Pediatric Metabolic Diseases with Ophthalmic Signs

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Principles

- Congenital Metabolic Pathway Errors
  - Most = Absent Enzyme Function
  - Usually Recessive Inheritance
  - Carriers have reduced enzyme function

Principles

- Many of these conditions have known causative genes
- Many have treatments that are most effective when instituted early
  - Clinical trials
- Any biochemical pathway can be affected and cause disease
- Neonatal screening in the US catches many of these conditions but State by State variations exist

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Iowa Neonatal Metabolic Screening Program

- http://www.idph.state.ia.us/genetics/neonatal_parent_page.asp
- Biotinidase deficiency
- Galactosemia- GALT, GALE
- Amino Acid disorders
- Fatty Acid Oxidation disorders
- Organic Acid Disorders
  - Errors in intermediate steps in metabolism of amino acids, carbohydrates and fats

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Multi-system Diseases

- Diagnosis and Treatment requires a team approach
  - Genetics/ Metabolic specialist
  - Nephrologist
  - Neurologist
  - Orthopedist
  - Otolaryngologist
  - Nutritionist
  - Ophthalmologist

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Classifications of Metabolic disorders

- Small Molecule Disorders
- Carbohydrate Metabolism
  Mucopolysaccharidoses, galactosemia
- Protein Metabolism
  Cystinosis, gyrate atrophy
- Lipid Metabolism
  Sphingolipidoses, Refusm disease
- Nucleic acid Metabolism
  Lesch-Nyhan syndrome
- Prophyrin metabolism
  Porphyrias
- Metal metabolism
  Wilson Disease
- Organelle Disorders
  - Lysosomal disorders
    Sphingolipidoses, mucopolysaccharidoses, gangliosidoses
  - Mitochondrial disorders
    Kearns-Sayre syndrome, Leber's hereditary optic neuropathy
  - Peroxisomal disorders
    Adrenoleukodystrophy

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How do I remember this Stuff?

- Memorize
- Note System
- Personal Wiki

Ocular Structure Affected

- Cornea
- Lens
- Retina
- Optic nerve
- Oculomotor

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Corneal Deposits

- Lysosomal disorders
  Mucopolysaccharidoses
  Mucolipidosis IV
  Glycoproteinoses
  Fabry disease
  Cystinosis
- Errors of lipid metabolism
  Familial hypercholesterolemia
  Lecithin-cholesterol acyltransferase deficiency (complete LCAT deficiency)
  Fish-eye disease (partial LCAT deficiency)
- Errors of amino-acid metabolism
  Tyrosinemia type II
- Errors of copper metabolism
  Wilson disease

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Cataract

- Lysosomal disorders
  Glycoproteinoses
- Errors of sugar metabolism
  Galactosemia
  Sorbitol dehydrogenase deficiency
- Errors of amino-acid metabolism
  D1-Pyrroline-5-carboxylate synthase deficiency
- Peroxisomal disorders
  Peroxisome biogenesis defects
  Rhizomelic chondrodysplasia punctata
- Errors of cholesterol metabolism
  Cerebrotendinous xanthomatosis (cholestanol lipidosis)
  Mevalonate kinase deficiency (classic form)
  Conradi-Hünermann syndrome
  Smith-Lemli-Opitz syndrome
- Mitochondrial oxidative phosphorylation defects
- Errors of copper metabolism
  Wilson disease

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Diseases with Ectopia Lentis

- Marfan syndrome
- Weill-Marchesani syndrome
- Homocystinuria
- Hyperlysemia
- Sulfite oxidase deficiency
- Ehlers-Danlos syndrome type 1

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Cherry Red Spot

Frequent	Occasional
GM2 gangliosidosis type IB (Tay-Sachs)	GM1 gangliosidosis, type I and II
Galactosialidosis	Neimann-Pick disease
Sialidosis Type I and II	Farber Lipogranulomatosis
	Metachromatic leukodystrophy

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Retinal Degeneration

- Errors of lipid metabolism
  Abetalipoproteinaemia
  Peroxisome biogenesis disorders (Zellweger spectrum)
  Isolated b-oxidation defects
  Refsum disease
  LCHAD deficiency
  MTP deficiency
  Sjögren-Larsson syndrome
- Errors of lysosomal functions
  Neuronal ceroid lipofuscinoses
  Mucopolysaccharidoses: except Morquio dz
  Mucolipidosis IV
  Krabbe disease (late onset)
- Errors in mitochondrial energy metabolism
  Kearns-Sayre syndrome
- Errors of copper metabolism
  Menkes disease
- Isolated retinal degeneration
  Gyrate atrophy
- Others
  Cobalamin C disorder
  Congenital disorders of glycosylation

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Optic atrophy

- Errors in mitochondrial energy metabolism
  - Leber's hereditary optic neuropathy (young adults males)
  - 3-Methylglutaconic aciduria type III (Costeff optic atrophy syndrome)
- Leukodystrophies
  - Krabbe globoid cell leukodystrophy
  - Metachromatic leukodystrophy
  - Canavan disease
  - Pelizaeus-Merzbacher disease
- PEHO syndrome (Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy)
- Friedreich ataxia
- Behr syndrome

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Ocular motor findings

Disorder	Disturbance of eye movement
Gaucher disease (type 2&3)	Horizontal and vertical gaze palsy
Neimann-Pick type C	Vertical gaze palsy
GM2 gangliodosis B, (Tay-Sachs)	Vertical gaze palsy
Abetalipoproteniemia	Horizontal and vertical gaze palsy
Respiratory chain Disorders- Kearnes-Sayre, Leigh's syndrome, CPEO	Ophthalmoplegia
Neurotransmitter disorders (tyrosine hydroxylase deficency & others)	Oculogyric crisis
Wilson Disease	Oculogyric crisis, upgaze palsy

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Lysosomal storage diseases and Early Corneal Clouding

- Mucolipidosis IV
  - Clouding by 6 weeks possible
  - Progressive visual impairment- retinal degeneration
  - Psychomotor delay, acholrydria- absent gastric acid
  - MCOLN1 gene mutation, codes for mucolipin-1
  - 70%-80% have Ashkenazi Jewish ancestry

http://www.ml4.org/our-children

- Mucopolysaccharidosis I (MPS I)
  - Clouding by 6 months in severe cases
    - 3 subtypes; Hurler MPS I-H, Hurler-Scheie MPS I-H/S, Scheie MPS I-S (most to least severe)

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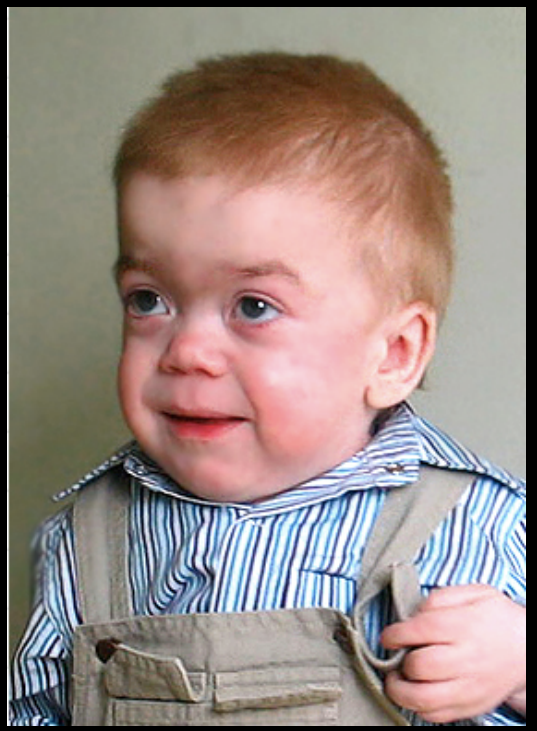
Hurler Syndrome

- MPS I-H; “Gargoylism”
- IDUA gene (4p16.3) mutation:
  - Complete deficiency of alpha-L-iduronidase enzyme and lysosomal accumulation of dermatan sulfate and heparan sulfate
- Skeletal abnormalities, psychomotor delay, cardiomyopathy, organomegaly and hearing loss
- Enzyme replacement therapy
- Less severe type : Scheie syndrome- biochemically same



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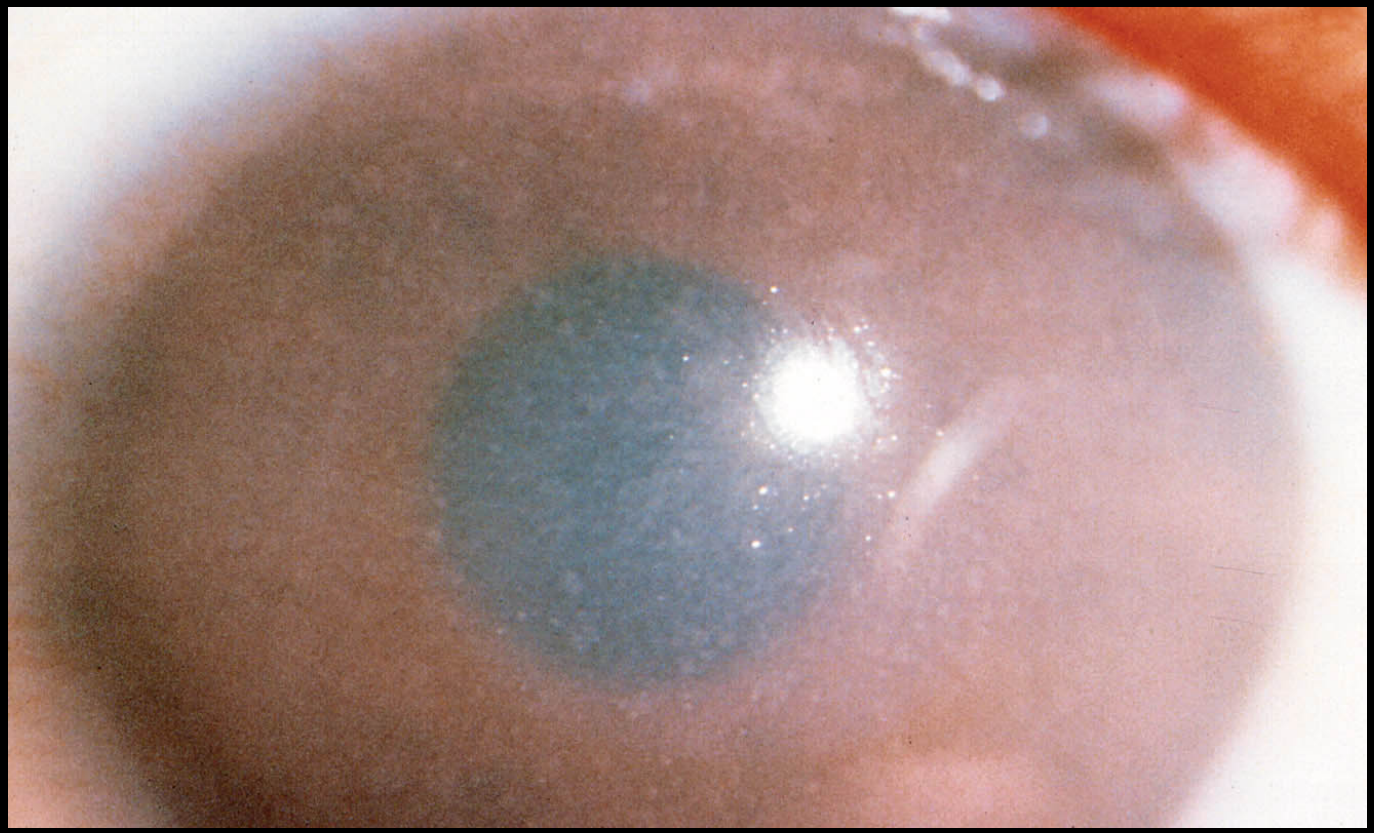
Hurler Syndrome



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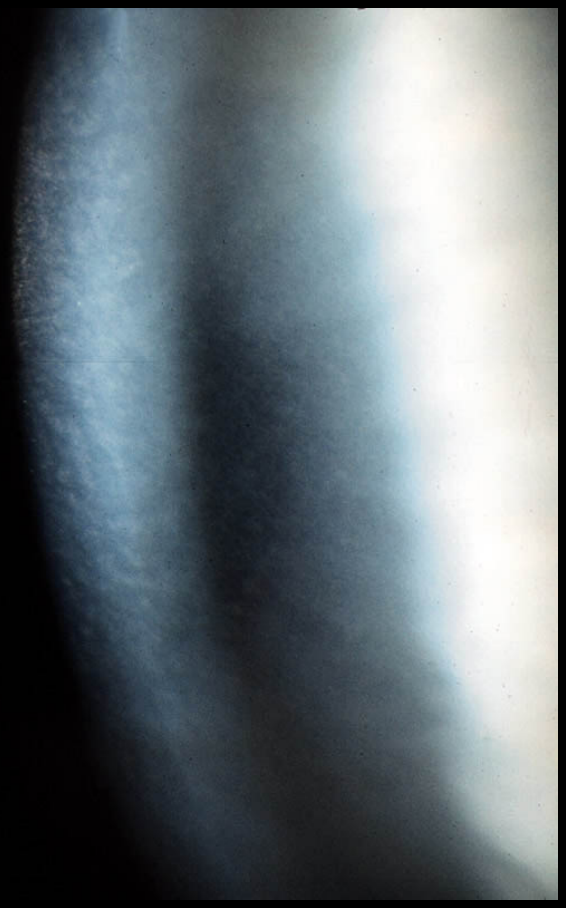
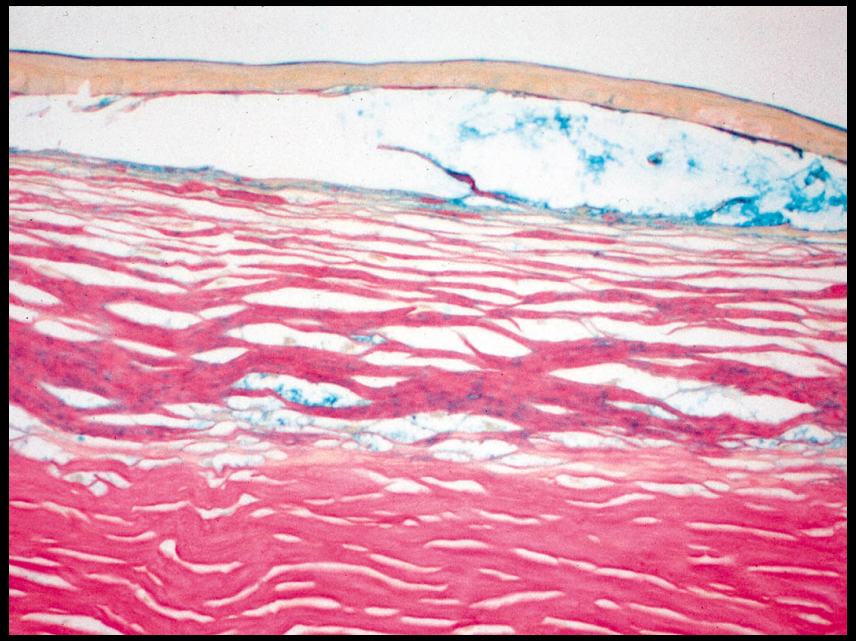
Hurler Syndrome





Mucopolysaccharide stains blue with alcian blue stain

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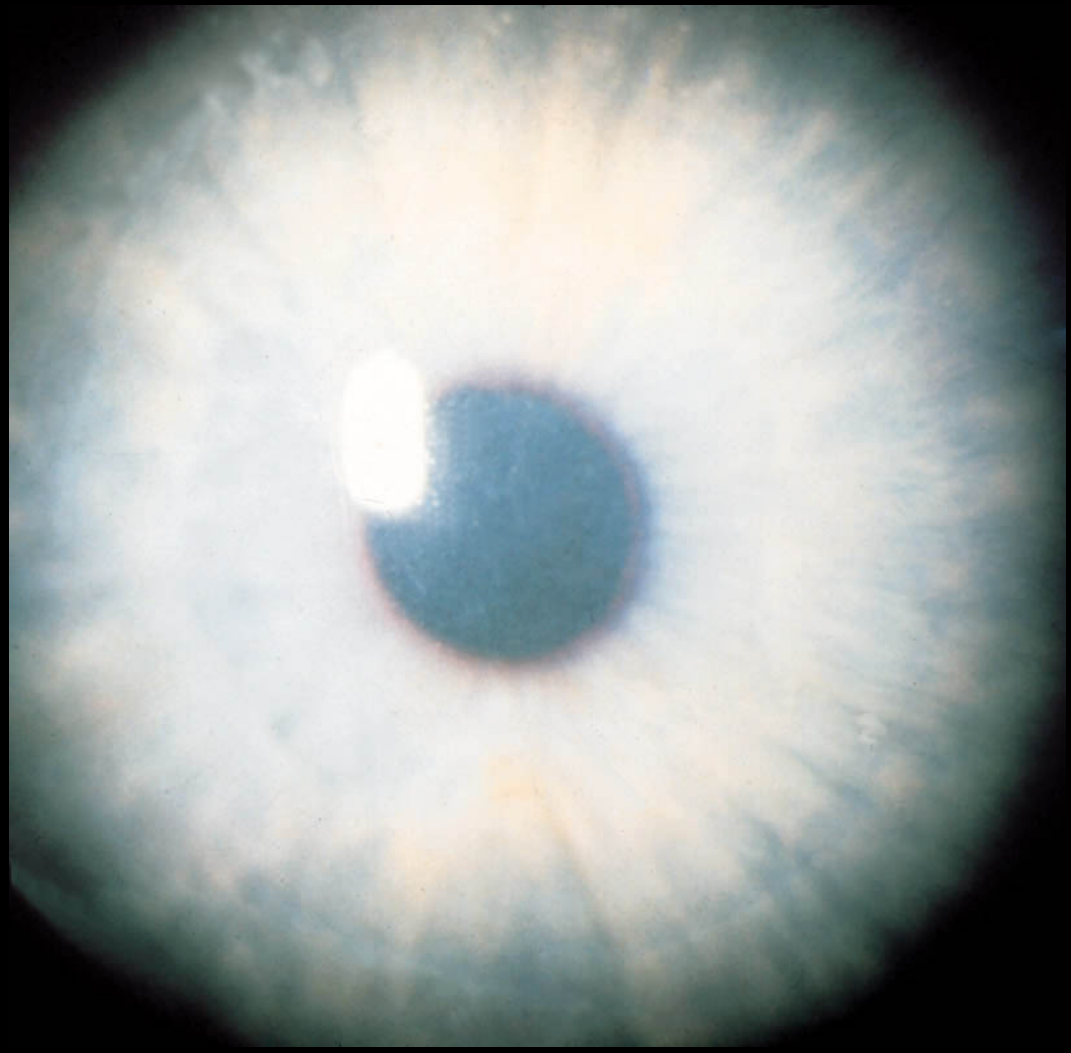
Scheie Syndrome



Cystinosis

- CTNS gene mutation
  - decrease in cystinosin- transports cystine out of cells
  - Increased lysosomal cystine
- Can lead to kidney failure, failure to thrive and corneal deposits
- Photophobia may be severe
- Treatment
  - Oral cysteamine for the systemic deposits- doesnt help eyes!
  - Topical cysteamine (q2h)- Cystaran (FDA approved)

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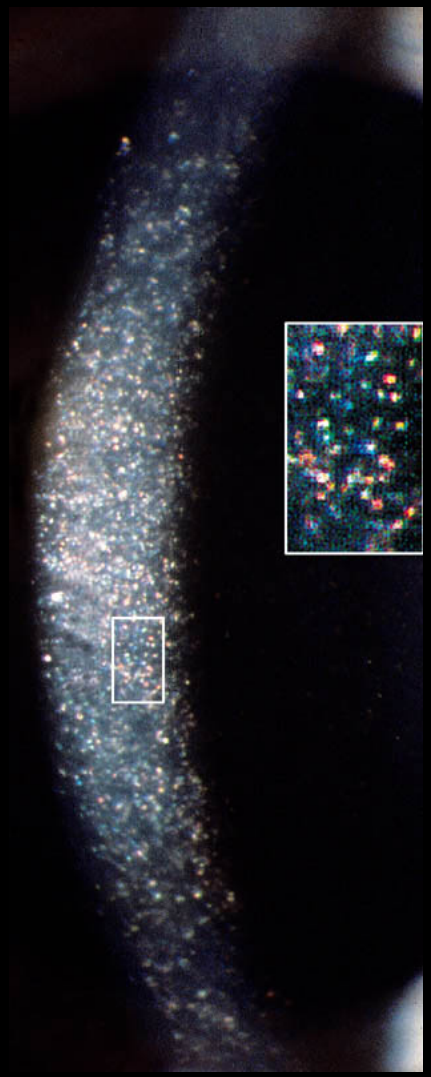
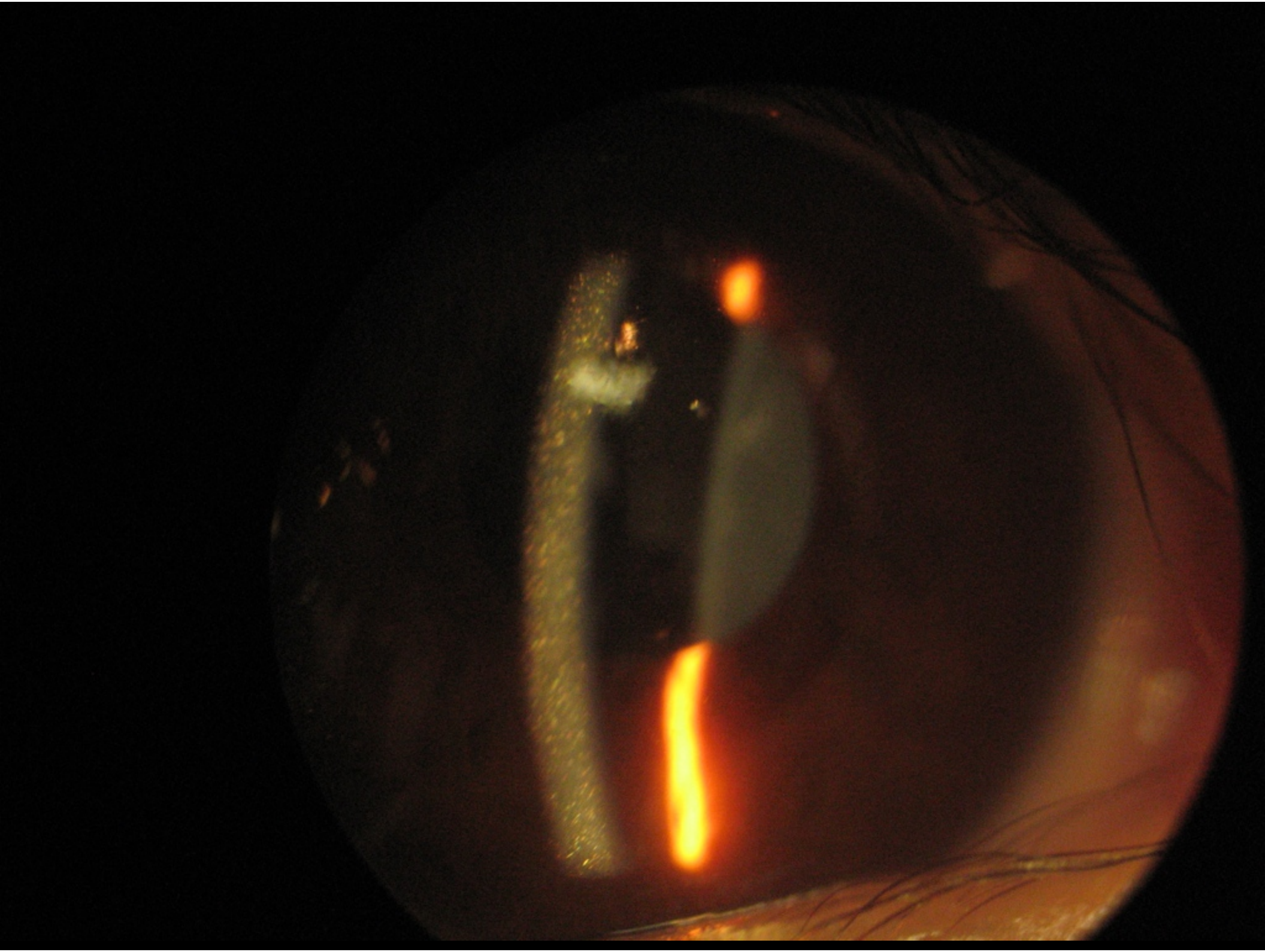
Cystinosis





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Wilson Disease

- "Hepatolenticular" degeneration
  - ATP7B gene mutation:
    - enzyme transports copper into bile and incorporates it into ceruloplasmin
  - Excess copper in liver, kidney, basal ganglia, eyes
    - Cirrhosis, kidney failure, movement disorder
- Kaiser-Fleischer ring
  - Copper deposition in Decemet's membrane
  - Initially at 12 and 6 o'clock
  - Resolves with systemic treatment
  - Late finding but occurs in nearly every case of CNS dysfunction

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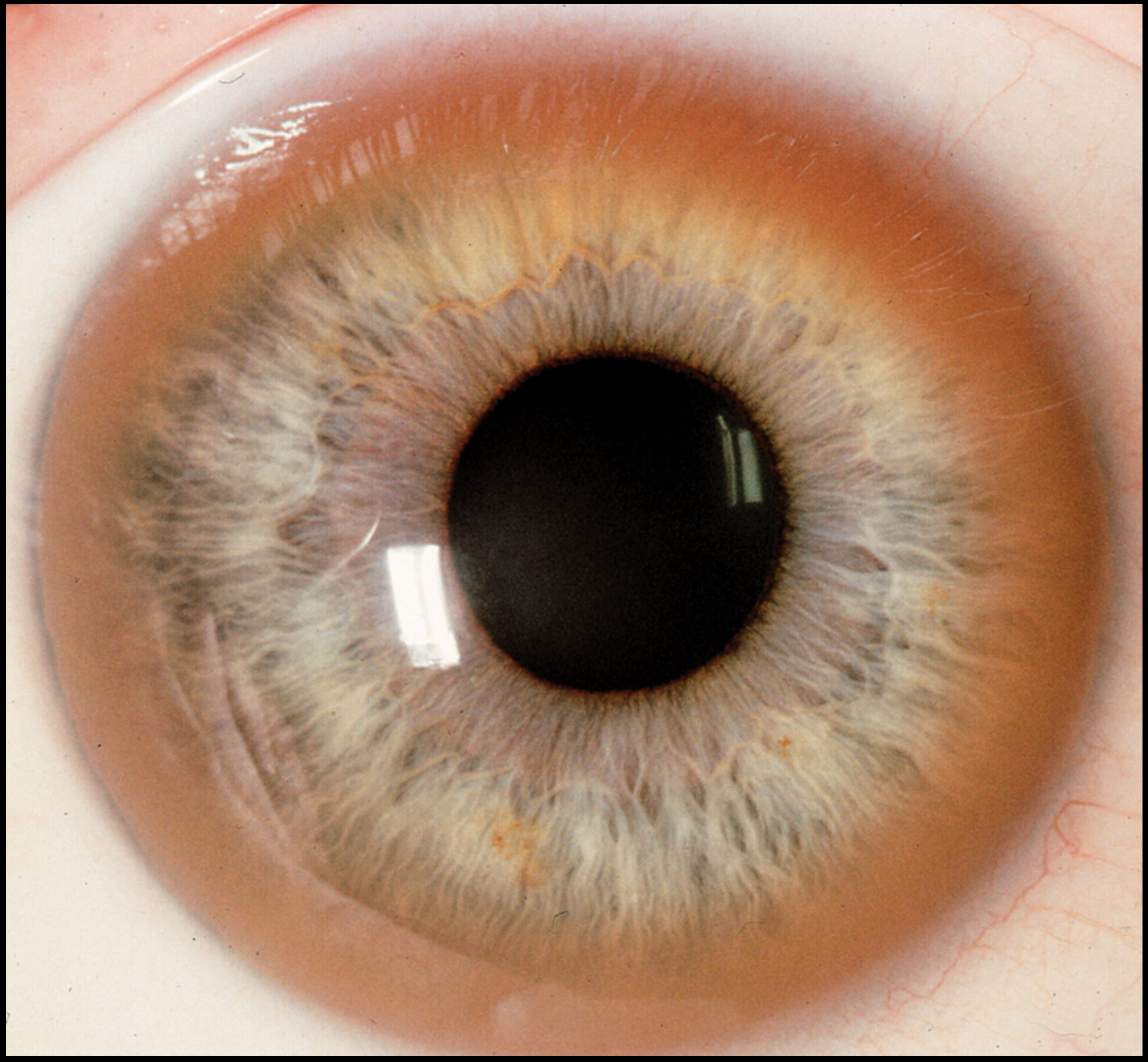
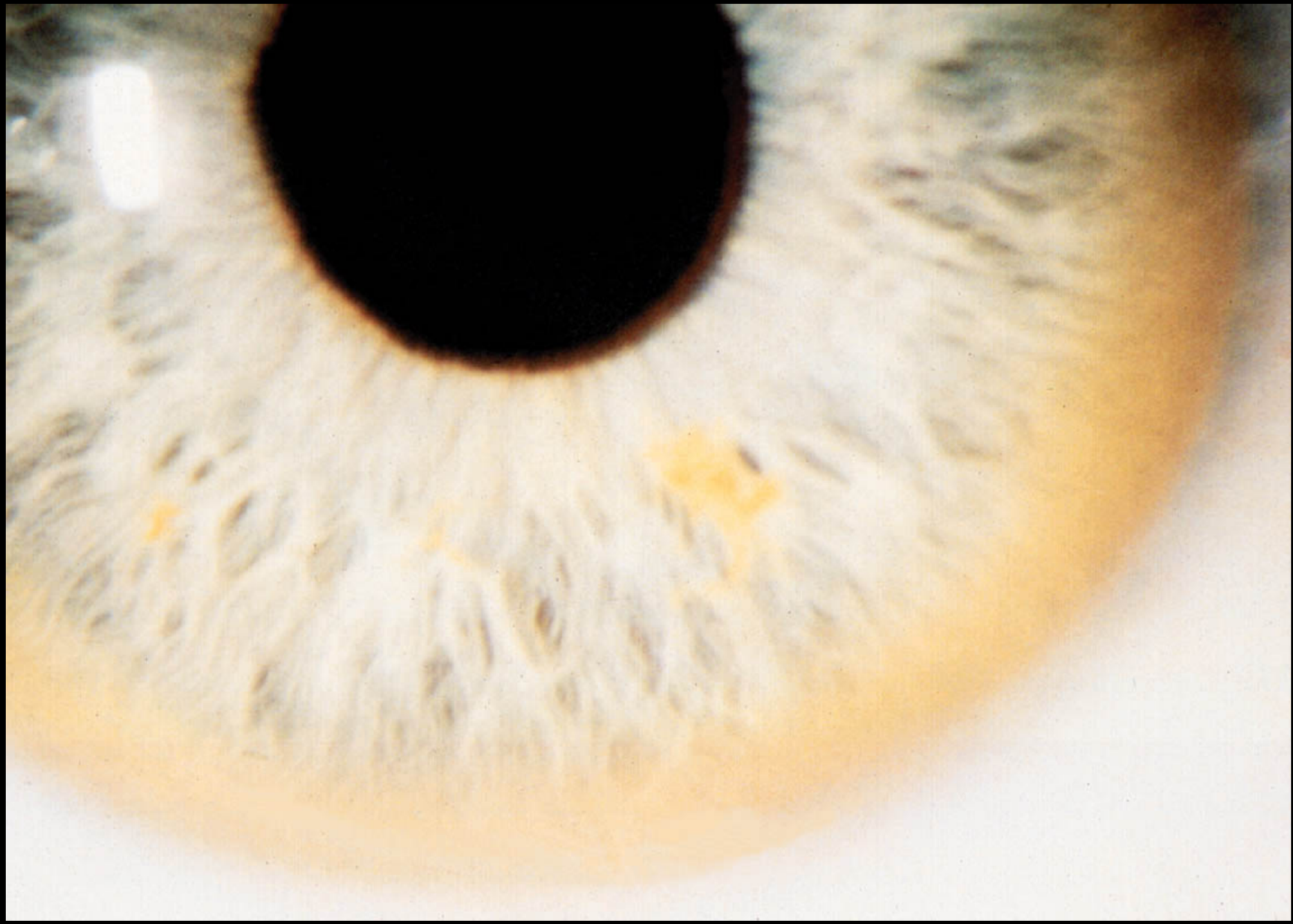
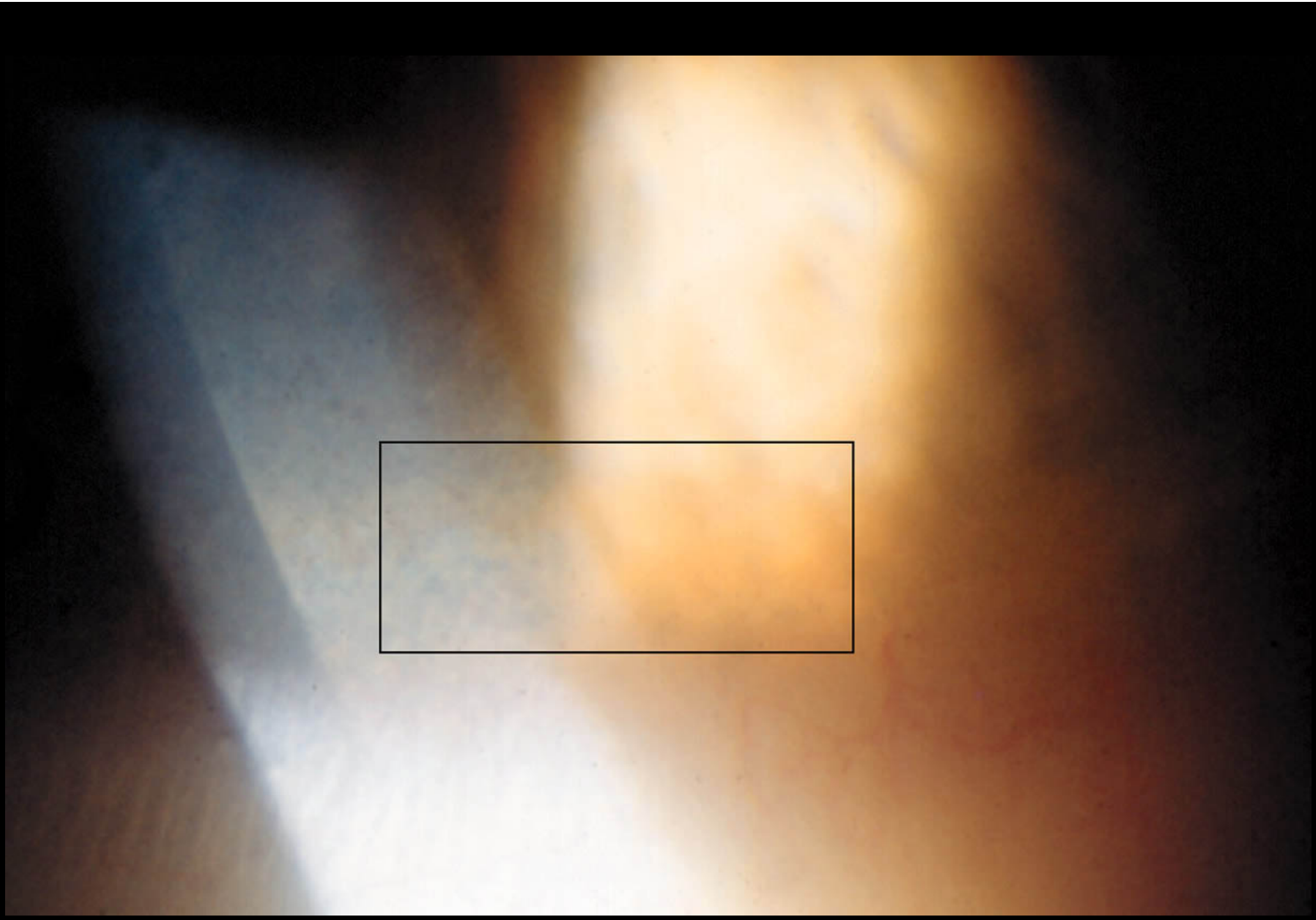
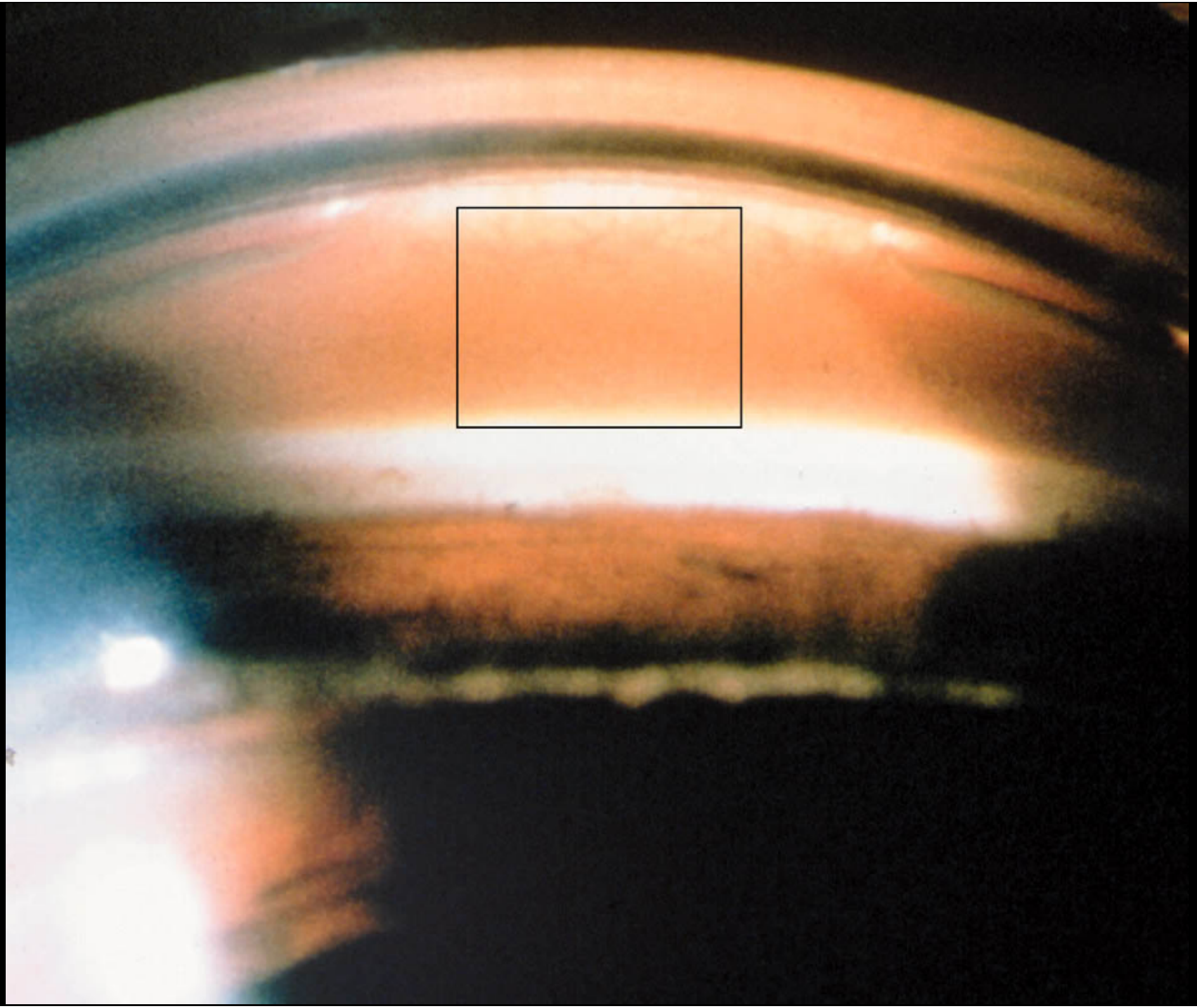
Wilson Disease

- Sunflower cataract: copper deposition in lens capsule
- Laboratory testing can detect condition earlier
  - Elevated serum and urinary copper
  - Low serum ceruloplasmin
- Treatment
  - Copper chelators
    - D-penicillamine, trientine
  - Zinc acetate (blocks copper uptake in gut)
  - Low copper diet







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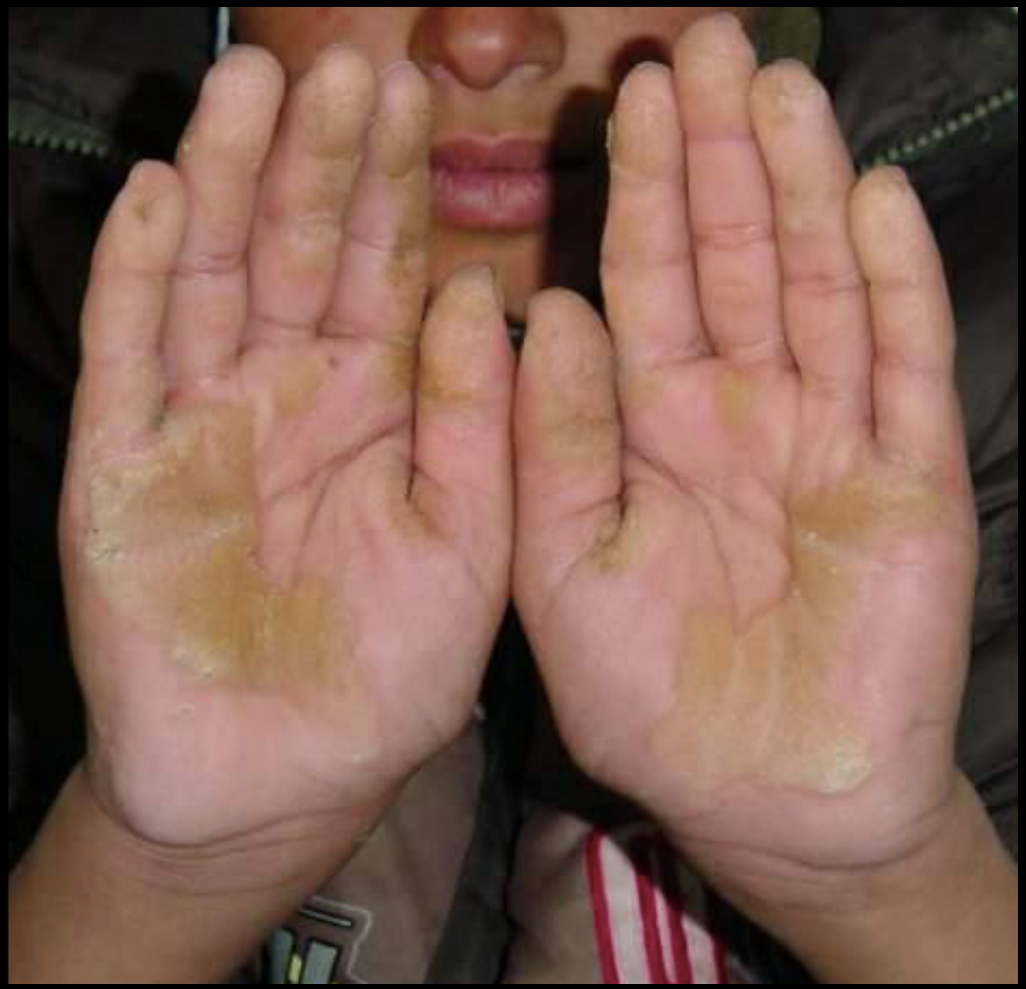
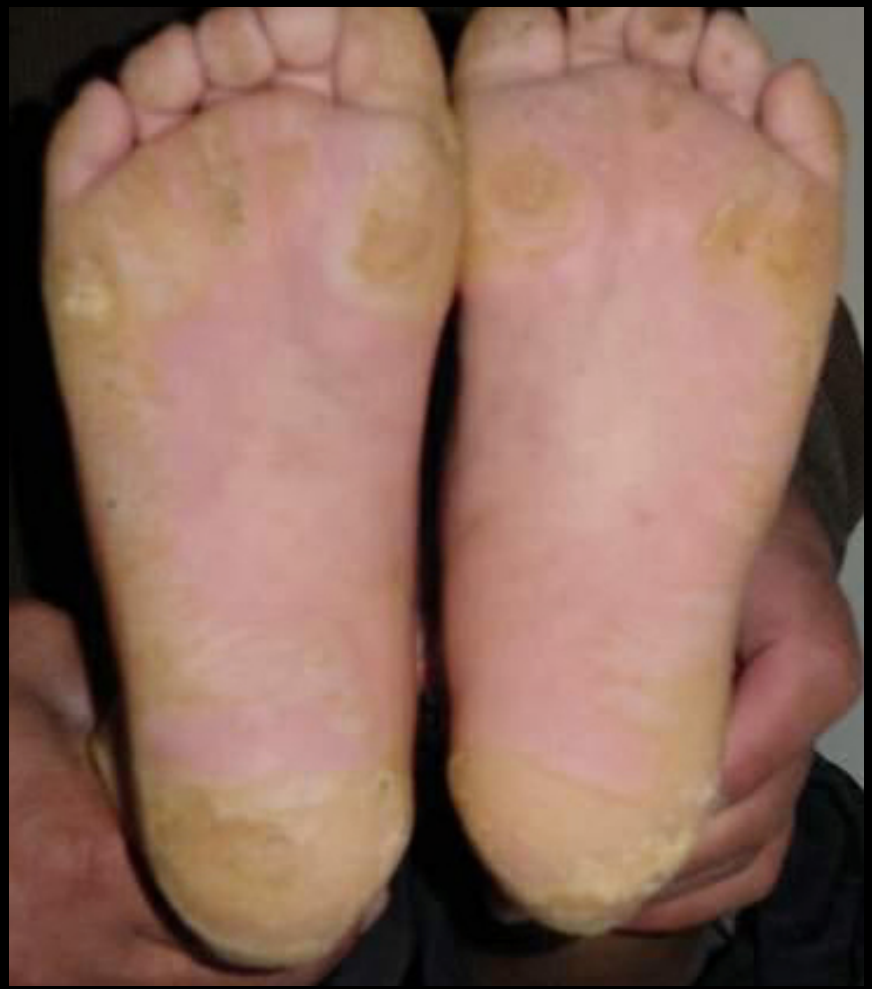
Tyrosinemia Type II

- Gene TAT defect leading to low tyrosine aminotransferase

- Build up of Tyrosine in tissues
  - Skin, eyes and brain
  - Painful circumscribed calluses
  - Mental deterioration





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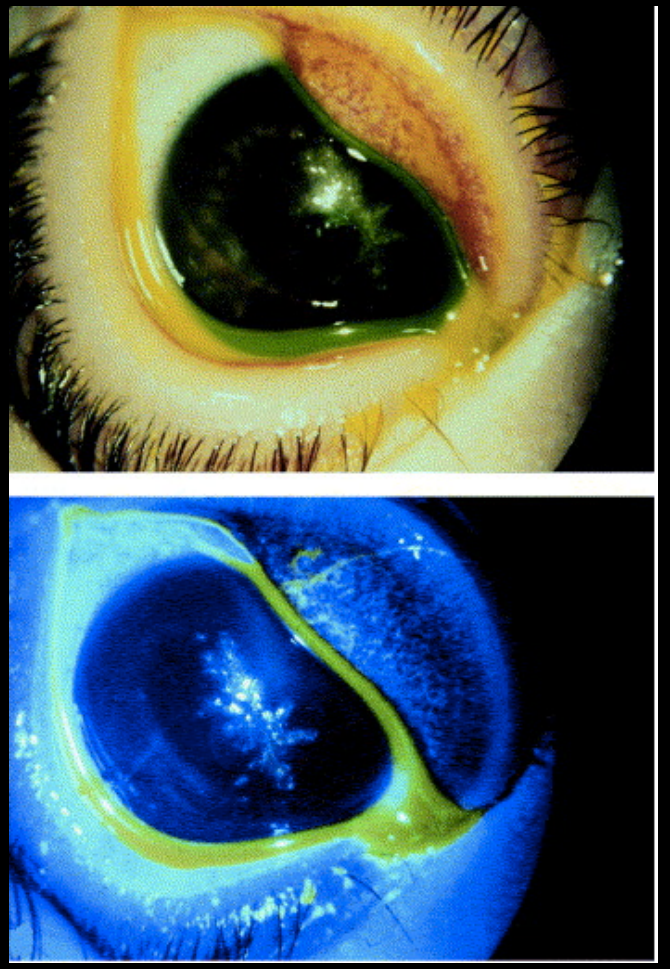
Tyrosinemia Type II

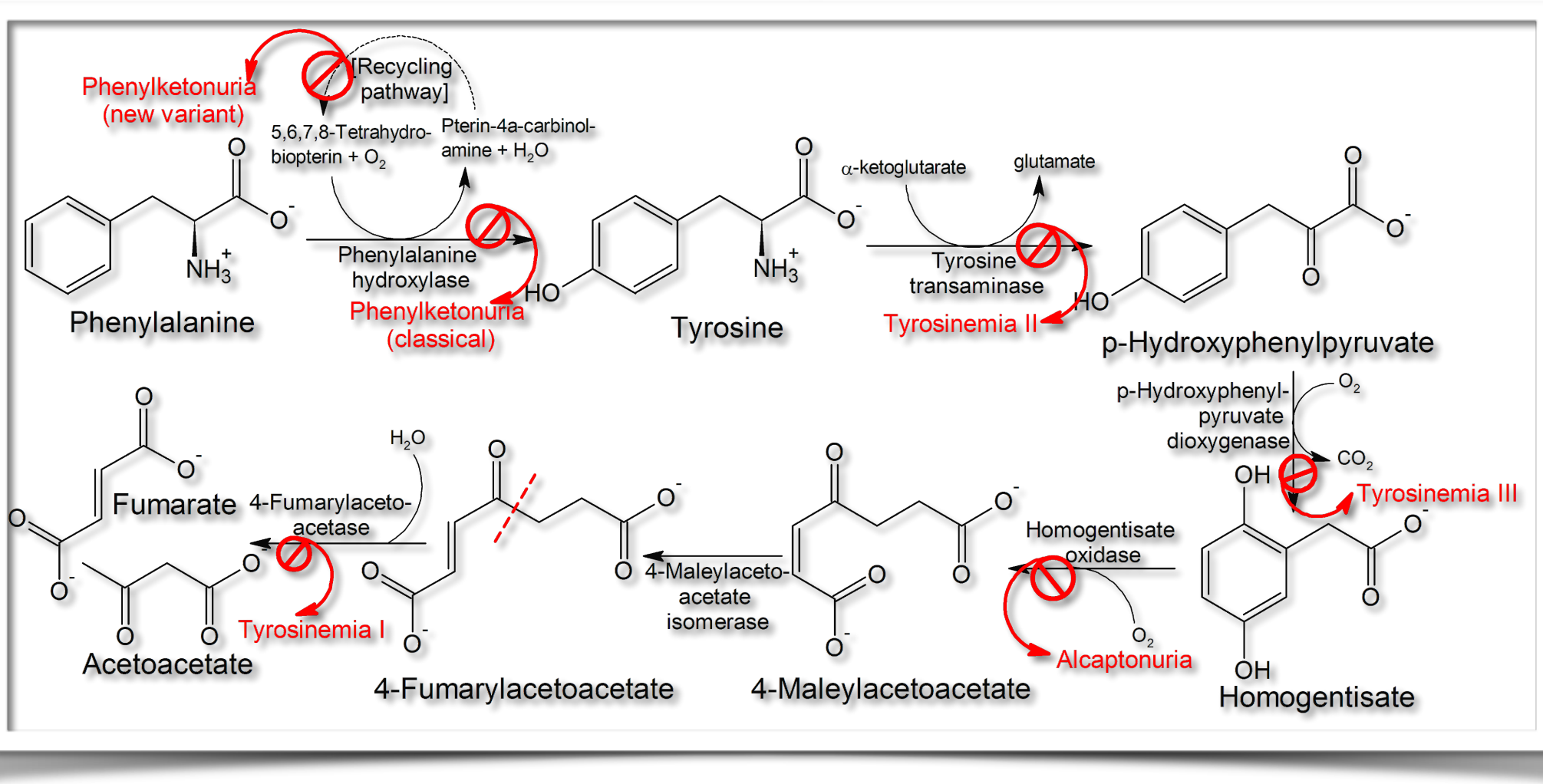
- Dendritiform corneal epithelial deposits
  - non staining
  - Tearing
  - Photophobia



American Journal of Ophthalmology
Volume 132, Issue 4 , Pages 522-527, October 2001

Tyrosinemia Type II

- Treatment:
  - Diet low in tyrosine, phenylalanine and methionine
  - Nitisinone (NTBC) “Orfadin”- inhibits the proximal tyrosine metabolic pathway


Phenylketonuria
(new variant)
[Recycling
pathway]
5,6,7,8-Tetrahydro-
biopterin + O2
Pterin-4a-carbinol-
amine + H2O
Phenylalanine
hydroxylase
Phenylketonuria
(classical)
Phenylalanine
Tyrosine
α-ketoglutarate
glutamate
Tyrosine
transaminase
Tyrosinemia II
p-Hydroxyphenylpyruvate
p-Hydroxyphenyl-
pyruvate
dioxygenase
O2
CO2
Tyrosinemia III
Homogentisate
Homogentisate
oxidase
O2
Alcaptonuria
4-Maleylacetoacetate
4-Maleylaceto-
acetate
isomerase
4-Fumarylacetoacetate
H2O
4-Fumarylaceto-
acetase
Tyrosinemia I
Fumarate
Acetoacetate

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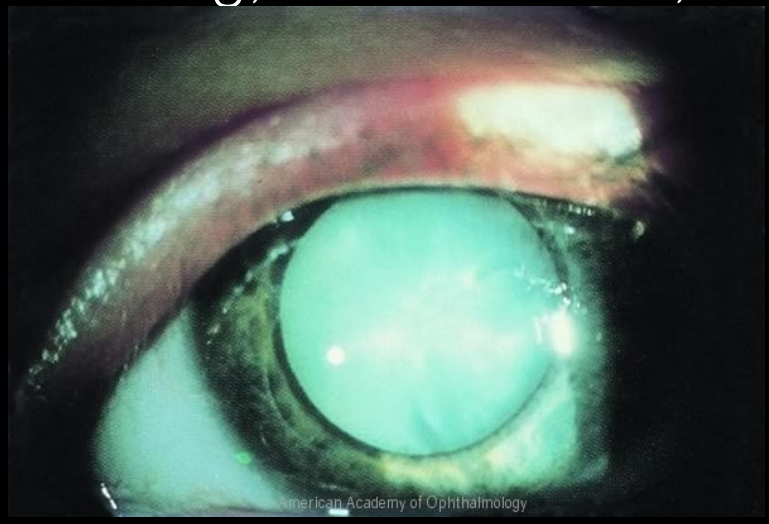
Galactosemia

- Galactose 1-phosphate uridylyltransferase (GALT) deficiency (Newborn screen in Iowa)
  - "Classic Galactosemia"or Type I
  - Symptoms begin within first few days of life
  - Jaundice, vomiting, diarrhea, poor feeding, failure to thrive, lethargy, sepsis
  - Cataracts 30%
  - Most mild and resolve with dietary intervention



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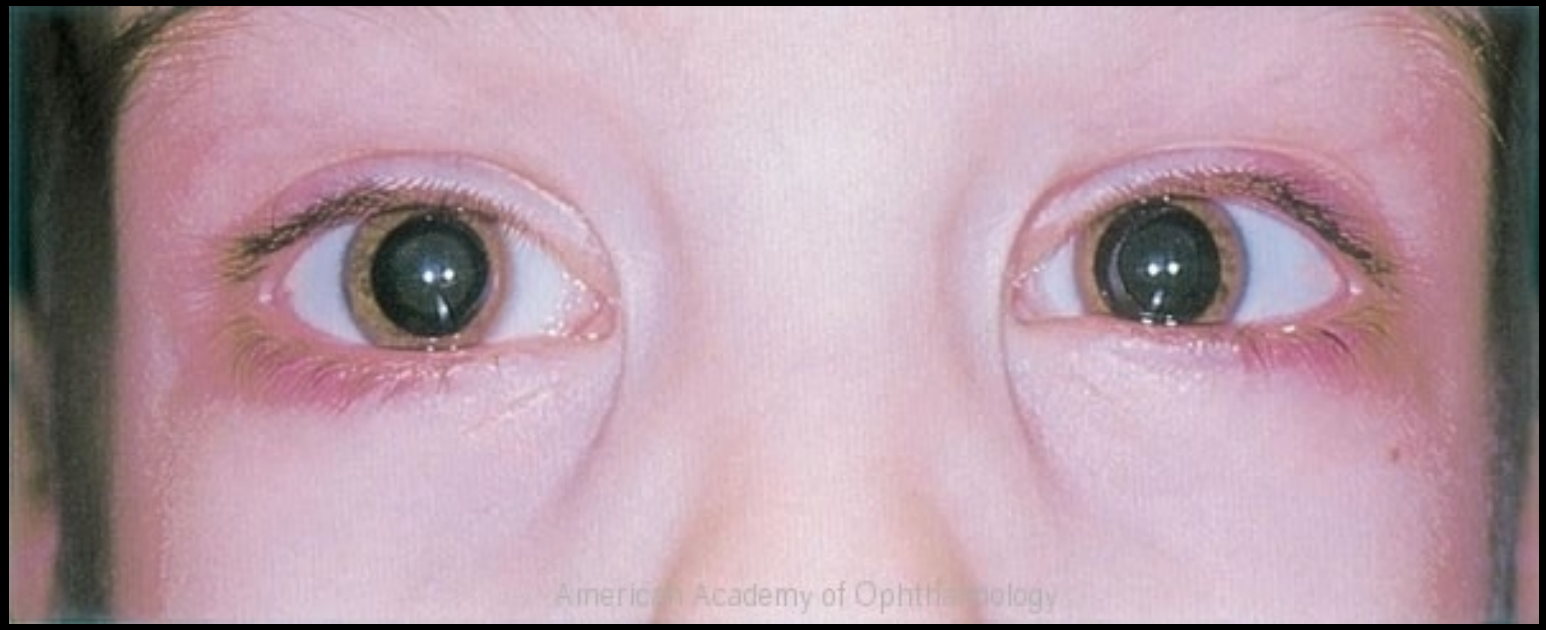
Galactosemia

- Galactokinase deficency (GALK)- not screened in Iowa
  - Type II galactosemia
- Systemic signs may be absent or very mild
- Cataract may be only sign



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Galactosemia

- GALE mutation
  - deficient UDP-galactose-4-epimerase
  - galactosemia type III

- Severe forms leads to
  - Cataract
  - Intellectual disability
  - Damage to the liver, kidneys, and brain.

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Galactose Metabolism