Inborn Errors of Metabolism: Introduction

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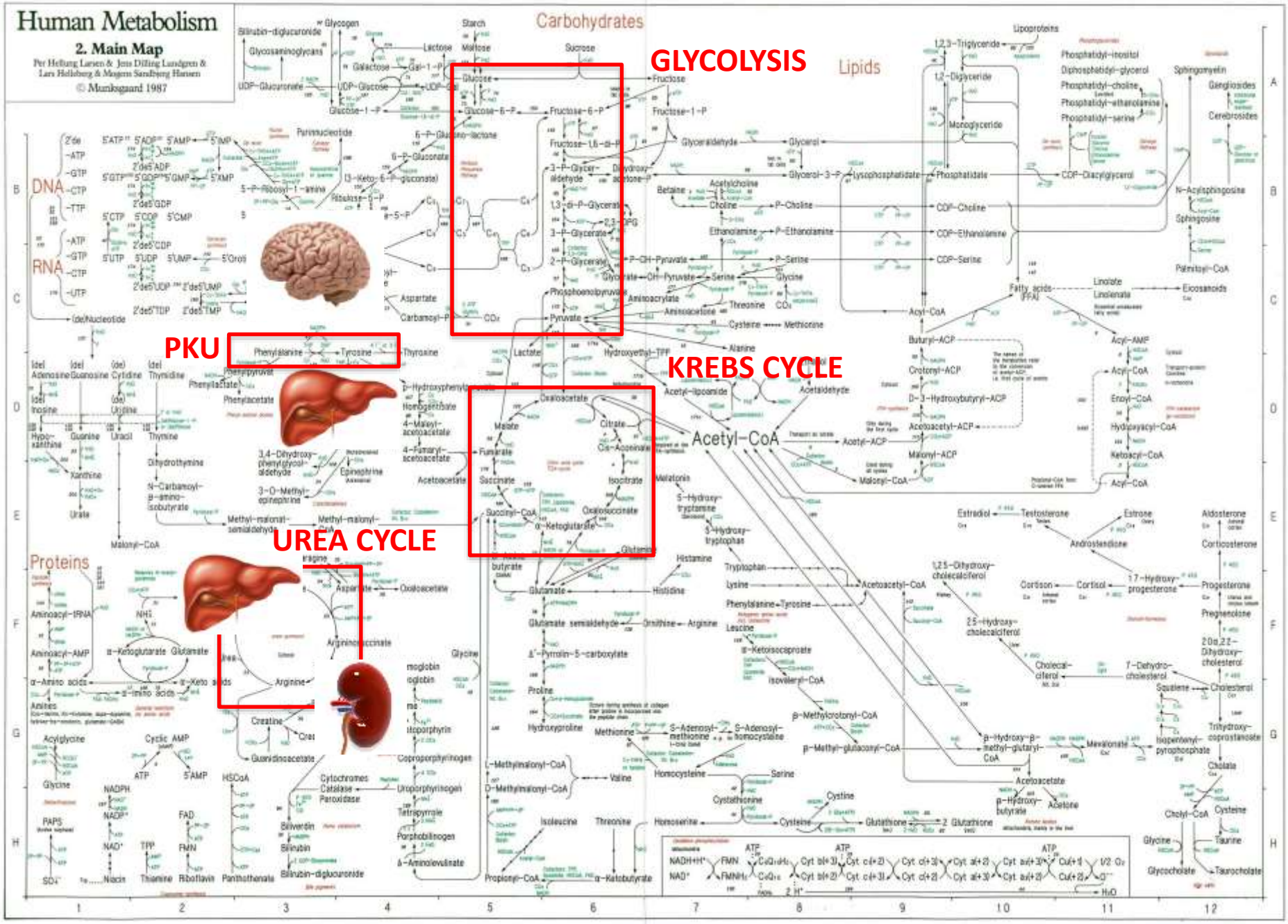
Inherited Metabolic Diseases

- Wide heterogeneous group of genetic disorders associated with disturbancies of metabolic pathways caused by enzyme deficiencies (or transporter defects)
- Rare, but innumerable…
- Clinical heterogeneity: any organ or system may be involved
- Specificity: contrasting with most genetic conditions, many **IEM are treatable diseases**, which justifies attempt for early diagnosis (i.e. newborn screening)


Human Metabolism
2. Main Map
Per Hellung Larsen & Jens Dilling Lundgren &
Lars Hellsberg & Magens Sandberg Hansen
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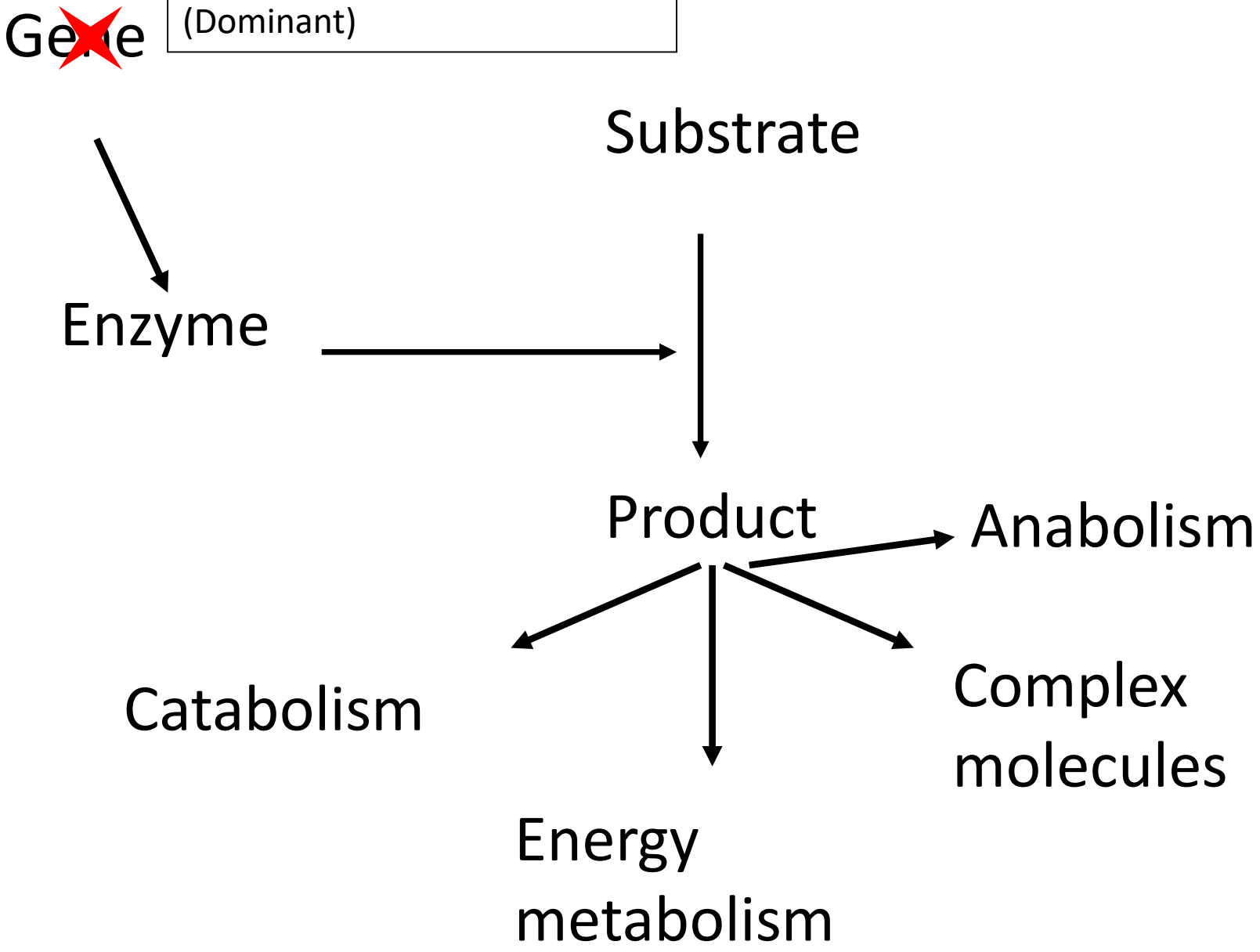
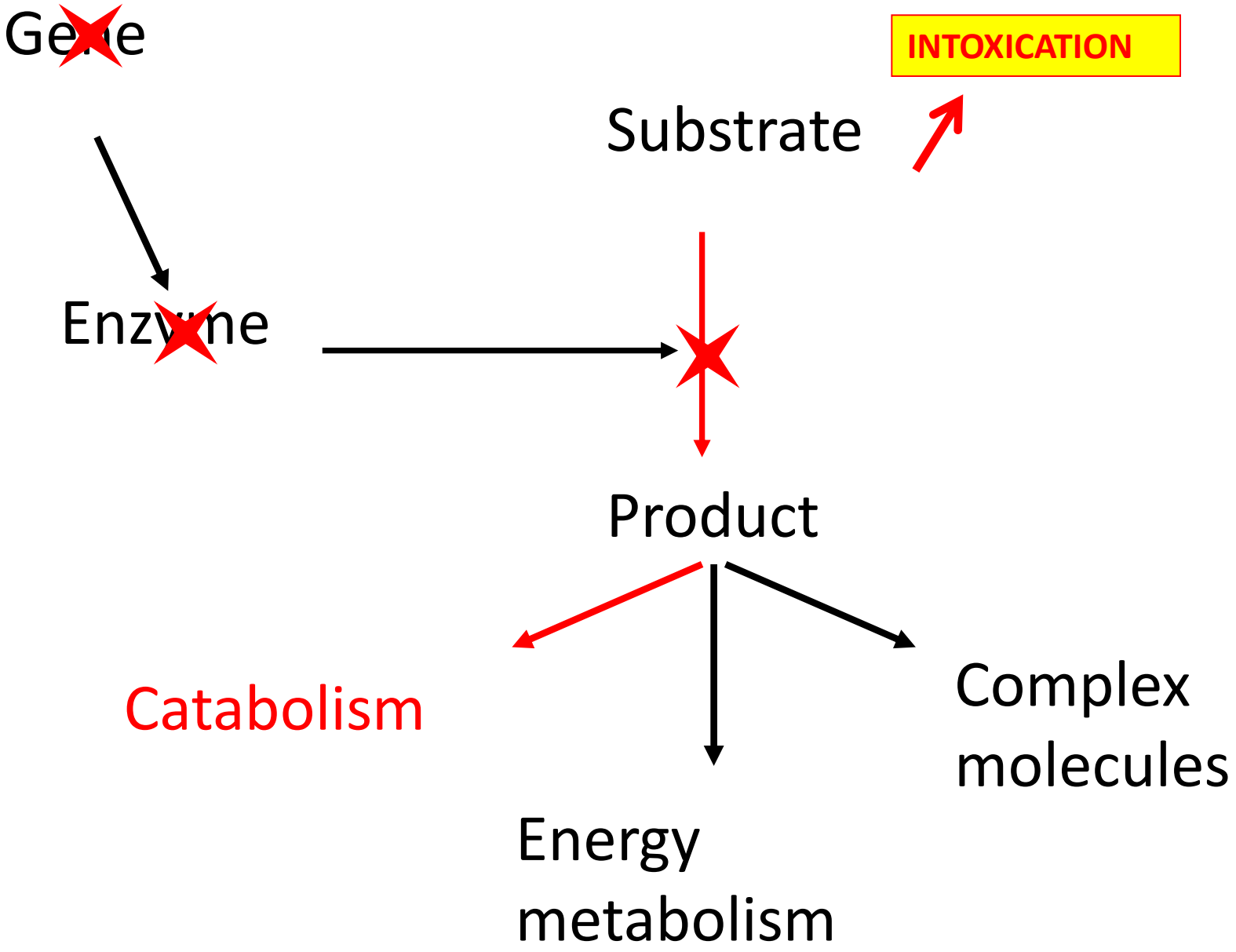
Carbohydrates
GLYCOLYSIS
Lipids
DNA
RNA
PKU
KREBS CYCLE
UREA CYCLE
Proteins
Acetyl-CoA

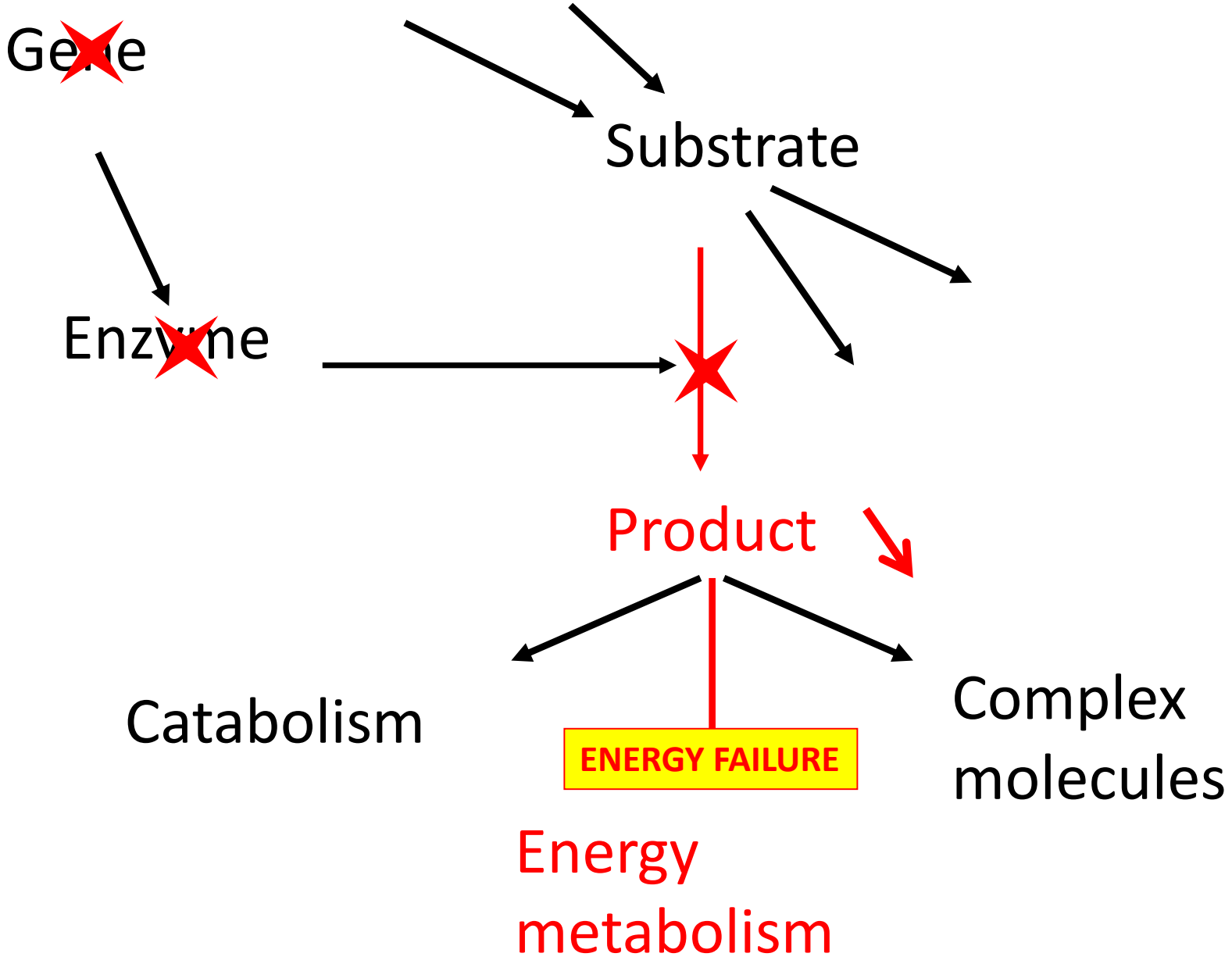
Autosomal recessive +++
X-linked
Maternal inheritance (mtDNA)
(Dominant)



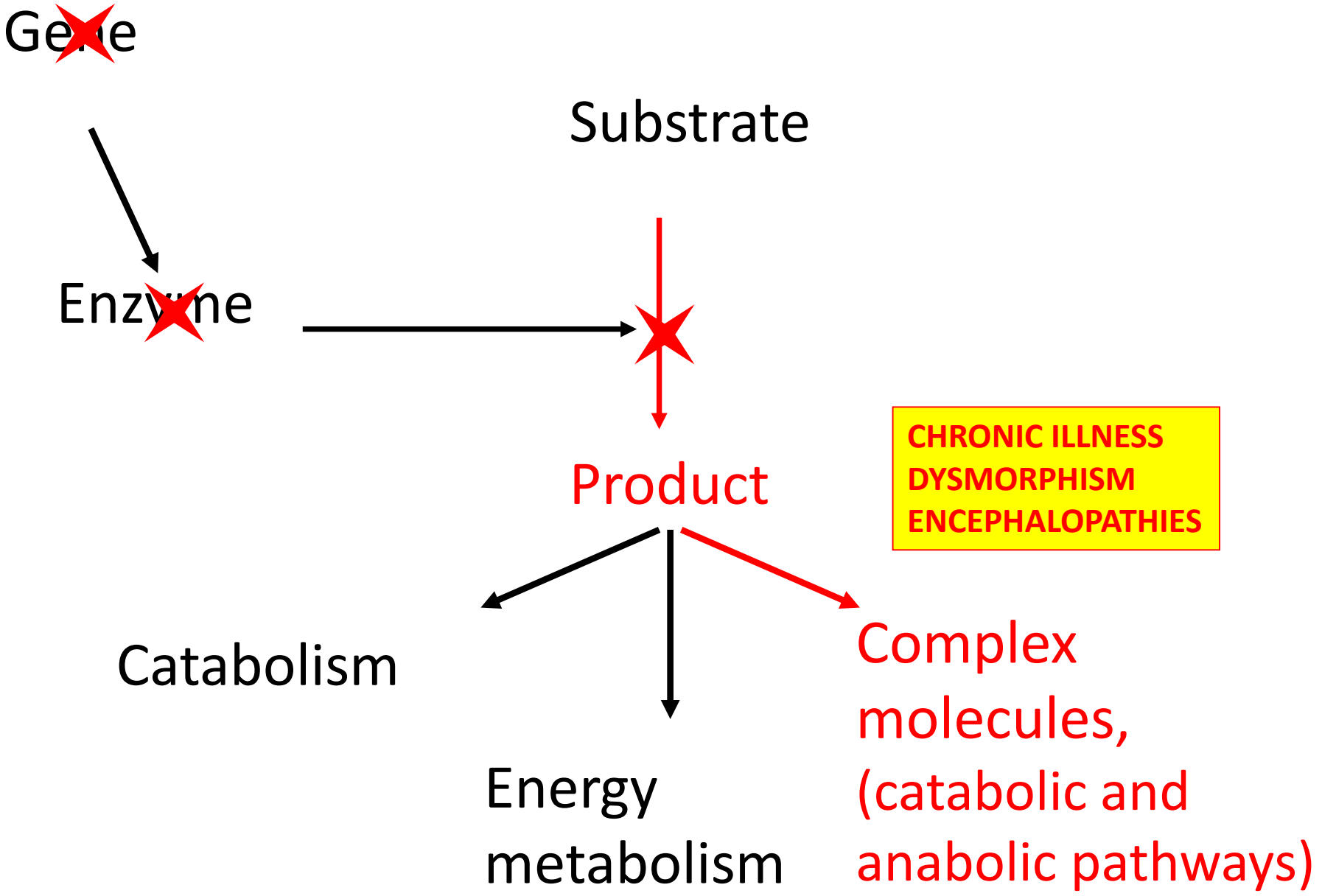
Pathophysiology I.



Pathophysiology II.



Pathophysiology III.



Classification of IEM

- Intoxication type
  - Aminoacidopathies, hyperammonmia, organic aciduria, galactosemia, (fuctosemia),…
- Energy metabolism
  - Glycogen storage diseases, glycolysis/neoglucogenesis defects, fatty acid oxidation disorders, ketogenesis/ketolysis defects, respiratory chain and mitochondrial diseases,…
- Macromolecules diseases
  - Lysosomal storage diseases, mucopolysaccharidosis, oligosaccharidosis, sphingolipidosis, peroxisomal diseases, congenital disorders of glycosylation,…

NB. Outside this classification : neurotransmitter metabolism, sterol metabolism, purine/pyrimidine and heme biosynthesis pathways, metal transport disorders…

IEM : pathophysiology and type of presentation

1. Intoxication:

THERAPEUTIC DIET & DRUGS, URGENT

RAPIDLY PROGRESSIVE

FREE INTERVAL

NON DYSMORPHIC

TRAITABLE : **DIET**,…

EMERGENCY !!! → **OUTCOME !**

2. Energetic failure:

THERAPEUTIC DIET & OTHERS, URGENT, FASTING AVOIDANCE

3. Macromolecules :

VERY SLOW PROGRESSION

DYSMORPHOLOGY, STORAGE SYNDROME

SOMETIMES TRAITABLE: **ENZYME REPLACEMENT THERAPY**

THERAPEUTIC DIET & OTHERS, URGENT, FASTING AVOIDANCE

Intoxication: Free interval

- Symptom free period between birth and appearance of symptoms
- This the time for progressive accumulation of toxic metabolites. During pregnancy, the mother protects the baby by placental clearance of toxic metabolites
- So, at birth, baby is normal, has no dysmorphism, no malformation and no symptoms. Rapidly, he develops symptoms like hypotonia, feeding difficulties, vomiting, losing weight, dehydratation, abnormal movements or tones,…

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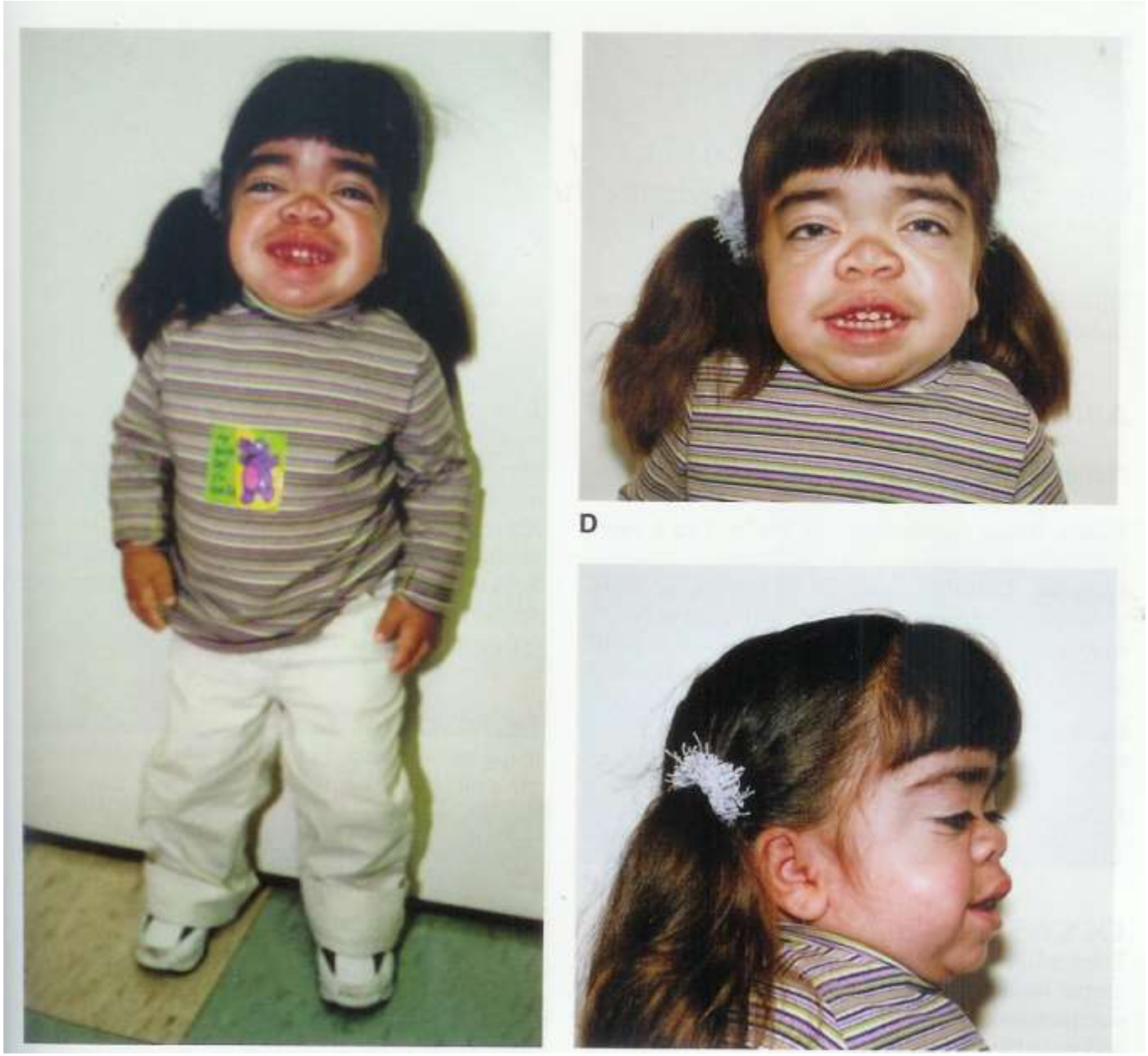

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Manifestations of IEM

DISTURBED HOMEOSTASIS

- ✓ Acidosis
- ✓ Hypoglycemia
- ✓ Ketosis
- ✓ Hyperammonemia
- ✓ Coma
- ✓ …

SYSTEMIC INVOLVEMENT

- ✓ Failure to thrive
- ✓ Hypotonia, weakness
- ✓ Poor feeding, vomitting
- ✓ Developmental delay, mental retardation, neurological deterioration
- ✓ Dysmorphism

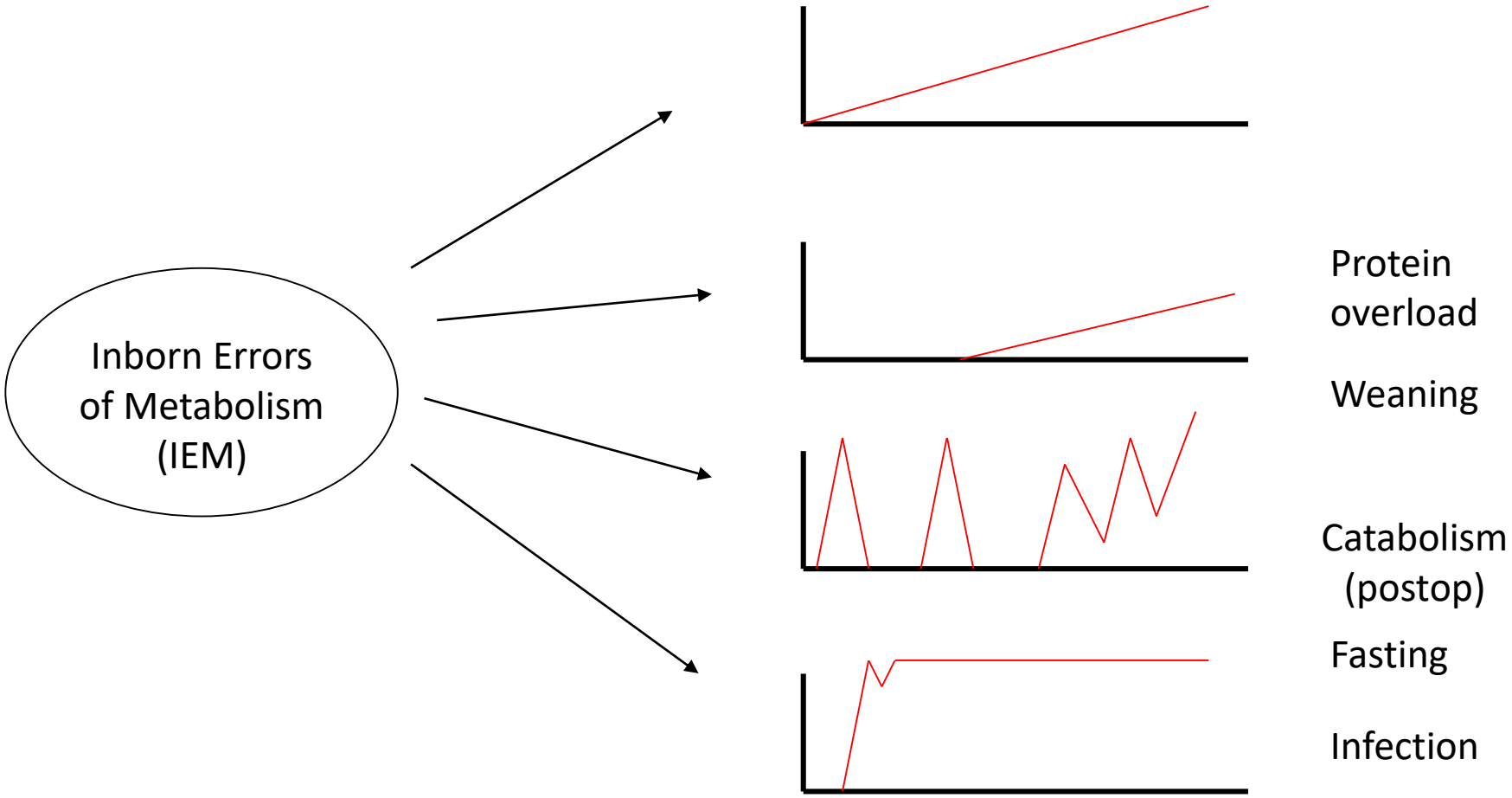
SPECIFIC ORGAN DYSFUNCTIONS

- ✓ Liver : Glycogen storage disease, Tyrosinemia, Galactosemi, Fructosmia, Wilson disease, Fatty oxidation (Reye-like syndrome…)
- ✓ Cardiomyopathy : Mitochondrial disease, Glycogen storage disease, Fatty oxidation defects, Carnitine deficiency, Storage diseases…
- ✓ Kidney: Tyrosinemia, Oxalosis, Cystinosis, Peroxisomal biogenesis,…
- ✓ …

IEM : clinical context

1. Presymtomatic diagnosis by newborn screening
2. Early acute symptoms in neonatal perdiod or early infancy
   - Intermediary metabolism, intoxication type or energetic, mainly neurological distress ± digestive signs and disturbed homeostasis
3. Later-onset acute or recurrent attack of symptoms
   - idem
4. Chronic and progressive generalized symptoms
   - Developmental delay, neurological signs, failure to thrive, digestive signs, (± storage phenotype)
5. Specific and permanent organ presentation
   - Hepatomegaly, liver disease, cardiomyopathy, lens dislocation…

Clinical courses in IEM



IEM intoxication type : general rules

- Free interval
  - Progressive product accumulation
  - Variable depending severity of enzyme deficiency
  - Variable depending feeding and anabolic state

- Signs of intoxication
  - Acute**: neurological** (vomitting, drowsines, ataxia, abnormal movements, coma…), (liver failure)
  - Chronic: developmental delay, mental retardation, failure to thrive, (organ::cataract, cirrhosis, cardiomyopathy),…

- Biological abnormalities
  - Acidosis, ketosis, hypo/hyperglycemia, hyperammonemia,…

IEM : Acute symptoms in the neonatal period

- **Highly suggestive picture**
  - ***Full term baby born after normal pregnancy and delivery, without malformation and dysmorphism, after an initial symptom-free period, relentlessly deteriorates for no apparent reason, and does not respond to symptomatic therapy***

- Clinical signs
  - Hypotonia, poor sucking, vomiting, grunting, respiratory distress, lethargy, dehydratation, seizures…

- Differential
  - Sepsis !!!
  - Respiratory distress syndrome (wet lung)
  - Perinatal anoxoischemic injury
  - Traumatic delivery (intracranial hemorrage)
  - Congenital cardiopathy
  - Polymalformation syndrome, cerebral dysgenesis…
  - Major electrolyte disturbances

Consider IEM in parallel to other frequent disorders,

Especially if the baby does not respond to early therapeutic

Major types of metabolic distress in NN

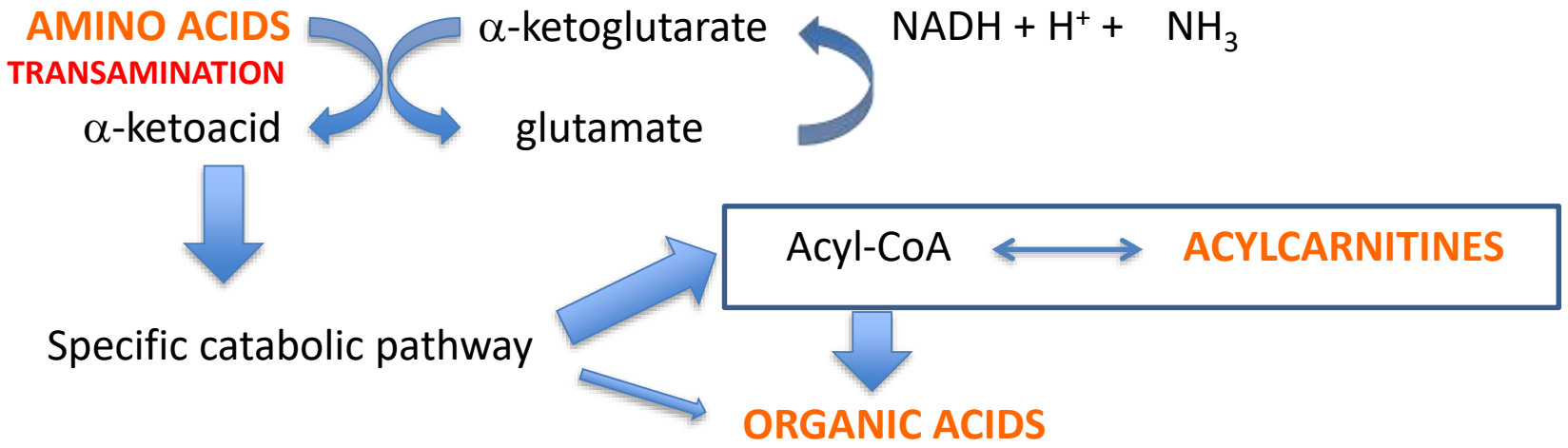
Type	Clinical phenotype	Ketoacidosis	Others	Most usual diagnosis
I a)	**Neurological deterioration** Intoxication type Slow movements, hypertonia	Acidosis -/± Acetest -/± **DNPH +++**	NH_3 N/±↑ Lactate N Glucose N	**MSUD**
b)	**Neurological deterioration** Intoxication type Fast movements, dehydratation	**Acidosis ++** **Acetest ++** DNPH +/±	NH_3 ↑+/++ Lactate N/↑+ Glucose N/↑/↓ Cytopenia, hypoCa	**Organic aciduria** (PA, MMA, IVA) Ketolysis defects
c)	**Neurological deterioration** Intoxication type Hypotonia seizures, coma	Acidosis – (alcalosis) Acetest -	**NH_3 ↑↑↑** Lactate N/↑+ Glucose N	**Urea cycle defects** **Fatty acid oxidation** **Organic aciduria**
II a)	**Neurological deterioration** Energy deficiency ± liver or cardiac symtoms	Acidosis++/± **Acetest -**	NH_3 ↑±/++ **Glucose ↓/↓↓↓** Hypoketotic hypogly	**Fatty acid oxidation** Ketogenesis defect
b)	**Neurological deterioration** Energy deficiency ± liver or cardiac symtoms	**Acidosis +/+++** **Lactate +/+++** Acetest ±/+	NH_3 N/±↑ Glucose N/↑/↓ ± anemia, RTA…	**Congenital lactic acidosis** PDH deficiency Respiratory chain defects
III	**Neurological deterioration** Predominant seizures	Acidosis – Acetest-	NH_3 N Lactate N/±↑	Non ketotic hyperglycinemia, B6 resp. seiz, Sulfite ox, Neurotransmitt, perox, CDG
IV	**Recurrent hypoglycemia** With hepatomegaly	Acidosis ++/- Acetest ±	**Glucose ↓↓↓** Lactate ↑+/++ NH_3 N/↑+/++	**Glycogenosis I/III** Fatty acid oxidation Hyperinsulinism (hm, acetest-)
V a)	**Hepatomegaly, jaundice,** **liver failure**, necrosis	Acidosis ± Ketosis ±	NH_3 N/±↑ Lactate N/±↑	**Galactosemia, tyrosinemia** **Fructosemia**, respiratory chain
b)	Cholestasis, Hepatomegaly FTT, diarrhea, rickets…	Acidosis - Ketosis -	NH_3, Lactate N Glucose N	α1AT, bile acid metabolism, cholesterol metab, NPC, Gala, Tyr, Fru
c)	Hepatosplenomegaly, storage	-	-	**Lysosomal**, perox, CDG

Adapted from Saudubray

Diagnosis: first line investigations

- Glycemia
- pH
- Electrolytes, **anion gap** : $[Na^+] - [Cl^-] - [HCO_3^-] = 8 – 16$ mEq/L
- Urines : ketostix, glucose, pH
- Blood lactate : < 2 mmol/L (x10 to convert mg/dl)
  - Venous sampling is informative in most cases, but sensitive to spurious elevation in venous stasis or if the child struggles during sample (sometimes, prefer venous catheter)
  - Secondary increase caused by hypoxia, hypoperfusion shock, sepsis cardiac failure
  - Does not alter pH by itself if < 5 mmol/L
  - May be more informative in cerebrospinal fluid (in context of suspicion of mitochondrial disease)
- Blood NH_3 : < 80 µmol/L (x1.7 to convert µg/dl) (until 120 in nn)
  - Uncuffed venous sampling informative, on ice, rapid analysis because spontaneous increase (glutaminase); spurious increase in venous stasis or damaged tissues (no micromethods for sampling)
- (Urinary DNPH)

Diagnosis: second line investigations



- Aminoacid chromatography: in blood
- Organic acid chromathography : in urine
- Acylcarnitine profile: in blood

Acute metabolic distress: first line treatment

- ABC : vital functions
- Correct hypoglycemia if present
- IV Glucose 10%
- Correct dehydratation, monitoring ions
- STOP Proteins
- Vitamine cocktail: hydroxocobalamine 1 mg IV, biotine 30 mg po, thiamine 50 mg PO, pyridoxine 100 mg, riboflavine 100 mg
- Collect specimen for specialized analyses

- NH_3: < 80 µmol/L (x 1,7 = µg/dL)

  healthy nn <110 µM; sick nn (sepsis, respiratory distress) : up to 180 µM

  glutaminase in blood: artifactual ↑ NH_3 if delay in analysis

  artifactually ↑ if poor sampling conditions

  (venous blood) sample, on ice

  rapidely analysed in lab (result should be avaiable < 30 minutes)

  NEVER FALL ASLEEP ON AN ABNORMAL NH_3 RESULT

- Lactate: < 2,2 mmol/L (x 10 = mg/dL)

  artifactually ↑ in stasis, difficult sample, crying/struggling baby

  physiological ↑ in case of hypoperfusion (shock, sepsis, cardiac failure…)

  May be more accurate in CSF