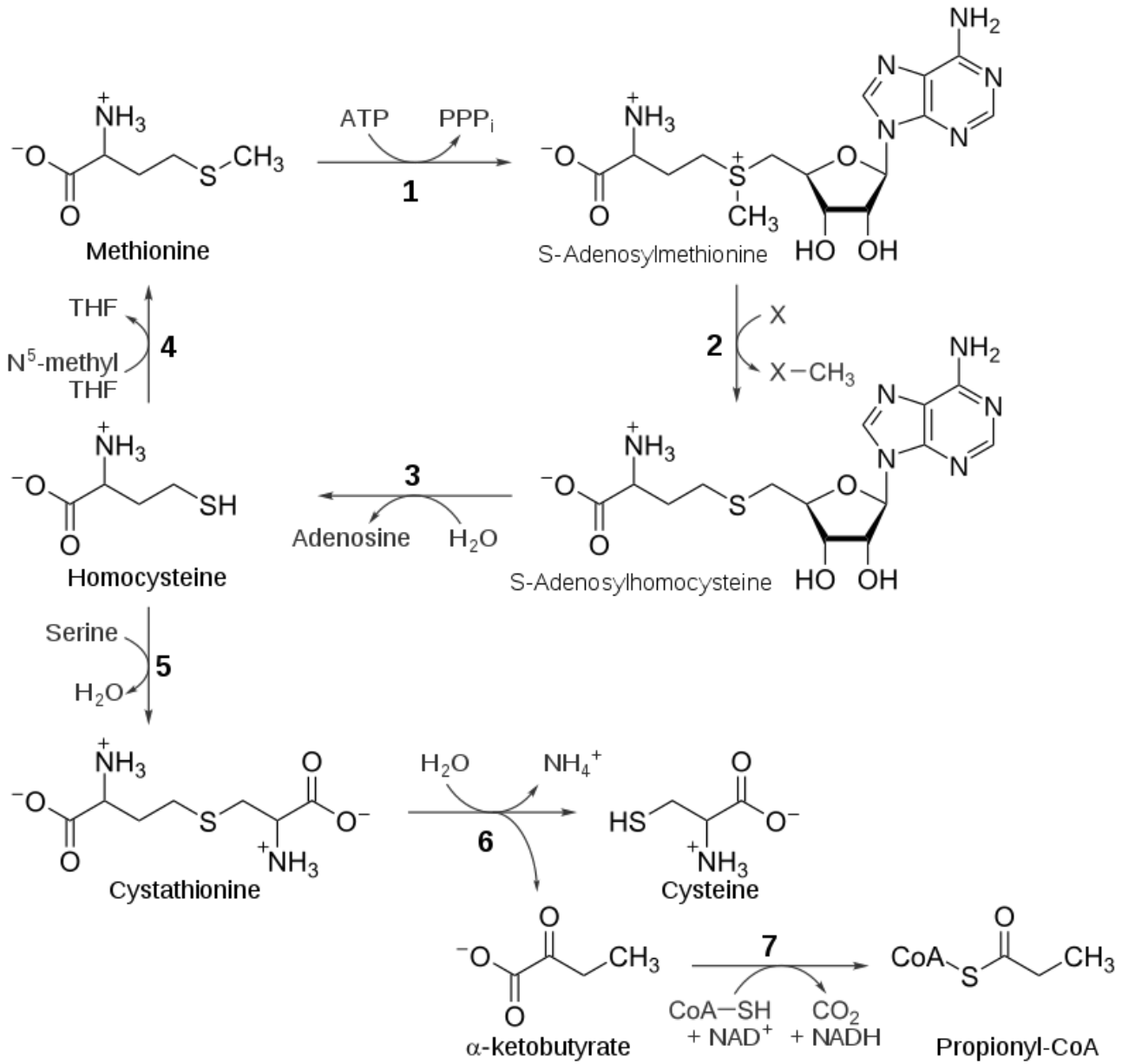
- Clinical
  - Self-limiting over 1 to 2 months
  - Apparently benign

- Incidence ~3-4:1,000
  - More common in premature infants

- Older literature suggests ascorbic acid (vitamin C) – 100 mg/day for 1-2 weeks – may speed up correction

An evolutionary moment

https://mamasgeeky.com/wp-content/uploads/2023/07/barbenheimer-meme-51.jpg



Conditions leading to an accumulation of homocysteine

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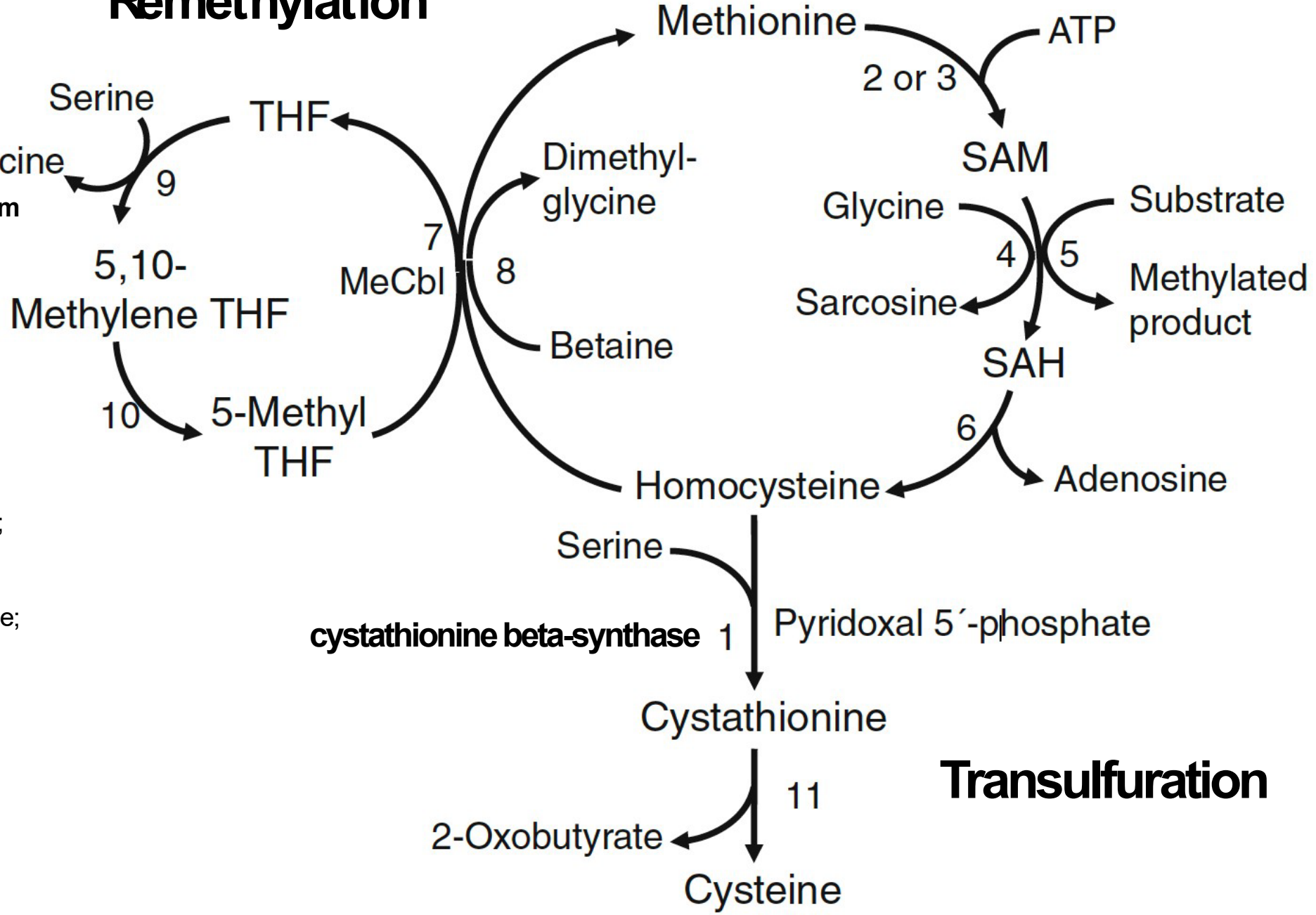
Remethylation



Transulfuration

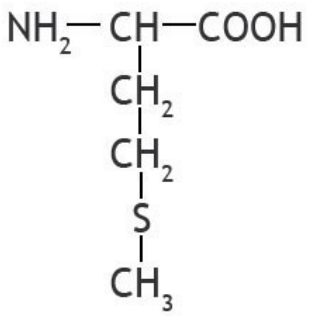
Pathways of methionine metabolism

SAM, S-adenosylmethionine;
SAH, S-adenosylhomocysteine;
THF, tetrahydrofolate;
MeCbl, methylcobalamin.

1 cystathionine beta-synthase;
2methionine adenosyltransferase I/III;
3methionine adenosyltransferase II;
4 glycine N-methyltransferase;
5 numerous methyltransferases;
6 S-adenosylhomocysteine hydrolase;
7 methionine synthase;
8betainehomocysteine methyltransferase;
9 Serine hydroxymethyltransferase;
10methylenetetrahydrofolate reductase;
11 cystathionine gamma-lyase

JInherit Metab Dis (2017)40:49–74

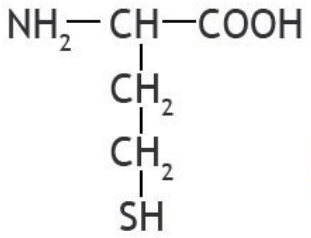
Disulfide bonds



Methionine

Normal Plasma Concentration

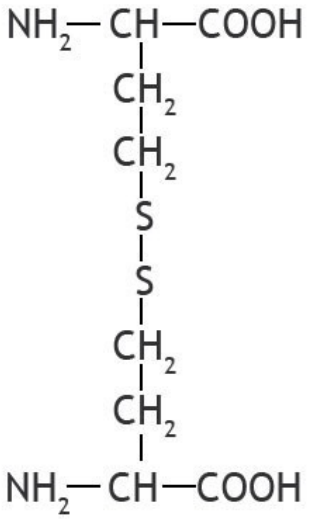
10-35μM



Homocysteine

Undetectable in normal plasma

5-15μM in plasma treated with a reducing agent



Homocystine

Undetectable

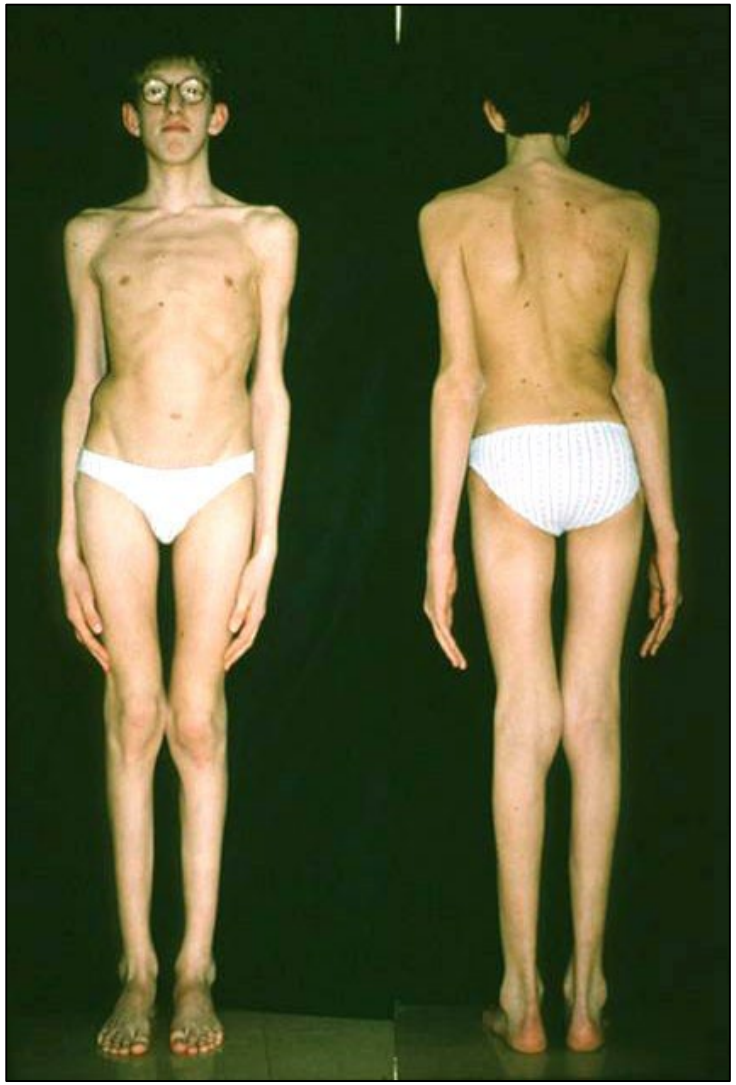
When accurate homocysteine measurements are important, measure “total homocysteine” and don’t rely on amino acid analysis, unless:

- You can make sure the specimen gets to the lab quickly, and…
- The specimen will be deproteinized soon after arrival in the laboratory

Classical homocystinuria

- Cystathionine β-synthase deficiency
- Autosomal recessive inheritance
- Incidence = 1/200,000 to 1/400,000 births
  - –Incomplete ascertainment
  - – Cases often missed on newborn screens obtained during the first week of life
- 50% of CBS mutations are pyridoxine (vitamin B_6) responsive

Classical untreated homocystinuria



Courtesy JM Saudubray

- Skeletal malformations
  - Marfanoid habitus
  - Osteoporosis
  - Scoliosis
  - Most common in B_6 non-responsive forms

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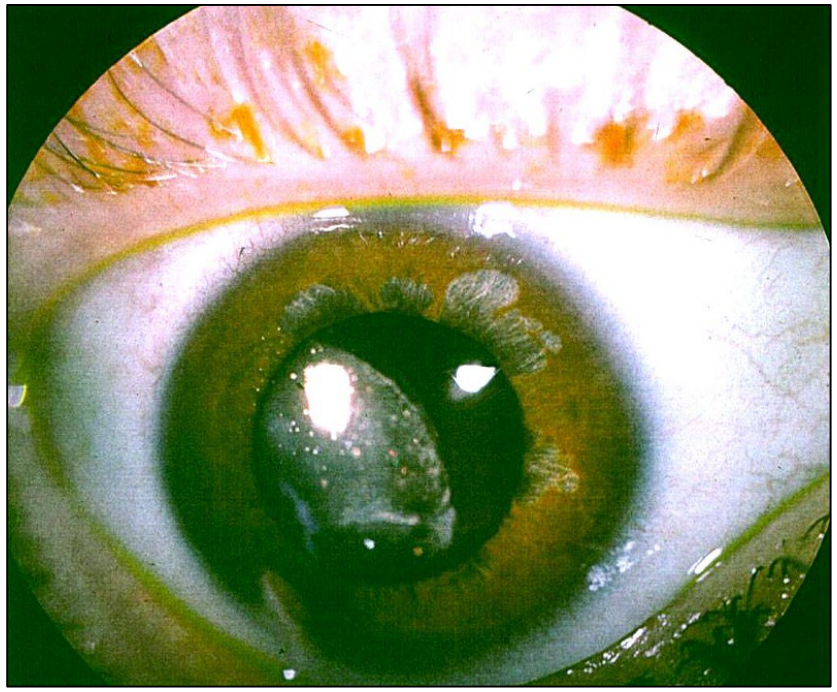
Other clinical findings

- Eye abnormalities
  - Ectopia lentis
    - 90% of affected individuals
    - Often bilateral
    - Typically, down and toward nose (opposite of Marfan)
  - Myopia
  - May be an isolated presentin g sign in children or adults
- Developmental disability and neuropsychiatric symptoms in many, but not



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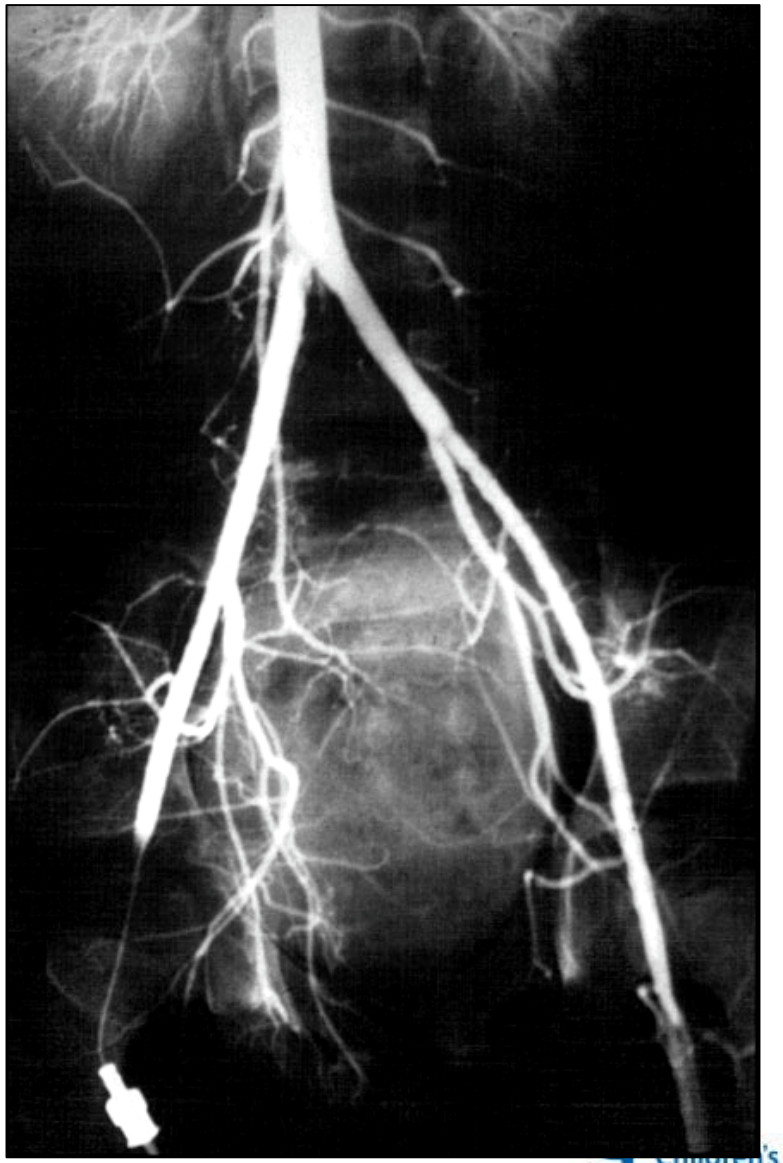
Recurrent thromboembolism

- May be an isolated presenting sign in late-onset B_6 responsive forms
- Thromboembolism can be a presenting sign
  - Phlebitis
  - Pulmonary embolism
  - Cerebrovascular accident
- Environmental triggers
  - Anesthesia
  - Catabolism
  - Smoking
  - Oral contraceptives

Atherosclerotic disease



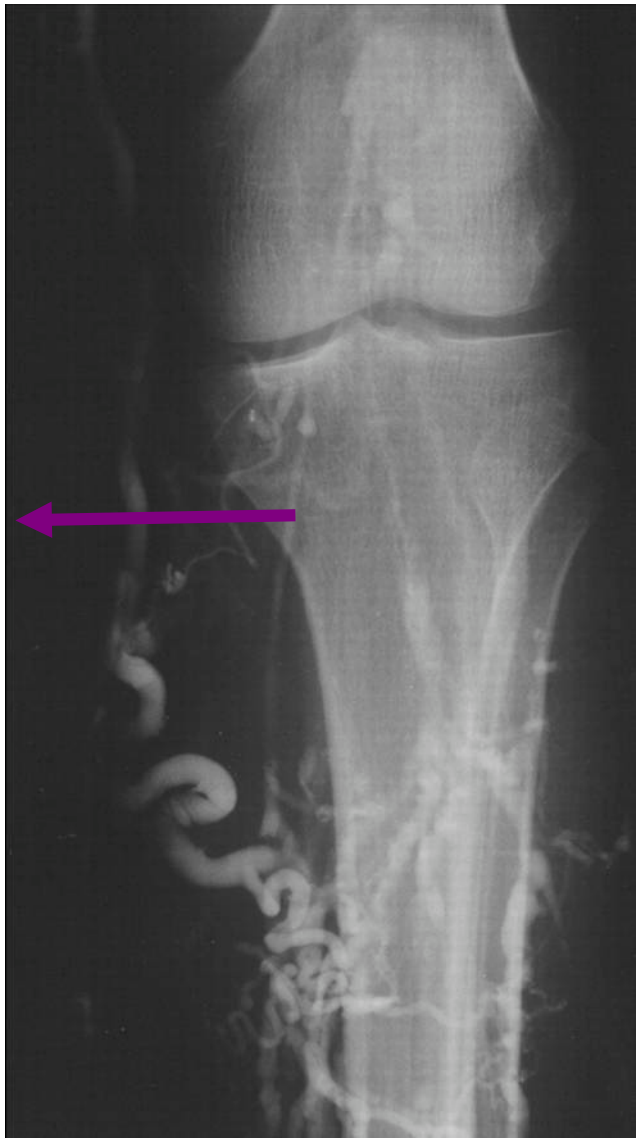
Courtesy of JM Saudubray

Thrombosis

Homocystinuria

Thrombus in popliteal vein

Note the collateral circulation



Sueyoshi E et al. Am J Roentgenol 2004;182:830

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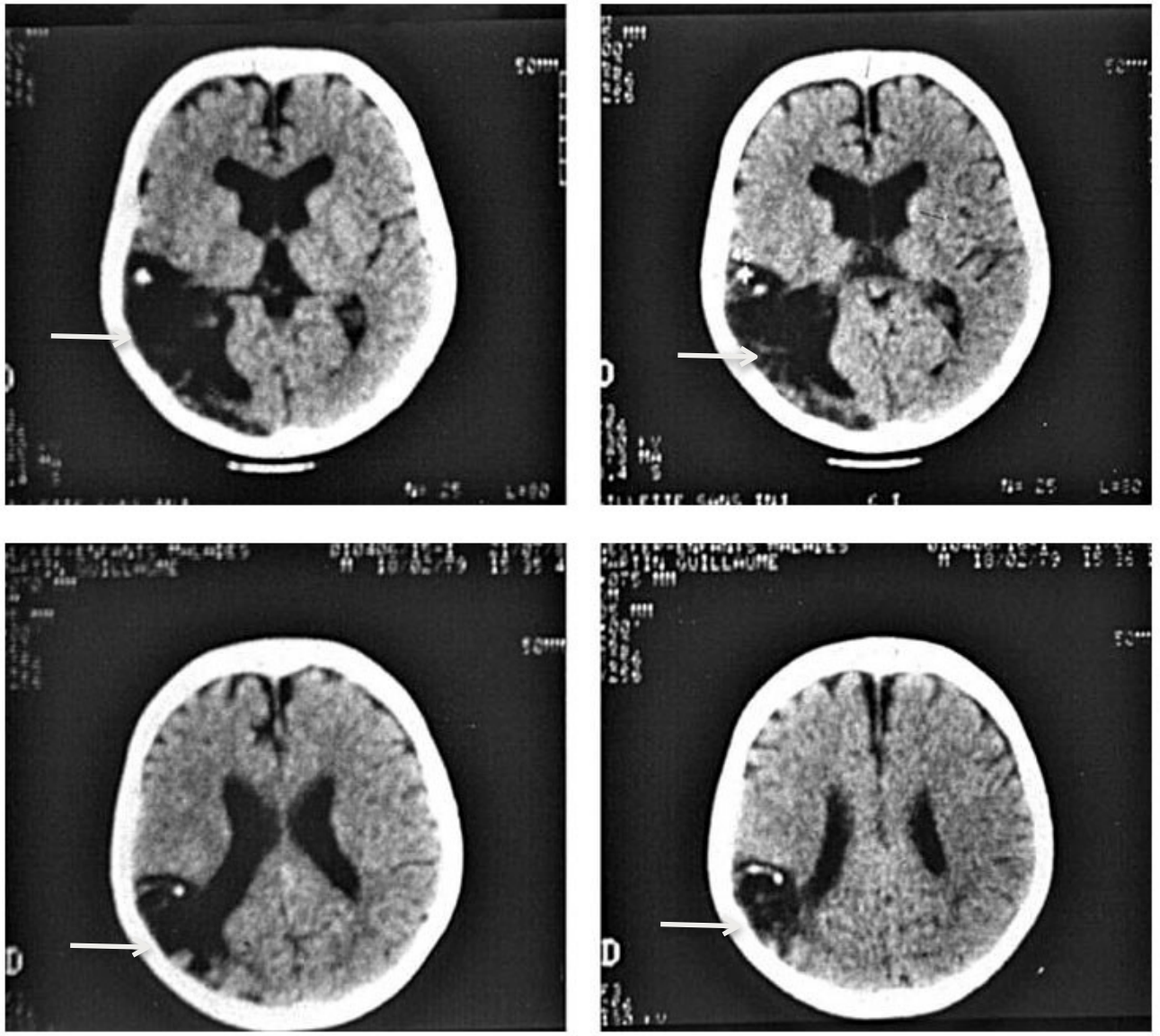
Thromboembolic stroke



Courtesy JM Saudubray

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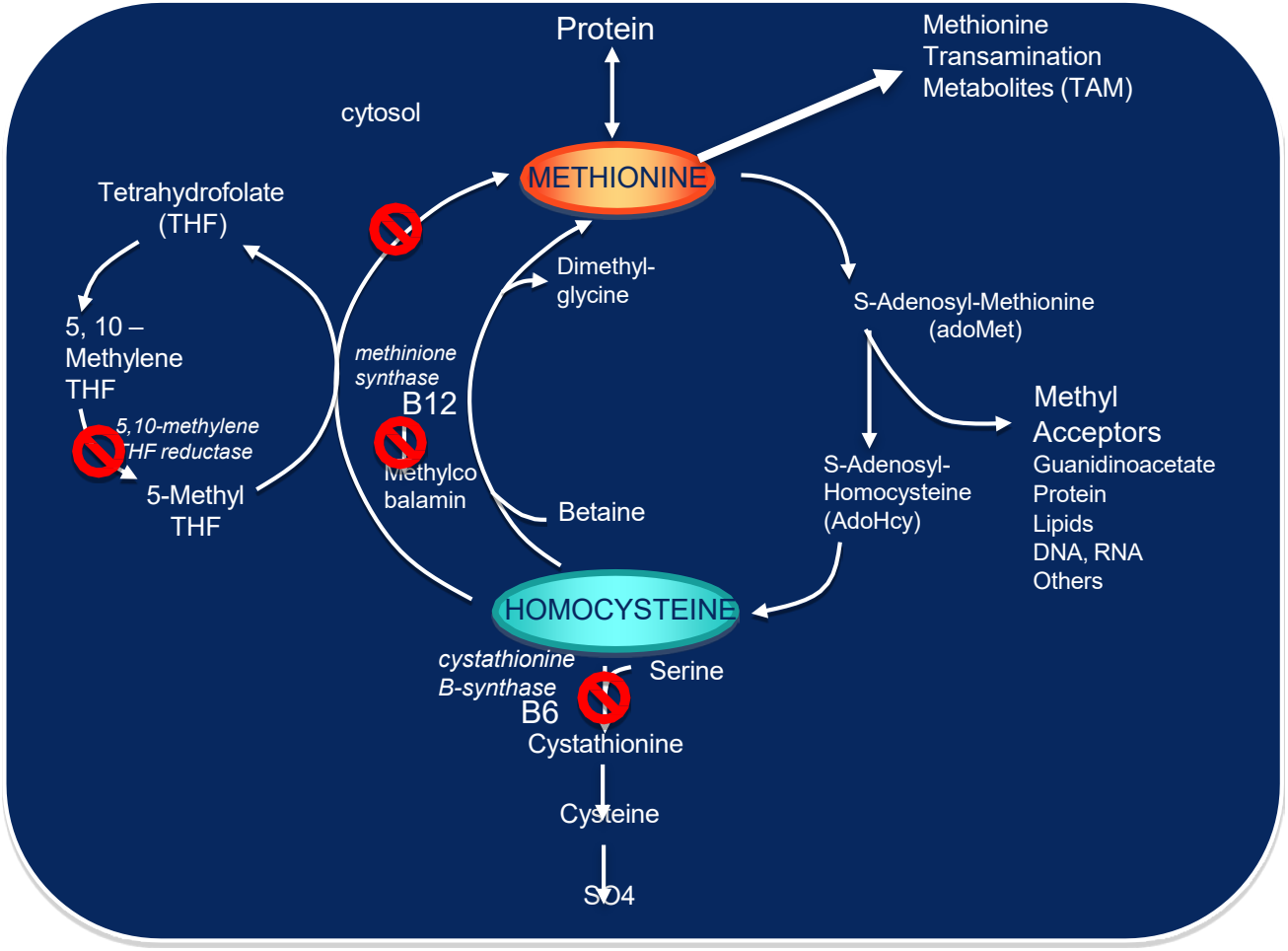
Other causes of homocystinuria



Yaghmai R et al. Am J Med Genet 2001;108:57

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Therapy (CBS deficiency)

- Pyridoxine responsiveness – 10 mg/kg/day (max. 500 mg)
  - Test total Hcy 2-3 X before Rx and 2-3 X on Rx after 4-6 weeks
  - >20% decrease is considered responsive (starting above 50 µmol/L)
  - High dose pyridoxine (>900 mg) can cause peripheral neuropathy
- Folate for all, B12 if deficient
  - HCU formulas usually have plenty of both
- Diet therapy – low protein, low-met formula
- Betaine – start at 50-100 mg/kg/day divided BID
  - Can increase up to 200 mg/kg/day, rarely benefit to higher dose
  - BHMT is satuable enzyme, so demonstrating additional benefit on plasma Hcy is helpful for higher doses

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Therapy (CBS deficiency) in the pipeline

- Enzyme replacement
- Intestinal substrate reduction – engineered probiotics
- Gene replacement/correction
- Proteosome inhibitors

Methionineadenosyltransferase I/III (Mat I/III) Deficiency

- Rare defect in conversion of methionine to s-adenosylmethionine
- SAM is an important methyl donor in a variety of pathways
- Clinical
  - Not clear whether there are clinical implications or not
  - SAM deficiency vs. excess met
- Treatment
  - Limiting met may lead to worse inadequacy of SAM
  - Excessive met may cause increased intracranial pressure
  - Consider both?

Acknowledgements

- Pete Baker – for on-going leadership of this series
- Johan Van Hove – originally suggested the idea after the 6th zoom call in one day in March (2020)
- Amazing speakers
- NAMA (Jerry, Mark and Jean-Marie for many borrowed slides)
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