

*Topic 5 - Sunday 15:15-16:45*

## **What is Required for Prevention and Cure?**

**Chairs:** Asla Pitkänen (Finland), Torbjörn Tomson (Sweden)

### **Current status: the unmet needs (10 min)**

*Asla Pitkänen (Finland), Torbjörn Tomson (Sweden)*

### **Identifying target populations and designing clinical trials (15 min)**

*Ettore Beghi (Italy)*

### **Revealing the mechanisms of epileptogenesis to design innovative treatments what are the tools? (15 min)**

*Holger Lerche (Germany)*

### **Removing obstacles in translation of preclinical discoveries to clinic (15 min)**

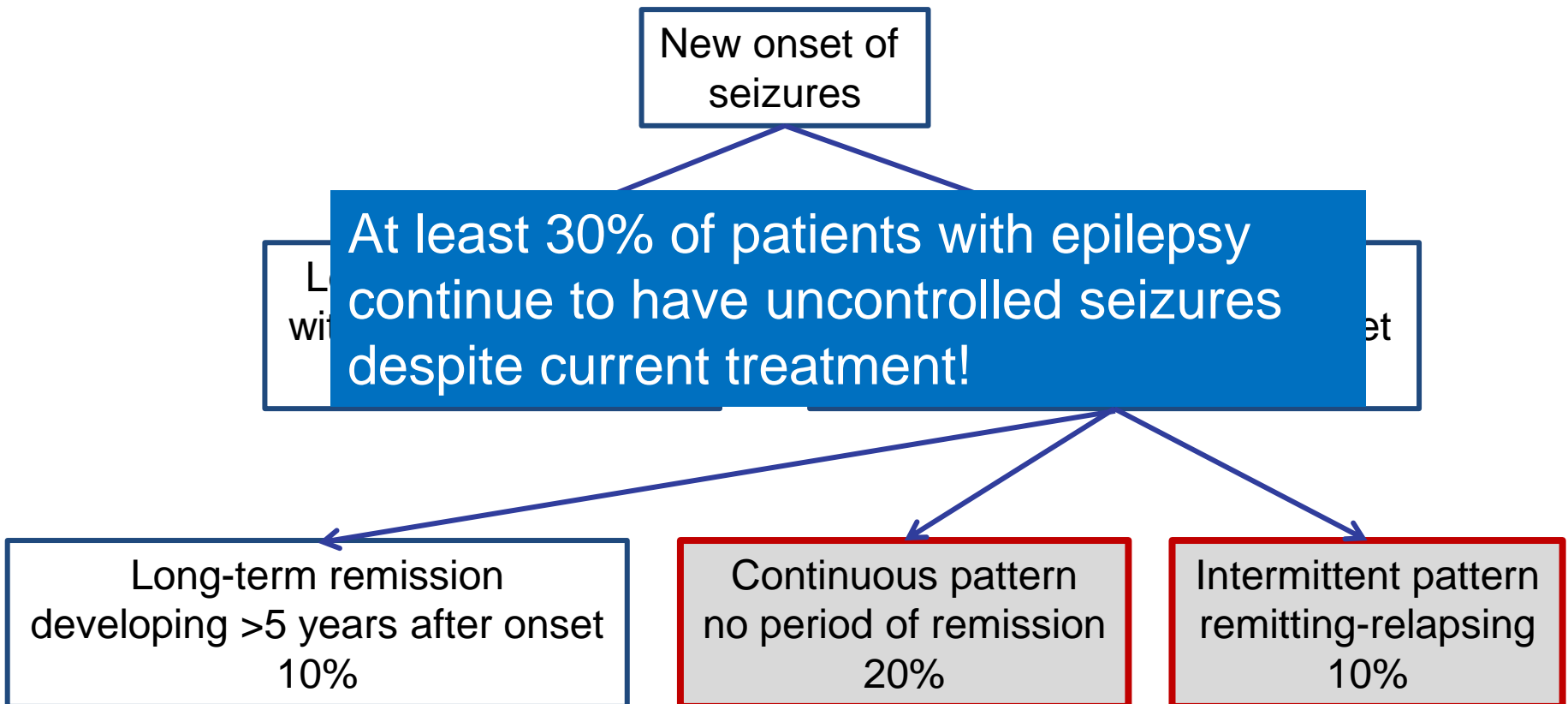
*Dimitri Kullman (UK)*

### **How to achieve the goal – European perspective? (15 min)**

*Dieter Schmidt (Germany)*

### **Discussion (20 min)**

# Dynamics of epilepsy and the unmet needs



# What is cure?

## 5-years remission 20 years after diagnosis

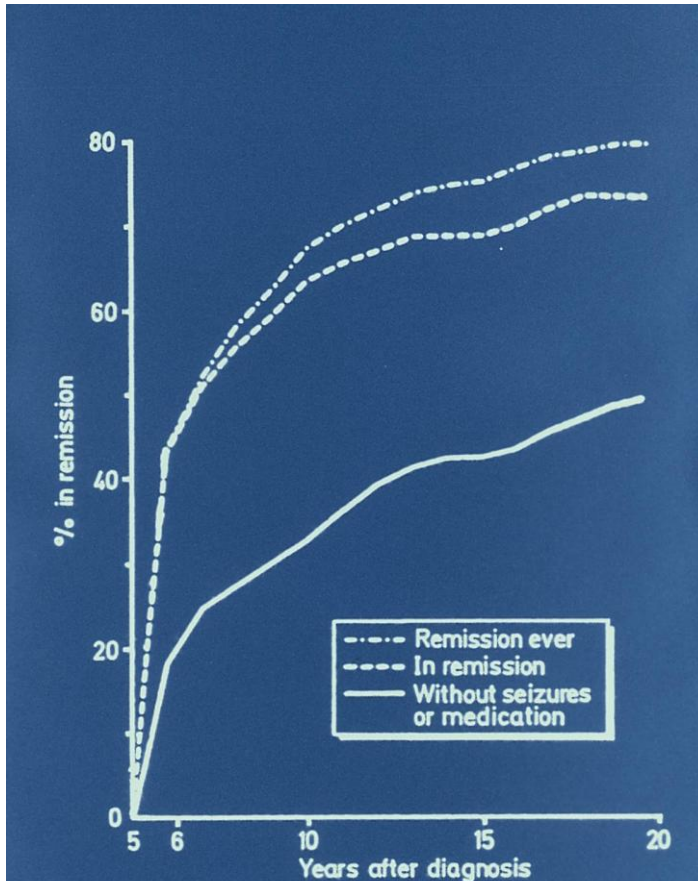


Fig 4 *The Rochester study:*<sup>46</sup> remission of seizures over a twenty year period in 457 cases from the onset of epilepsy.

Less than 50% seizure free without medication after 20 years

Current medication does not affect the natural course

Symptomatic (anti seizure) not curative

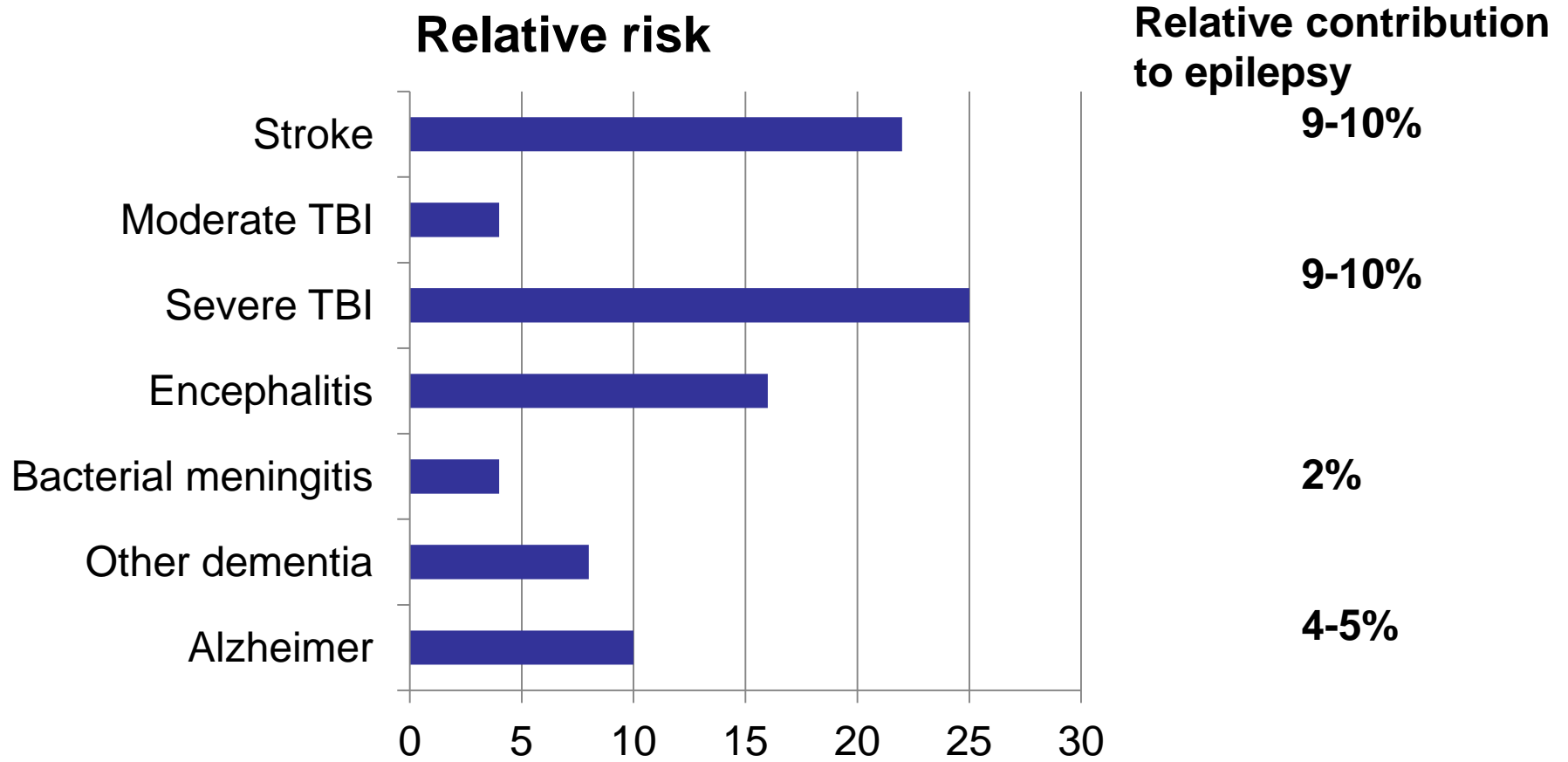
# Epilepsy is a serious condition

- Overall mortality rates increased 2-3-fold
- Life expectancy reduced by up to
  - 10 years
  - 20% of vital importance at all stages of epilepsy
- Risk of epilepsy development increased 20-fold
- 12% cumulative risk of Sudden Unexpected Death at 40 years after childhood onset epilepsy

# Prevention

- Primary
  - Preventing occurrence of epileptogenic lesions
- Secondary
  - Preventing development of seizures after an epileptogenic insult
- Tertiary
  - Preventing epilepsy-related adverse outcomes

# Risk factors & their contribution



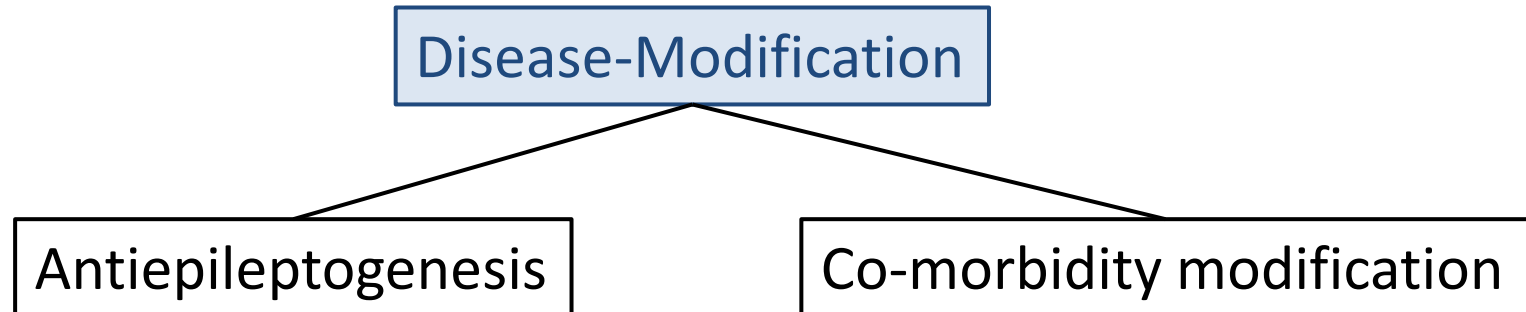
# Concepts and Terminologies

- disease-modification
  - epileptogenesis – antiepileptogenesis
  - co-morbidity modification

# Disease-Modification

A treatment or intervention that affects the **underlying pathophysiology** of the disease and has a beneficial effect on **clinical outcome** (natural history)

- prevention of signs and symptoms ***even after*** therapy withdrawal

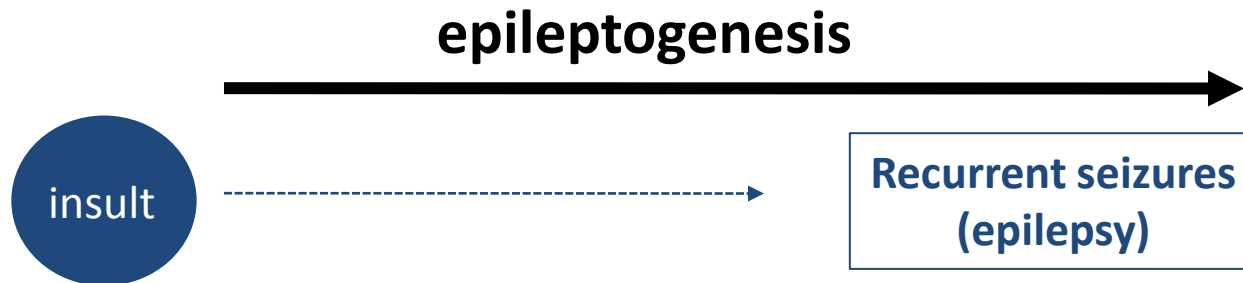




# *Epileptogenesis*

The development and extension of tissue capable of generating spontaneous seizures, including

- Development of an epileptic condition
- Progression after the condition is established



# ***Antiepileptogenesis***

- a process that counteracts the effects of epileptogenesis, including

## ***Treatment prior epilepsy onset***

- prevention or delay of epilepsy onset
- alleviation of severity of epilepsy (frequency/duration of seizures)

## ***Treatment after epilepsy onset***

alleviation of

- severity of epilepsy (frequency, duration)
- progression
- refractoriness

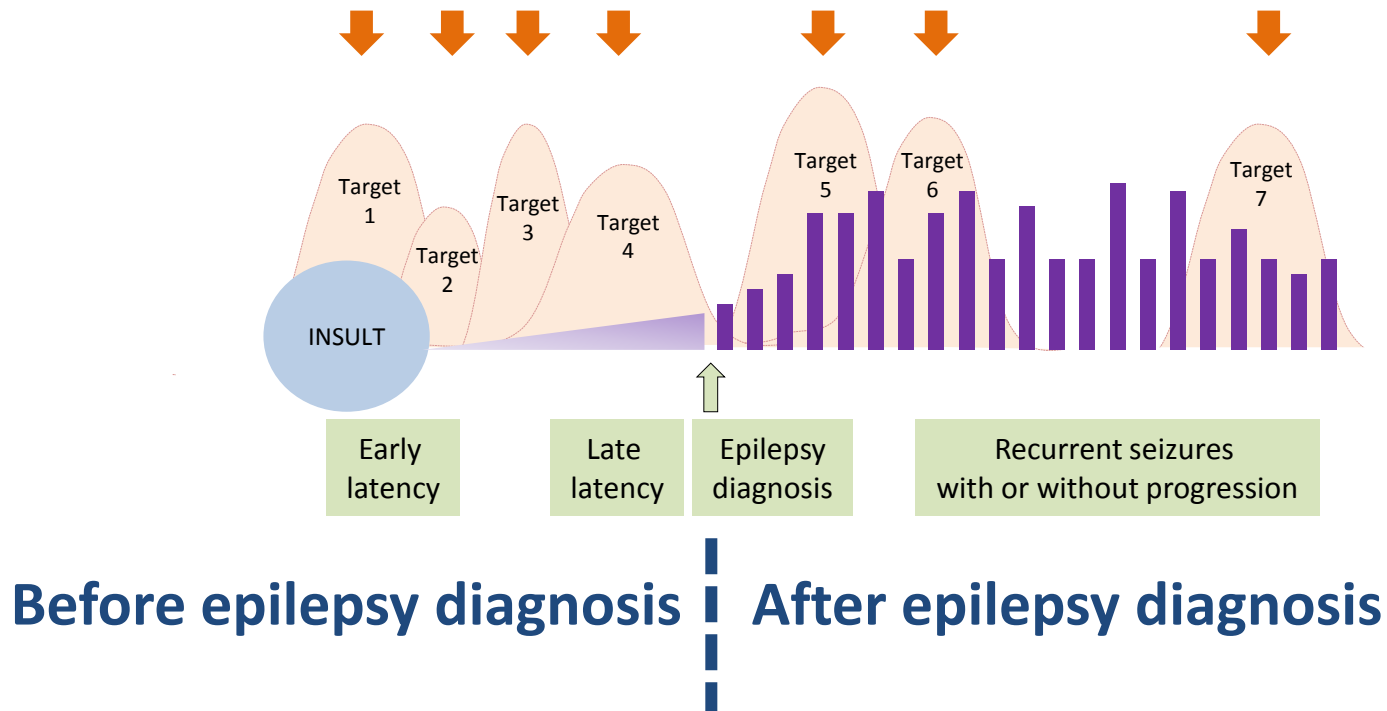
## ***Cure***

- complete and permanent reversal of epilepsy such that no seizures occur after treatment withdrawal

# *Co-Morbidity Modification*

- treatment alleviates or reverses the symptomatic development or progression of epilepsy-related co-morbidities such as anxiety, depression, somato-motor impairment, or cognitive decline

# Target Expression and Intervention Points for Antiepileptogenesis and Co-Morbidity Modification



# Recent "12 Proof-of-Principle Success Stories"

## - Administration Before Epilepsy Onset -

1. Atipamezole	$\alpha$ 2-adrenergic receptor	(Pitkänen et al., 2004)
2. Levetiracetam	SVA2	(Yan et al., 2005)
3. Celecoxib	COX-2 inhibition	(Jung et al., 2006)
4. Rapamycin	mTOR inhibition	(Zeng et al., 2008)
5. $\alpha$ 4 integrin-specific mAb	integrin alpha-4	(Fabene et al., 2008)
6. Erythropoietin	erythropoietin receptor	(Chu et al., 2008)
7. Ethosuximide	T-type Ca-channels	(Blumenfeld et al., 2008)
8. BDNF+FGF-2	FGF and NTRAK2	(Paradiso et al., 2009)
9. Rimonabant	CB1 receptor	(Echegoyen et al., 2009)
10. Parecoxib	COX-2 inhibition	(Polascheck et al., 2010)
11. Minozac	cytokine production ↓	(Chrzaszcz et al., 2010)
12. Hypothermia		(Atkins et al., 2010)

None of these has progressed to rigorous preclinical or clinical testing

**The unmet need – treatments to prevent or cure epilepsy**

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