# Methylmalonic aciduria

## Introductory information

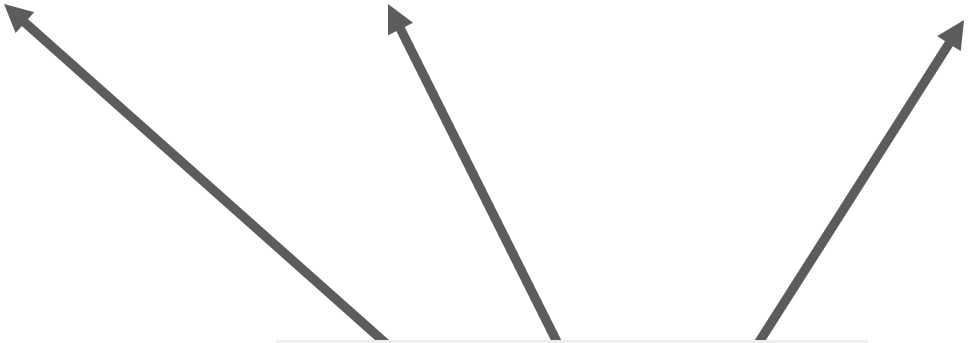
**Written by:**
**F. Hörster, S. Kölker & P. Burgard**

Reviewed & Revised for North America
by: S. van Calcar

Supported by NUTRICIA
as a service to metabolic medicine

TEMPLE
Tools Enabling Metabolic Parents LEarning

# Methylmalonic aciduria



# MMA

# Methylmalonic aciduria

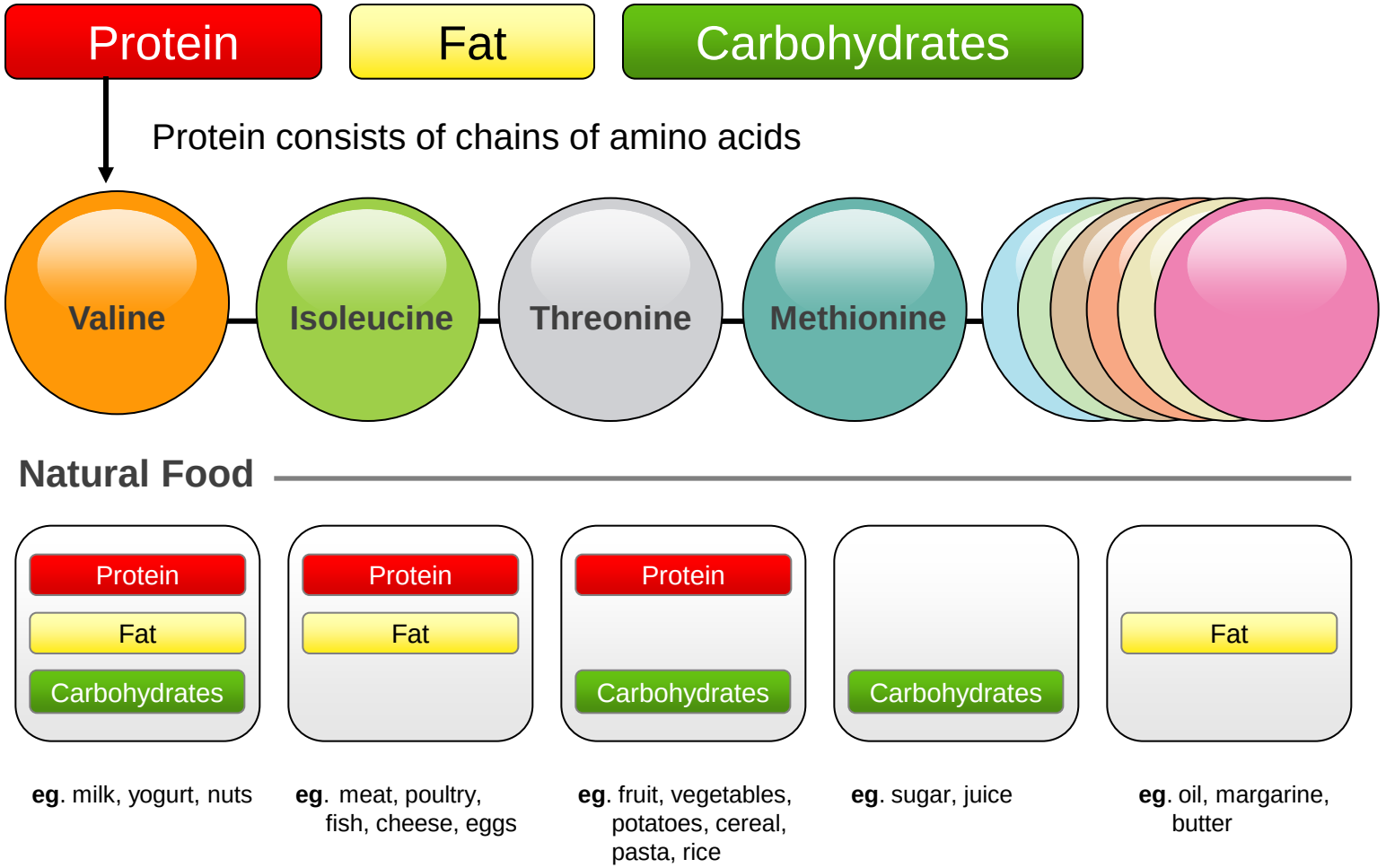
**Methylmalonic** **acid in urine**

# MMA



Written by: F. Hörster, S. Kölker & P. Burgard
Reviewed & revised for North America by: S. van Calcar

# Food – Components of a normal diet



# Enzymes

**Enzymes** are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all the substances in the body. This is called metabolism.

**M**etylmalonyl-**C**oA **m**utase (MCM) is an enzyme that is necessary for the metabolism of **the amino acids: valine, isoleucine, threonine and methionine**.

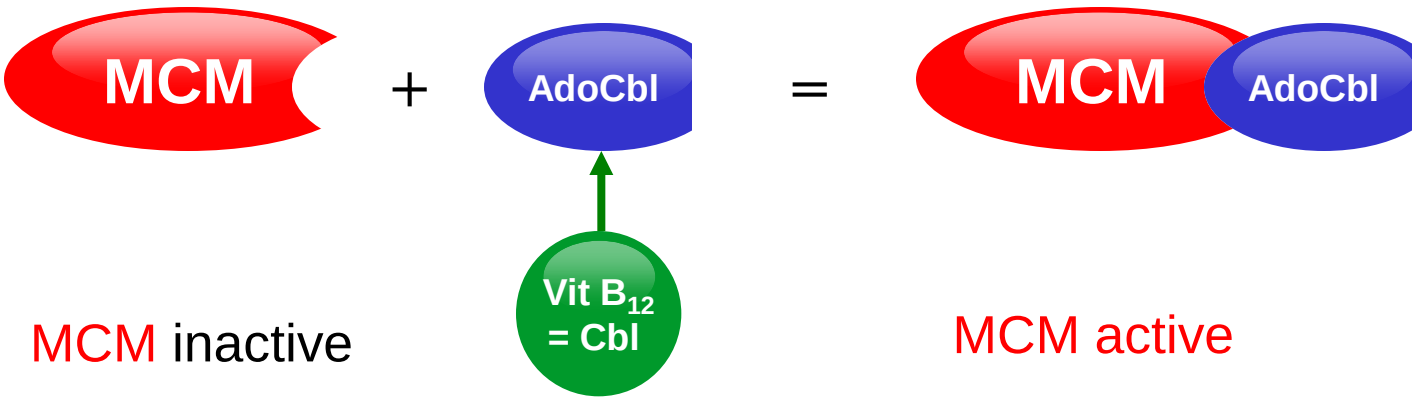
In MMA, the activity of the MCM enzyme is decreased.

# Enzymes

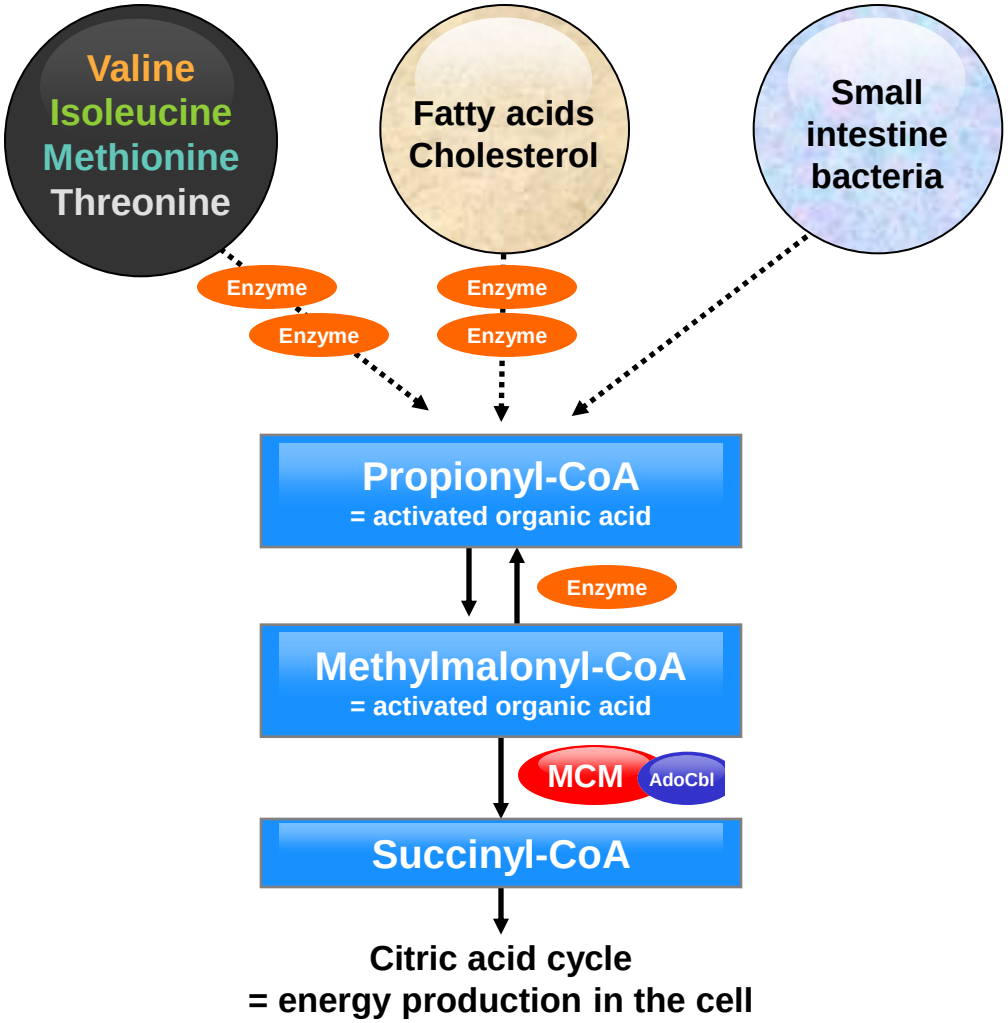
In order to function correctly, some enzymes cannot work without the help of vitamins called cofactors.

Methylmalonyl-CoA mutase (MCM) is such an enzyme.

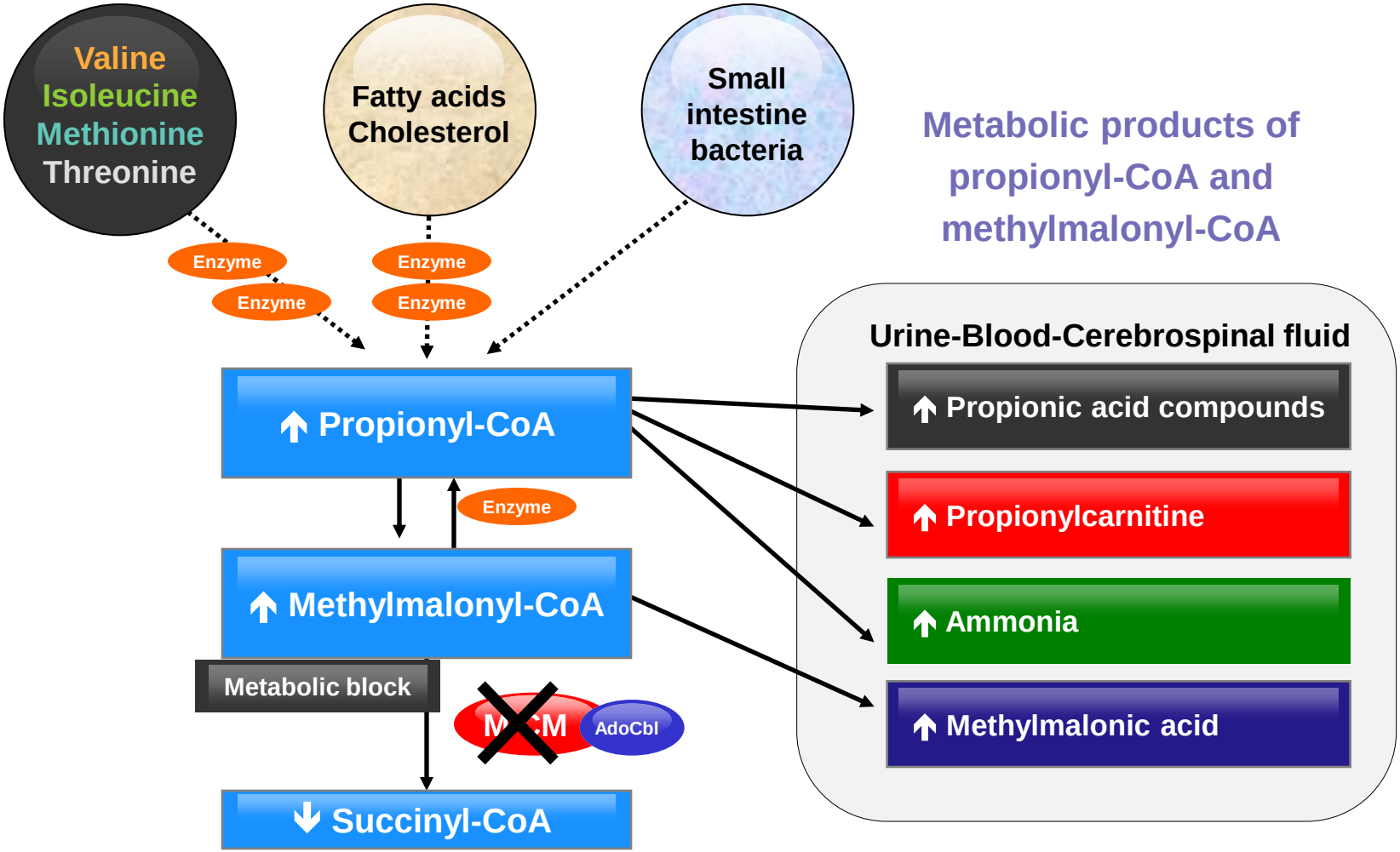
Its cofactor is adenosyl-cobalamin = AdoCbl. It is produced from vitamin $B_{12}$.



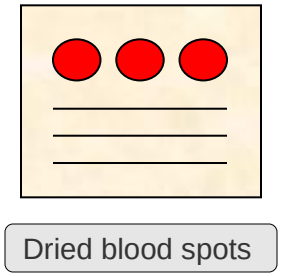
# In a person without MMA: MCM works



# In a person with MMA: MCM is deficient



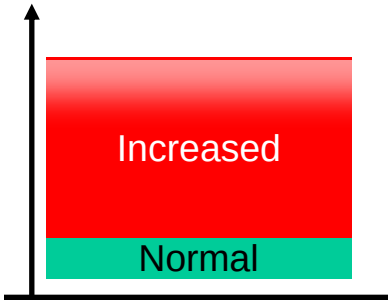
# Diagnostic investigations

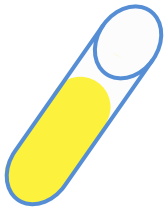


Dried blood spots

**Newborn Screening**

**Propionylcarnitine**

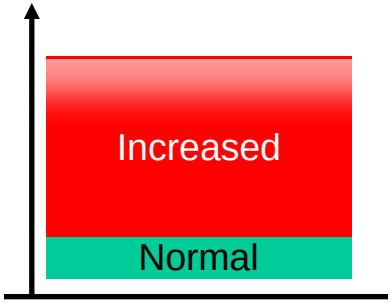


Urine sample

**Confirmation of diagnosis**

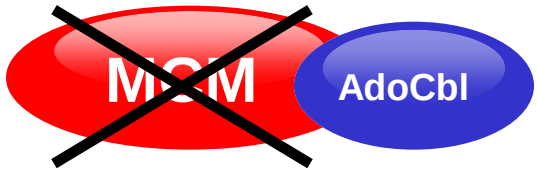
**Methylmalonic acid**

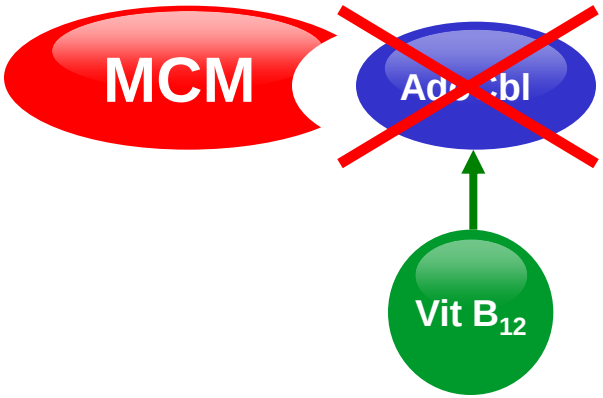


# Types of MMA

**Enzyme is defective**
**(mut$^0$, mut$^-$)**

**Cofactor production is defective (e.g. CblA, CblB)**

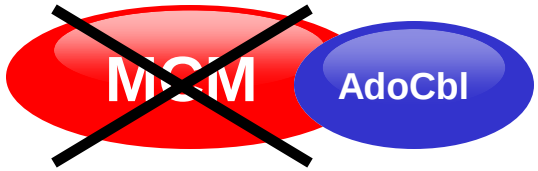


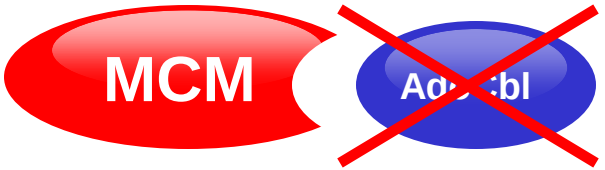




**Enzyme activity is absent or decreased**

**Uptake, transportation, production of AdoCbl from vitamin $B_{12}$ can be defective**

# Types of MMA




**Enzyme is defective**

**Cofactor production is defective**

**The activity of the enzyme methylmalonyl-CoA mutase is decreased in both cases**

**How can the different types of MMA be identified?**

- By using **vitamin $B_{12}$**
- By means of laboratory tests of **cultured skin cells**
- By means of **genetic tests**

Various types of MMA differ in the severity of the disease and are managed with different methods

# Pathogenesis

## 1. Toxic effects of organic acids

**Accumulation of**

- **Propionyl-CoA**
- **Propionic acid compounds**
- **Ammonia**
- **Methylmalonic acid**

→

**can result in damage to various organs**

- **Brain**
- **Kidneys**
- **Blood, pancreas, heart, eyes (rare)**

# Pathogenesis

## 2. Problems resulting from a carnitine deficit

**Propionylcarnitine** **reduces the amount of carnitine in the body**

The increased production of propionylcarnitine and its elimination in the urine reduces the amount of carnitine in the body.

**Carnitine** is important to assure a sufficient supply of energy to many organs to maintain their function.

**Low amounts of carnitine concentration can reduce the production of energy.**

# Pathogenesis

## 3. Metabolic crises

**The accumulation of propionyl-CoA, propionic acid compounds, ammonia and methylmalonic acid can be especially high during metabolic crises. The following situations can lead to a metabolic crisis in MMA:**

- **Febrile illnesses**
  e.g. diarrhea, fever, infectious disease, etc.
- **Vaccinations**
- **Surgery**
- **Malnutrition**

### In these situations catabolism develops

The term **"catabolism"** refers to the metabolic reactions leading to the breakdown of body tissues.

Propionyl-CoA, propionic acid compounds, ammonia and methylmalonic acid are produced from body proteins, especially the breakdown of muscle!

# What are the symptoms of a metabolic crisis?

- Unusual tiredness, unresponsiveness
- Loss of appetite, vomiting
- Quick and deep breathing
- Seizures
- Movement disorders (the child cannot sit or stand anymore, becomes “floppy”, develops abnormal movements)
- The child is very difficult to wake up or you cannot get him to wake up at all (coma)

**It is critical that treatment be started immediately to prevent the patient’s condition from deteriorating. Metabolic crises can be fatal.**

# Catabolism in a newborn

**In the first days of life, catabolism causes the degradation of body tissues. This can lead to a metabolic crisis with encephalopathy (brain involvement).**

| | |
|---|---|
| **Symptoms:** | poor sucking, vomiting, weak response to stimuli, muscle weakness, reduced movements, dehydration, deep breathing, neurological symptoms, coma |
| **Laboratory tests:** | ⬆ ammonia, ketoacidosis, blood smear abnormalities |
| **Management:** | prompt detoxification |

# Developmental abnormalities

1. Some children may have delayed development, abnormal psychomotor development and can develop various neurological symptoms

2. Children may **lose developmental skills** following a **metabolic crisis**. The risk of developmental abnormalities increase with the severity and number of metabolic crises.

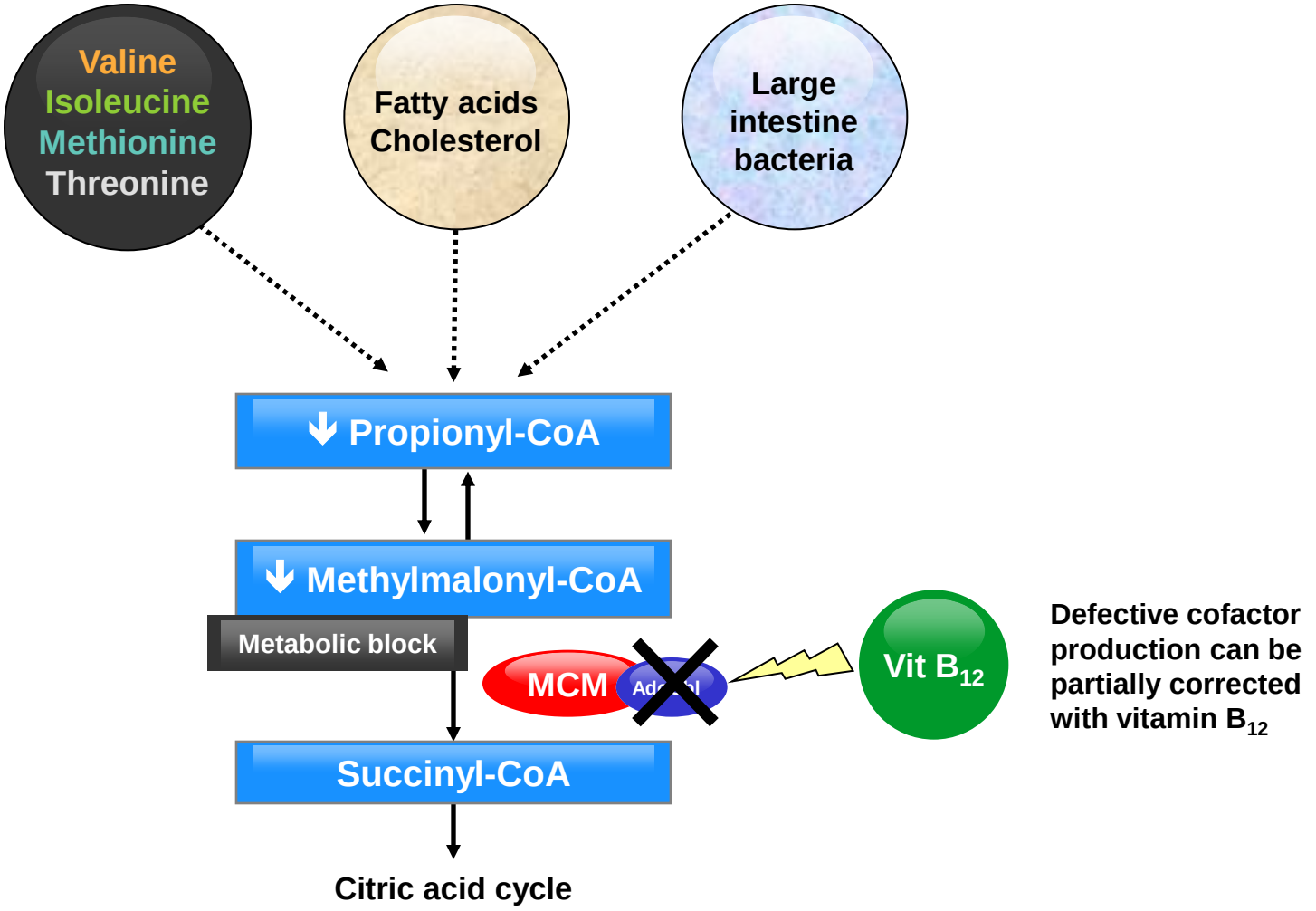
# Various organs can be affected in MMA

**In many patients with MMA, renal (kidney) failure develops gradually over time**

Less commonly affected are **the blood, pancreas, heart and eyes**

# Treatment with vitamin $B_{12}$

## Only possible for those with defective cofactor production



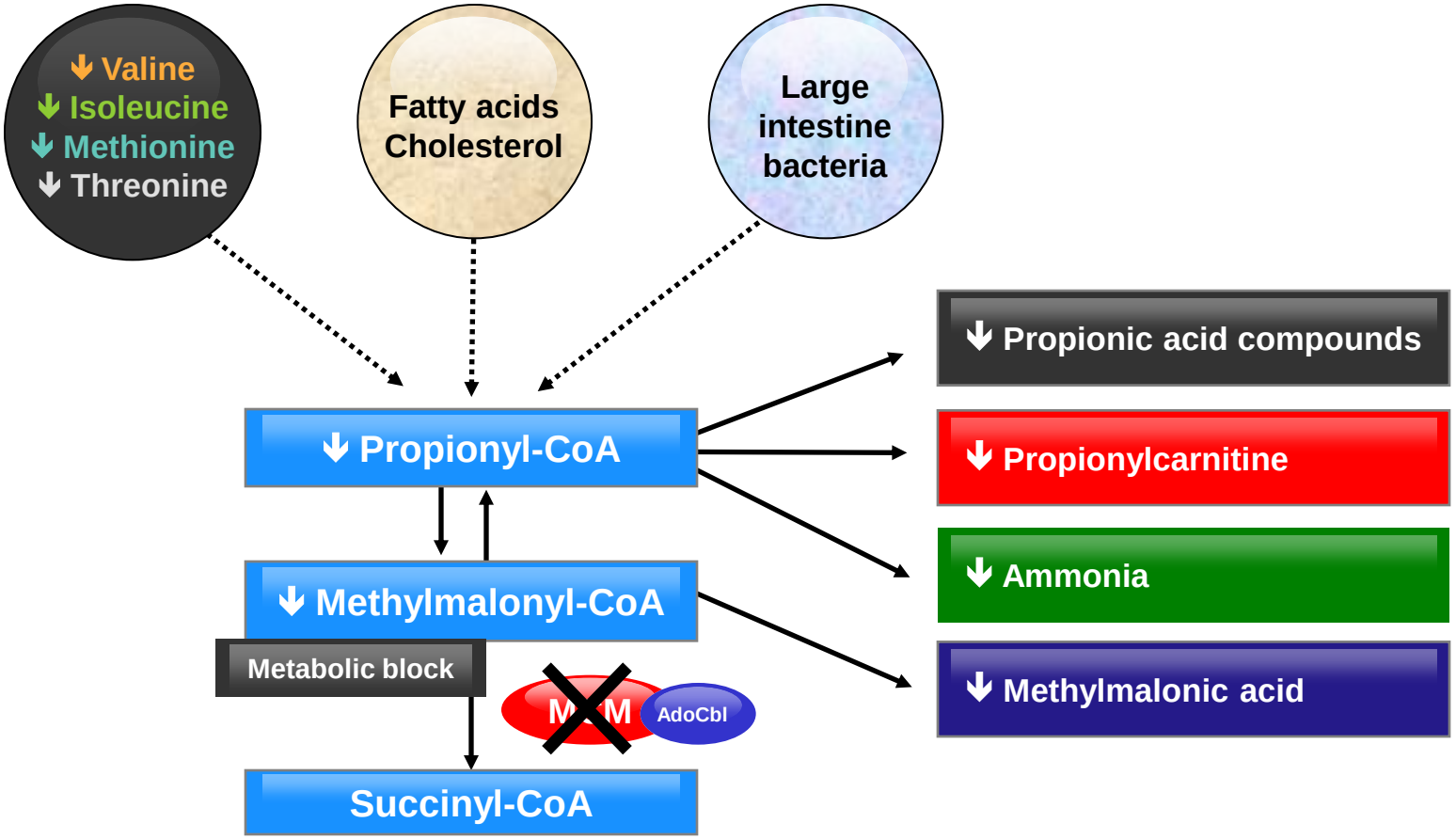

**Defective cofactor production can be partially corrected with vitamin $B_{12}$**




Written by: F. Hörster, S. Kölker & P. Burgard
Reviewed & revised for North America by: S. van Calcar

# Principles of Management = Diet

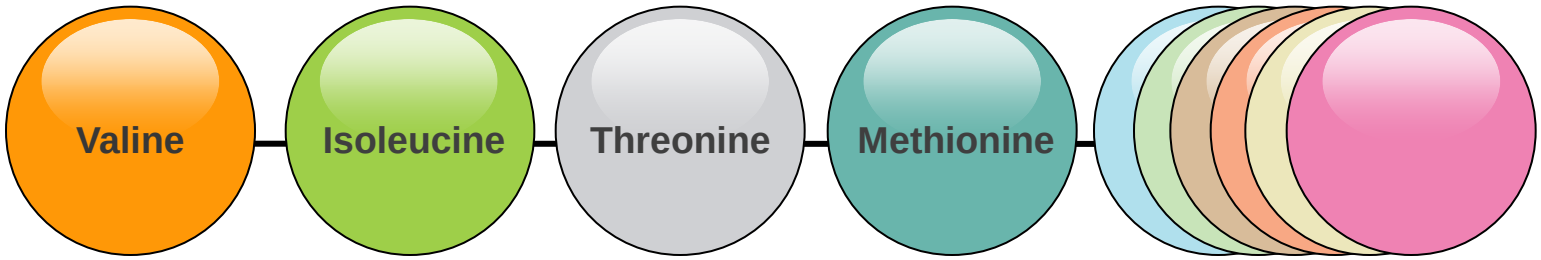
## Diet management decreases intake of valine, isoleucine, methionine and threonine



# Food – Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids

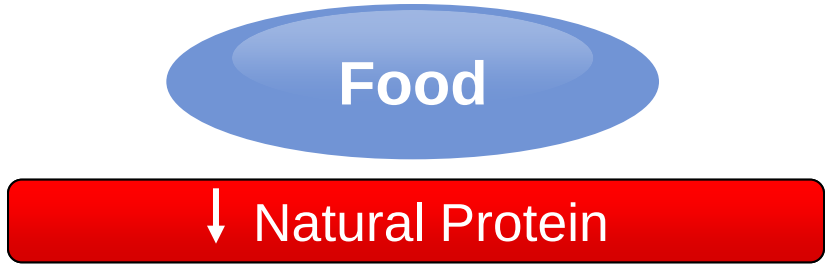


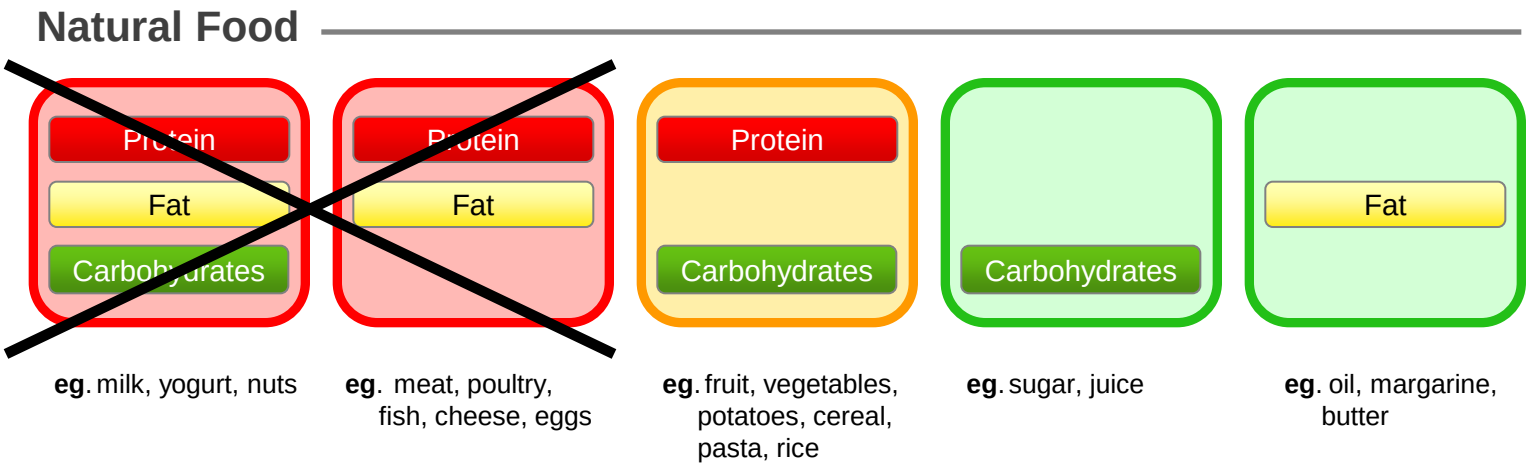

## Natural Food

| Protein, Fat, Carbohydrates | Protein, Fat | Protein, Carbohydrates | Carbohydrates | Fat |
|---|---|---|---|---|
| **eg**. milk, yogurt, nuts | **eg**. meat, poultry, fish, cheese, eggs | **eg**. fruit, vegetables, potatoes, cereal, rice, pasta | **eg**. sugar, juice | **eg**. oil, margarine, butter |

# Principles of management:

## 1. Low in natural protein food



# Principles of management:

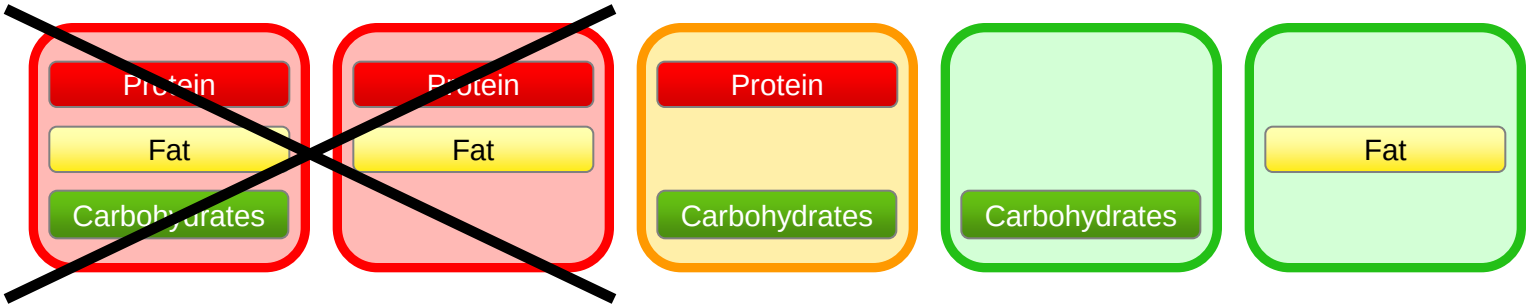
## 2. Low in natural protein diet + metabolic formula without valine, isoleucine, methionine and threonine

**Food**

↓ Natural Protein

**+ MMA formula contains all amino acid except valine, isoleucine, methionine and threonine**

### Natural Food




**eg**. milk, yogurt, nuts

**eg**. meat, poultry, fish, cheese, eggs

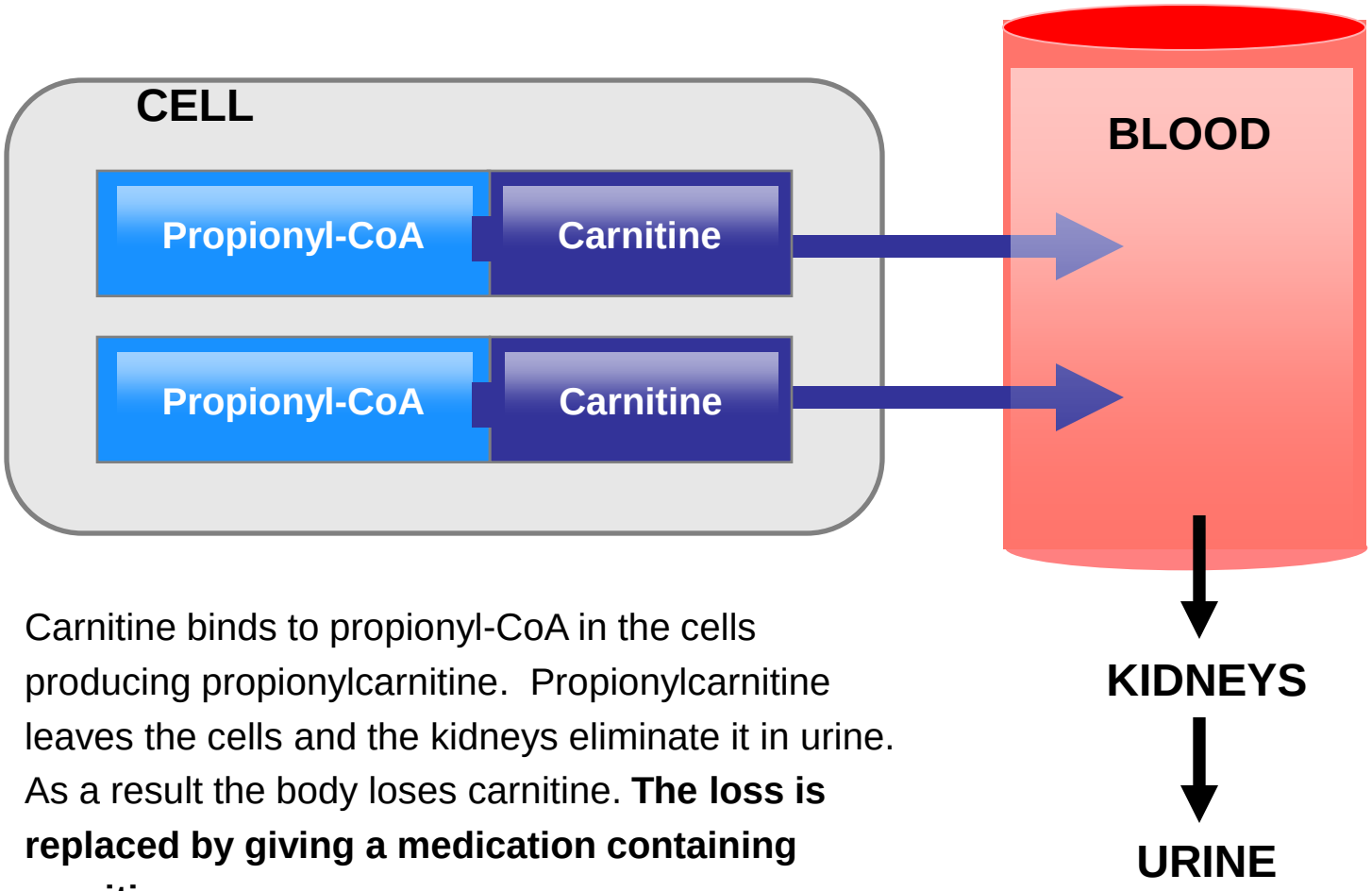
**eg**. fruit, vegetables, potatoes, cereal, pasta, rice

**eg**. sugar, juice

**eg**. oil, margarine, butter

# Principles of management:

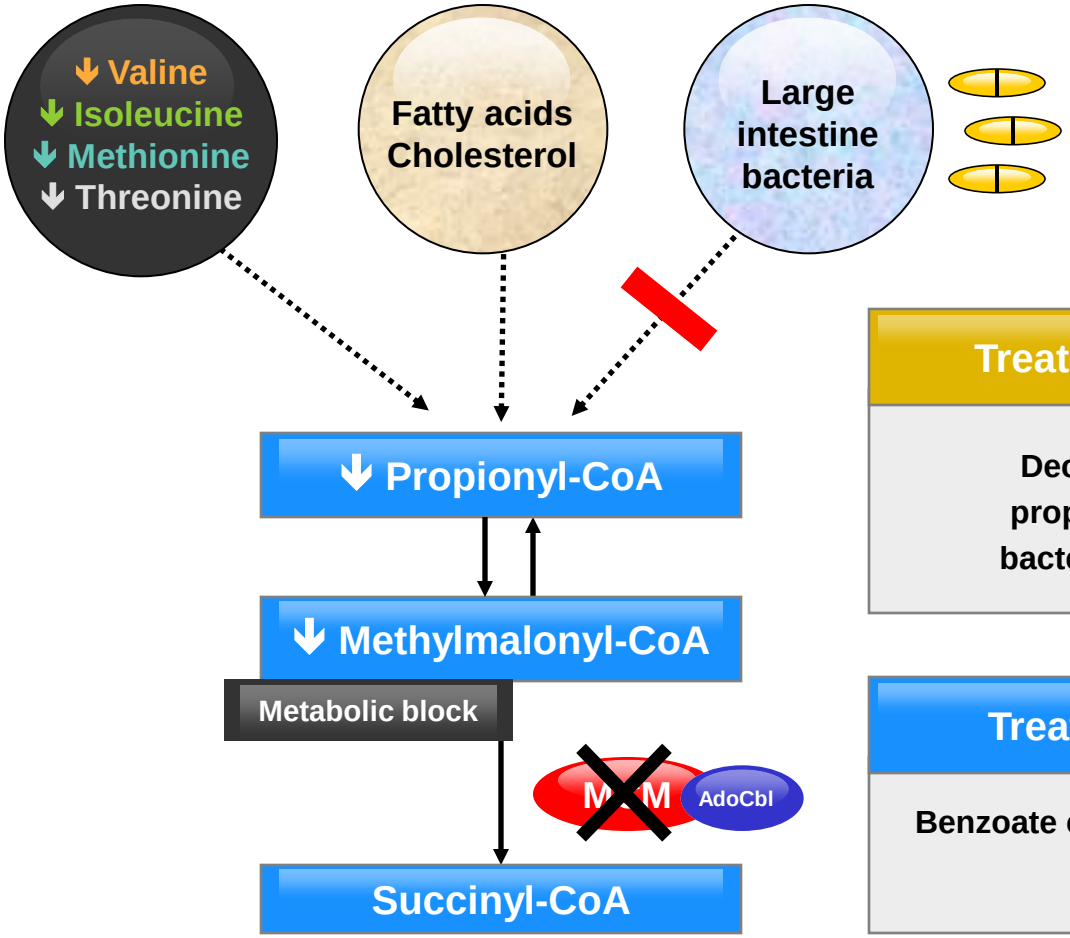
## 3. Carnitine supplementation




Carnitine binds to propionyl-CoA in the cells producing propionylcarnitine. Propionylcarnitine leaves the cells and the kidneys eliminate it in urine. As a result the body loses carnitine. **The loss is replaced by giving a medication containing carnitine.**

# Principles of management:

## 4. Drugs




**Treatment with antibiotics**

Decrease of the amount of propionyl-CoA produced by bacteria in the large intestine

**Treatment with benzoate**

Benzoate can be prescribed to decrease the ammonia level

# Five management components

1. Diet low in natural protein + metabolic formula with all amino acids except valine, isoleucine, methionine and threonine
2. Carnitine supplementation
3. Vitamin $B_{12}$ (only in cases of defective cofactor production)
4. Antibiotics to reduce bacteria in the large intestine
5. **Emergency management:** Follow an **emergency plan** including prompt management during acute illness:
   a) Decrease the amount of natural protein from food
   b) Frequent carbohydrates-rich meals
   c) Continue carnitine
   d) If the patient's condition deteriorates, contact the metabolic clinic immediately for further directions. An ER visit may be necessary.

**Important:** All patients with PA need an emergency protocol and plans for emergency treatment at the nearest children's hospital

# Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

A **gene** is like a recipe in the cookbook.

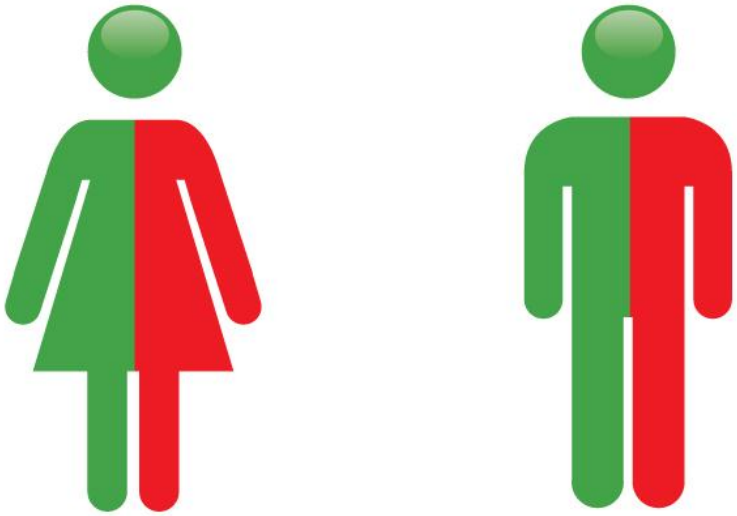
A **mutation** is like an error in the recipe or even a complete lack of a recipe.

The **enzyme** methylmalonyl-CoA mutase (MCM) is produced constantly in the body following a specific recipe (**gene**). If the gene contains abnormal **mutations,** the **enzyme** cannot be properly produced.

# Inheritance of MMA

**Both parents are carriers in autosomal-recessive inheritance**

Mother is a carrier of **MMA**



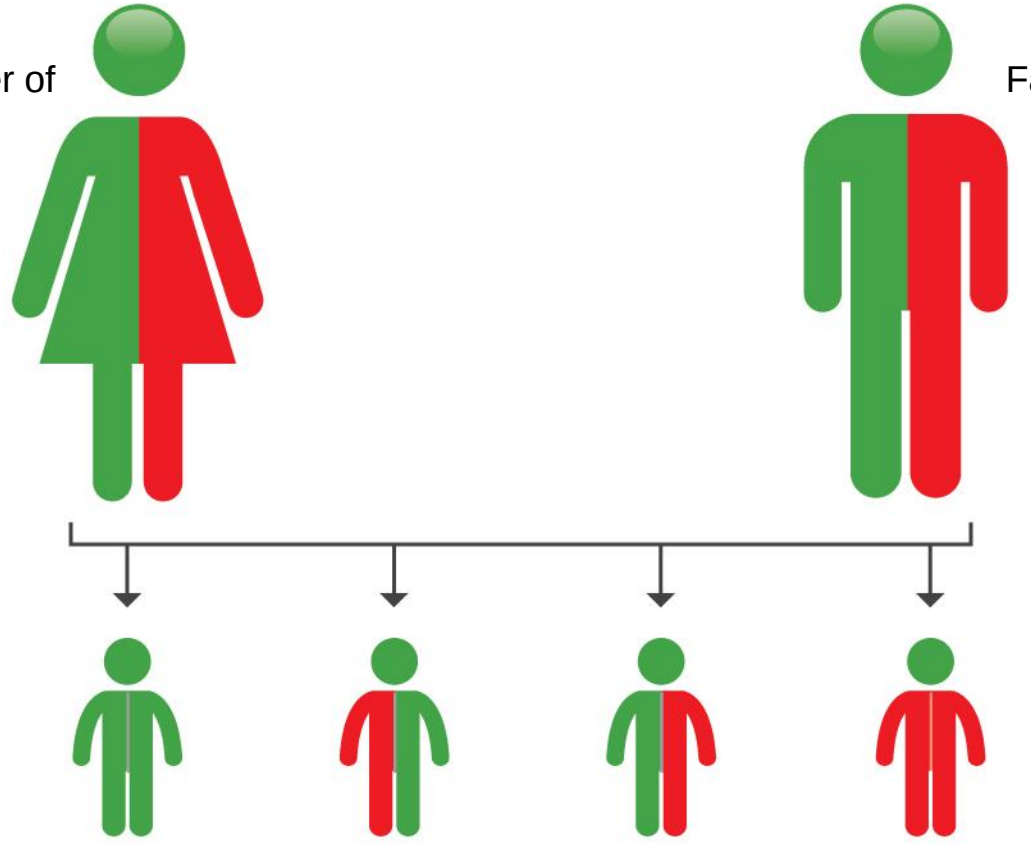
Father is a carrier of **MMA**

# Inheritance

**There are 4 possible combinations for any child born to parents who are carriers**

Mother is a carrier of **MMA**

Father is a carrier of **MMA**



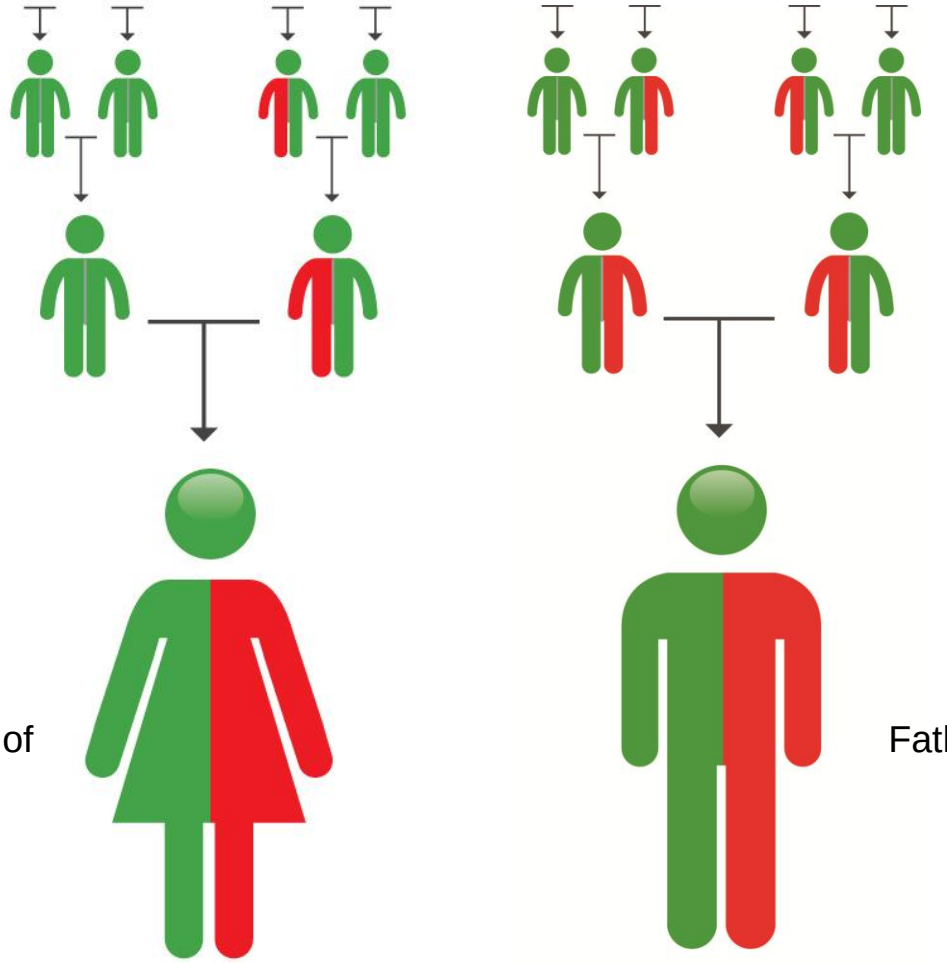
Child will not be a carrier of **MMA**

Child will be a carrier of **MMA**

Child will have **MMA**

# Inheritance

**How MMA is inherited in families**



Mother is a carrier of **MMA**

Father is a carrier of **MMA**

# Summary

| What is MMA? | Disturbance of metabolism of valine, isoleucine, methionine, threonine |
|---|---|
| | ⬆ Propionyl-CoA, ⬆ Methylmalonyl-CoA, ⬆ Methylmalonic acid, ⬆ Ammonia |

## Optimal management

1. **Diet low in natural protein + MMA formula**
2. **Early and effective management of metabolic crises**
3. **Pharmacological treatment with use of vitamin $B_{12}$ carnitine, antibiotics, benzoate**

## Follow-up

**Laboratory tests**
**Special tests: a**mino acids, acylcarnitines, carnitine, ammonia, organic acids
**Routine tests**
**Physical development**
**Neuropsychological tests**
Intelligence (IQ), motor patterns
**Brain imaging**
Ultrasound, MRI
**Renal function tests**
**Cardiologic examination**

## Management results vary and may include:

- **Developmental delay of various degree**
- **Neurological abnormalities of various degree (movement disorders, spasticity, dystonia)**
- **Epilepsy**
- **Abnormalities in brain MRI**
- **Renal failure**
- **Cardiomyopathy**



Written by: F. Hörster, S. Kölker & P. Burgard
Reviewed & revised for North America by: S. van Calcar