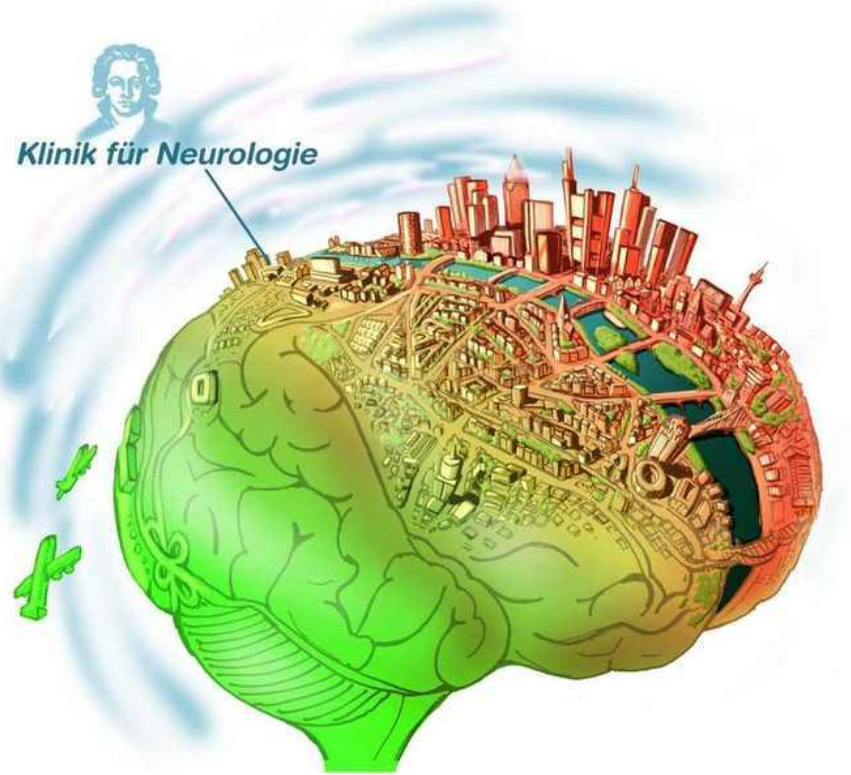
Basics in Pharmacology and Medicine

Neurology



Waltraud Pfeilschifter

Department of Neurology

Goethe University Hospital

Overview

In this lecture, you will

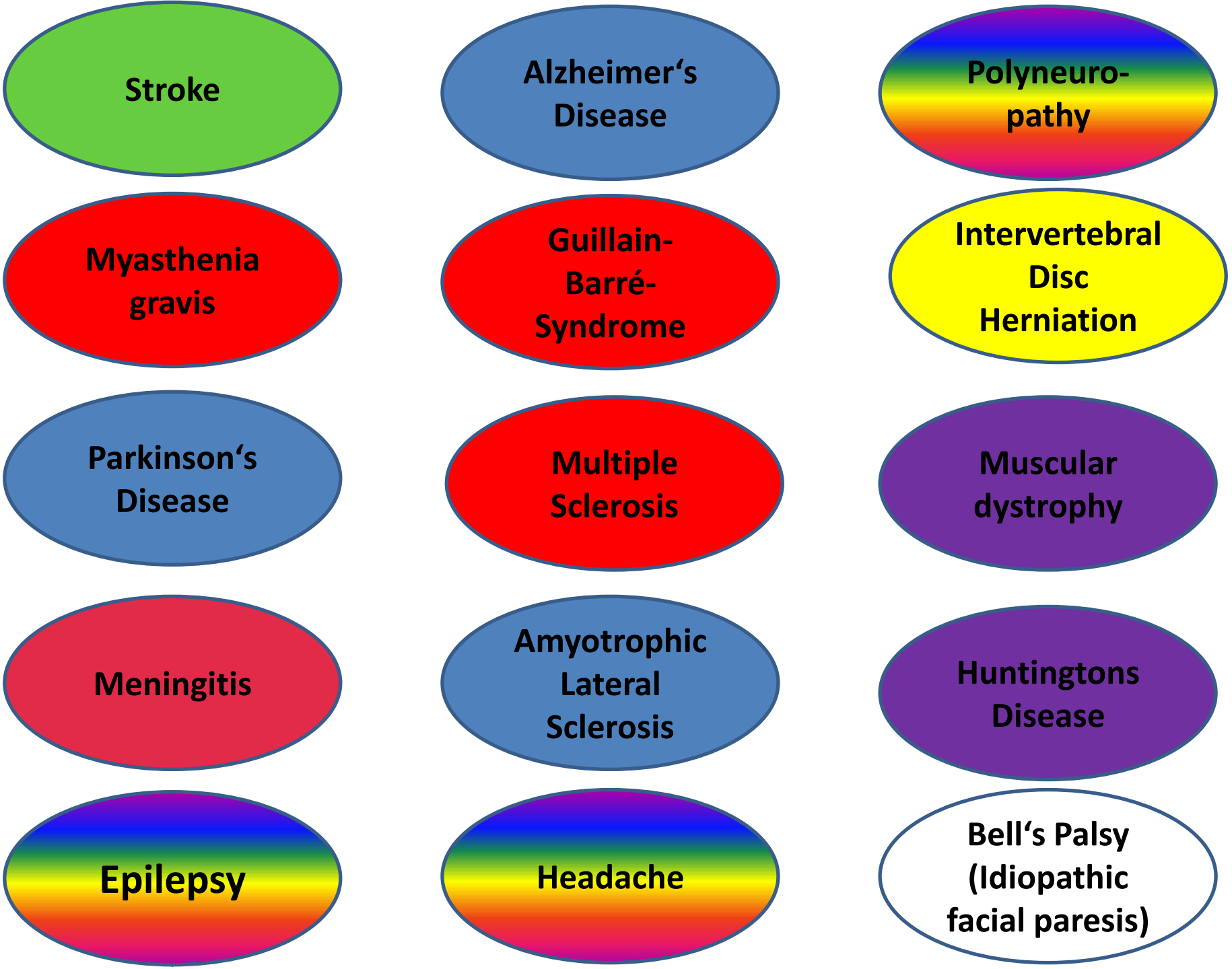
… revise some basic anatomic and physiologic principles of the nervous system

… get an overview over the broad spectrum of neurological diseases

… learn more about a handful of important neurological diseases, their pathomechanisms and their current treatment

What do we need neurologists for?

Translation: Oh, a nerve bundle! – German term for a very irritable person.


Stroke
Alzheimer‘s Disease
Polyneuro-pathy
Myasthenia gravis
Guillain-Barré-Syndrome
Intervertebral Disc Herniation
Parkinson‘s Disease
Multiple Sclerosis
Muscular dystrophy
Meningitis
Amyotrophic Lateral Sclerosis
Huntingtons Disease
Epilepsy
Headache
Bell‘s Palsy (Idiopathic facial paresis)

As any other organ,
the brain can be affected by very diverse pathomechanisms…

Vascular disease (e.g. ischemic stroke, subarachnoid hemorrhage)
Degenerative (e.g. Alzheimer‘s disease, Parkinson‘s disease)
Hereditary (e.g. Duchenne‘s muscle dystrophy)
Autoimmune-inflammatory (e.g. Multiple sclerosis, Guillain-Barré)
Infectious (e.g. bacterial or viral meningitis)
Cancer (primary brain tumors and brain metastases)
Mechanic compression (e.g. vertebral disc herniation)

Specific for the nervous system:
Aberrant neuronal excitation (e.g. epilepsy, trigeminal neuralgia)

Alzheimer's Disease

Prevalence:
30-59yrs – 0.02%
60-69yrs – 0.3%
70-79yrs – 3.2%
80-90yrs – 10.8%

Parkinson's Disease

Prevalence:
1-2% of the population
< 60 yrs
Germany

Epilepsy

Prevalence:
0.5-1% of the population
2-5 % of the population will suffer an epileptic seizure once in their lives!

Multiple Sclerosis

Incidence:
4/100.000/yr
Prevalence:
80-120/100.000
Germany

Stroke

Incidence:
182/100.000/yr
Prevalence:
Currently > 500.000 patients
in Germany

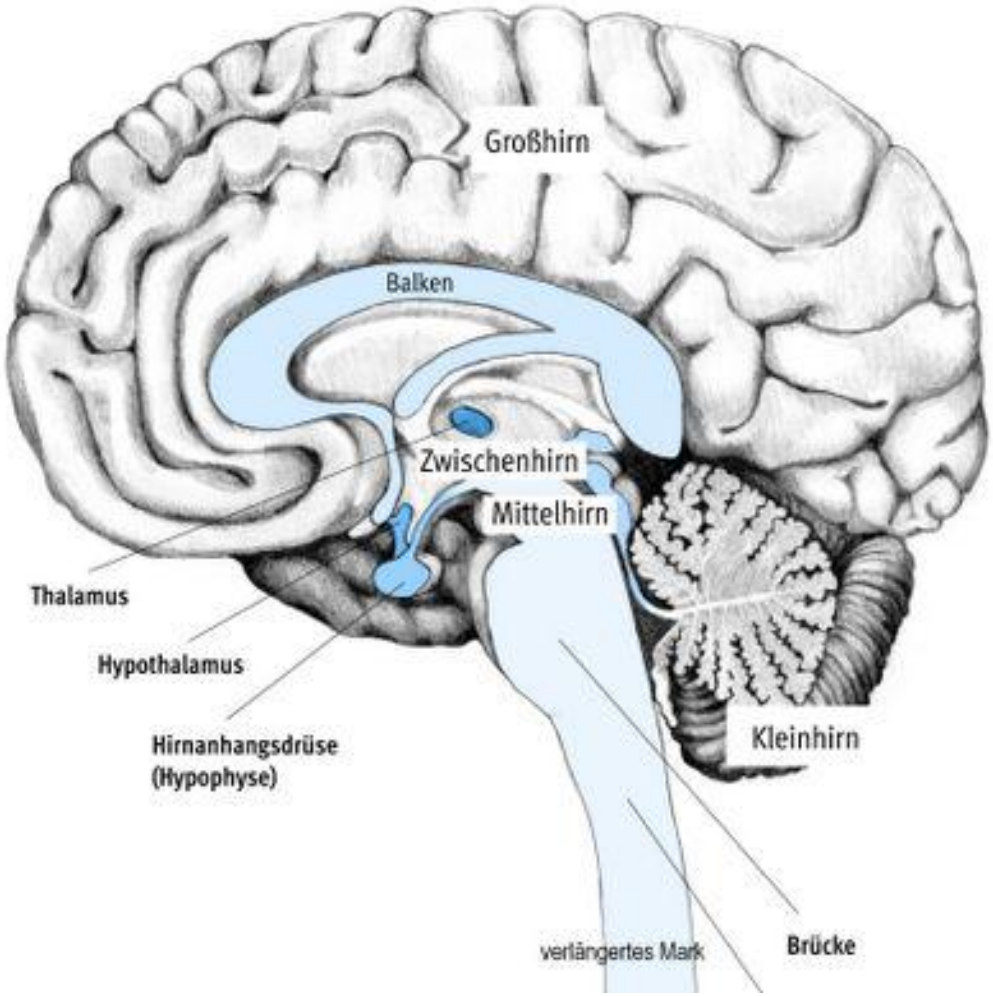
From Berlit, Klinische Neurologie, 2. Aufl., Springer Verlag

The Nervous System

- Brain

  Cortex, Basal Ganglia, Cerebellum, Pons and Medulla oblongata
- Eye, Ear, Cranial Nerves
- Spinal cord
- Nerve roots, nerve plexus, nerves
- Neuro-muscular synapse
- Muscles

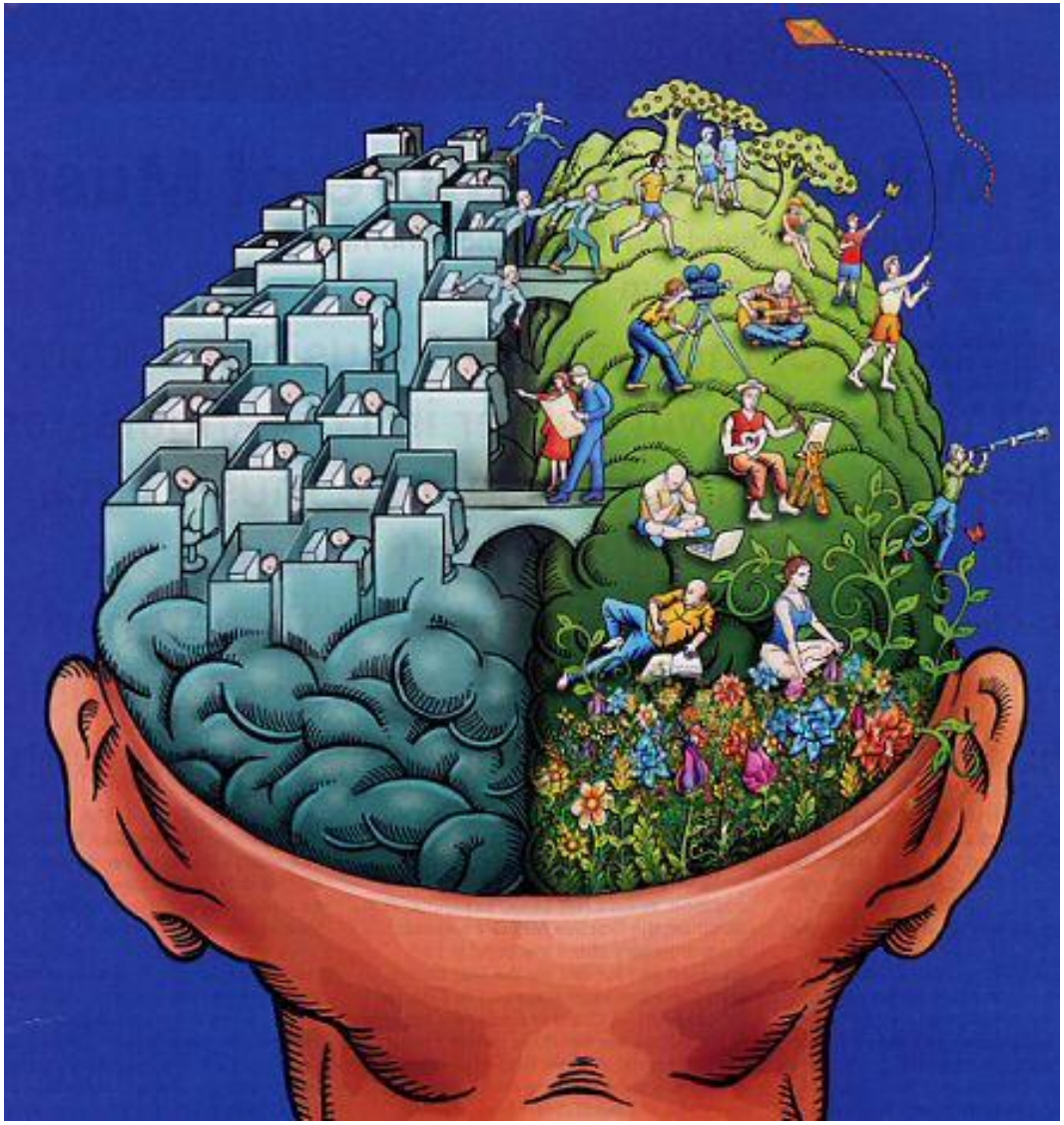
The Brain



taken from the website of the Hannelore-Kohl-Stiftung

Cortical functions

left



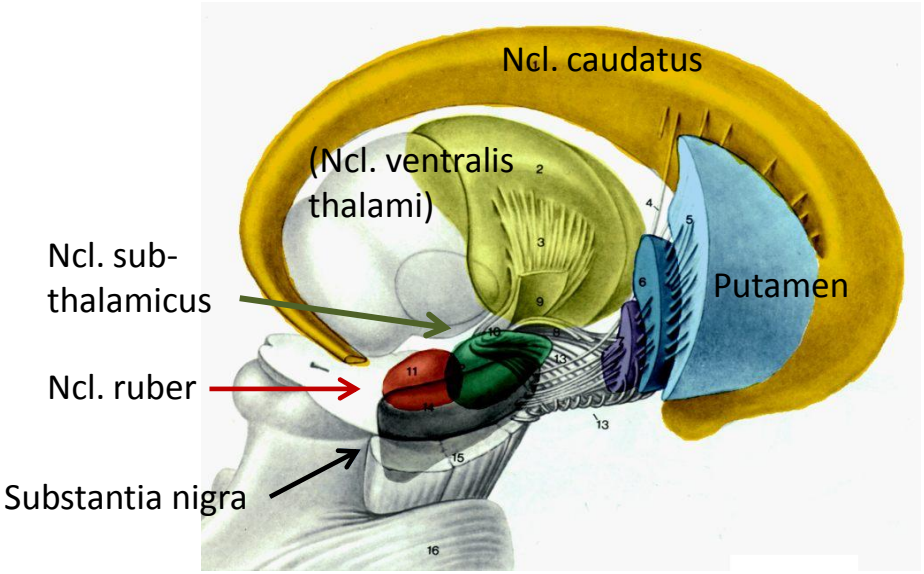
right

Subcortical functions

Gating and propagation of information (Thalamus)

Subcortical functions

fine tuning of movements (basal ganglia)

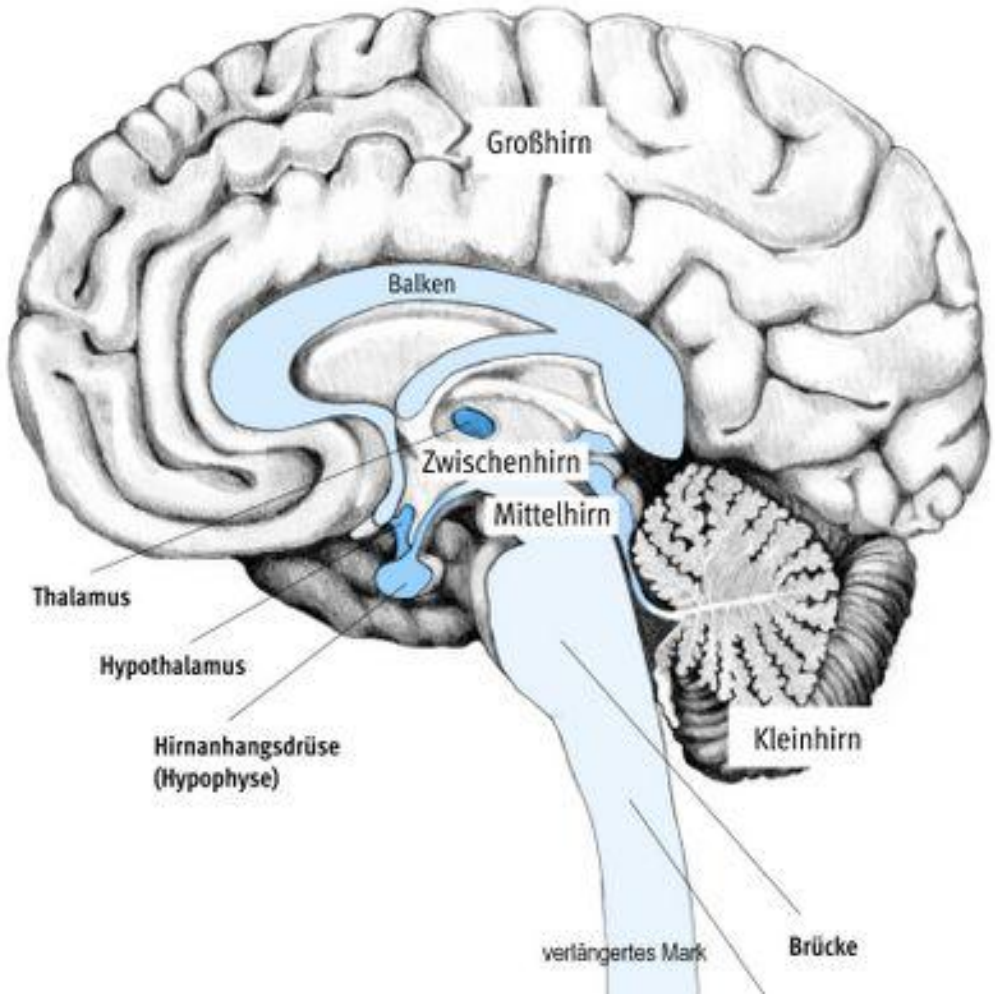


Subcortical functions

Memory storage (limbic system)

Brain stem

Coordination, conduction and cranial nerves



Spinal cord

Nerve roots

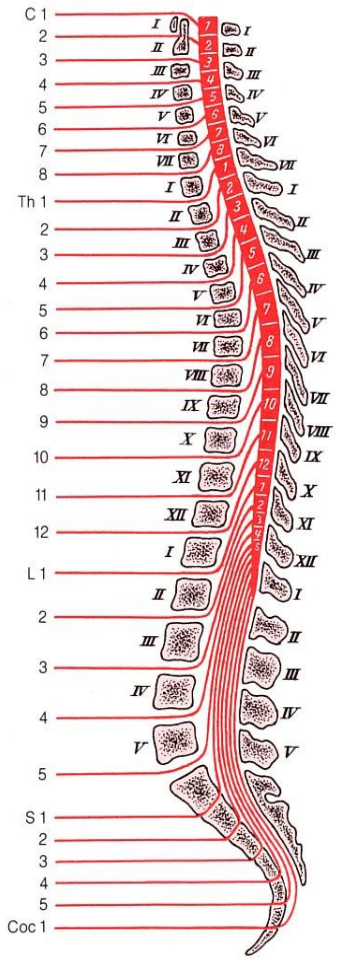
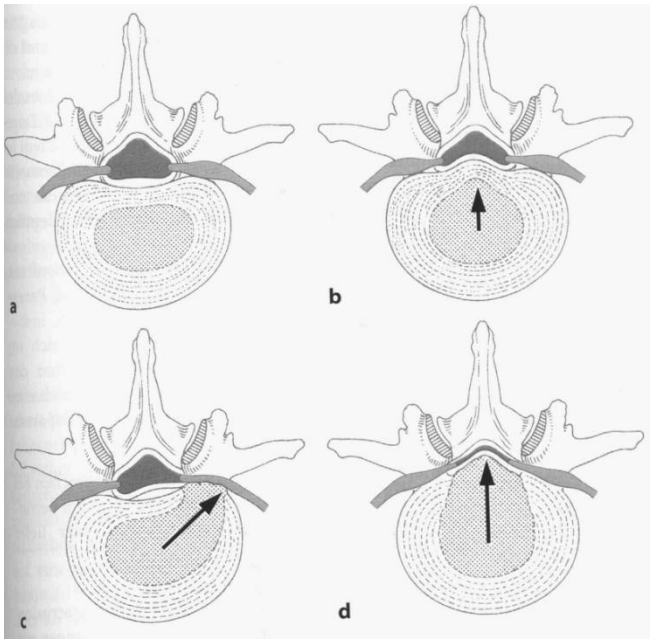
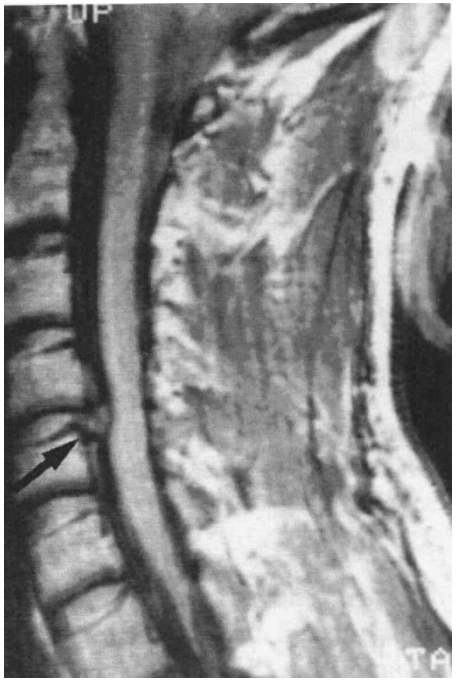


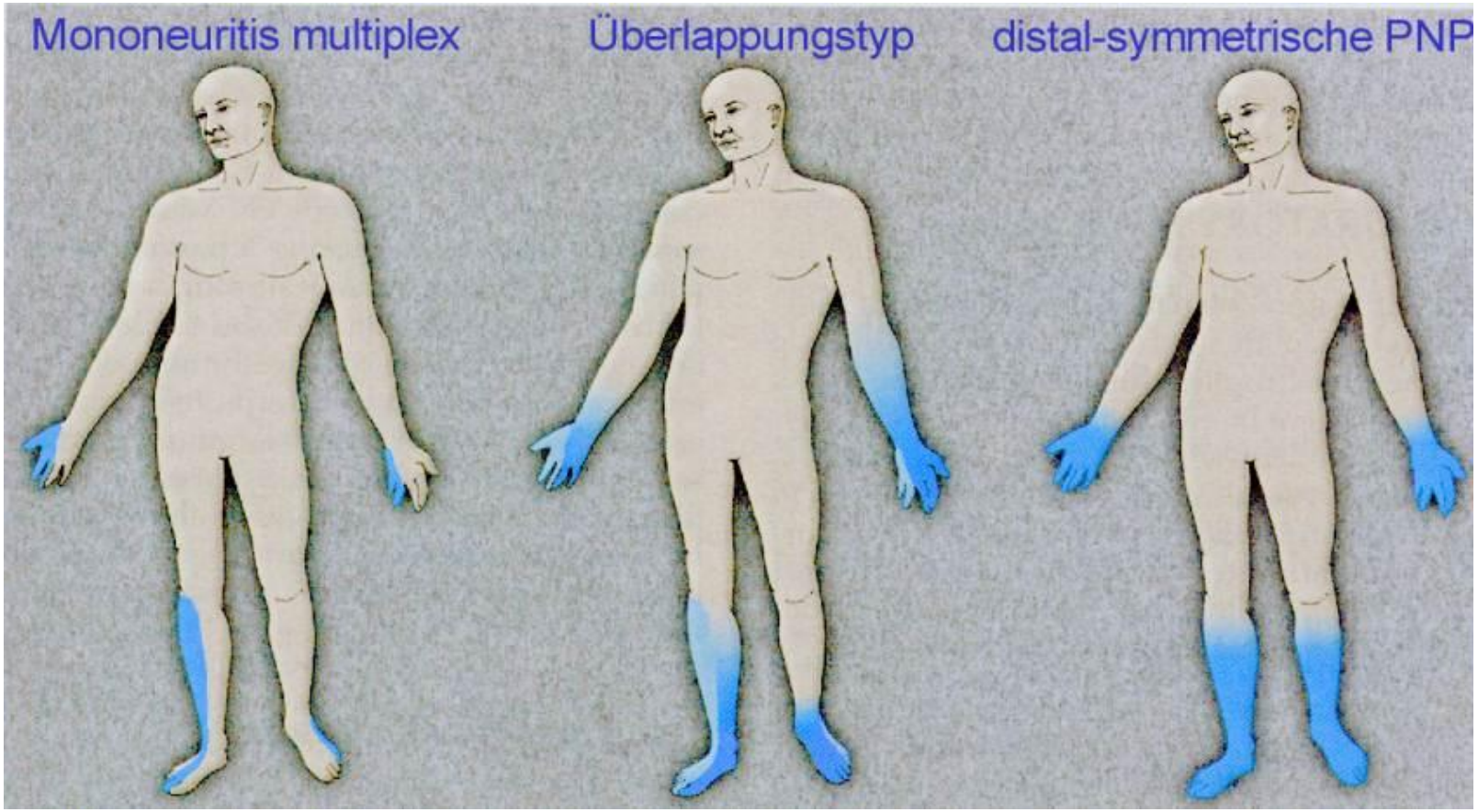
Abb. 2.34. Topographische Beziehungen der Rückenmarkssegmente und -wurzeln zur Wirbelsäule. Beachte: Die Wurzel C1 ist nur motorisch. Aus ihr entsteht der N. suboccipitalis für die Innervation der langen Halsmuskeln. Das oberste sensible Segment ist C2





Nerve Plexus, Nerves

Polyneuropathies



Neuromuscular Synapse and Muscles

Representative Neurological Diseases,
how to treat them
and open questions for basic scientists…

Stroke: WHO Definition

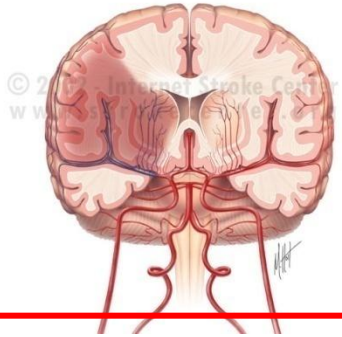
Neurological Dysfunction caused by a cerebrovascular occlusion or rupture with a sudden onset of focal neurological symptoms that are caused by an affection of the respective brain area.

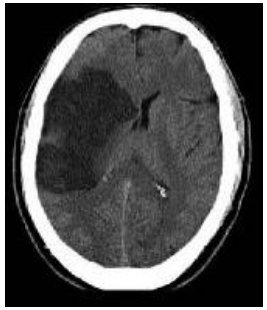
typical symptoms:

Hemiparesis
Speech disturbance
Impaired Vigilance

Disease Spectrum of „Stroke“

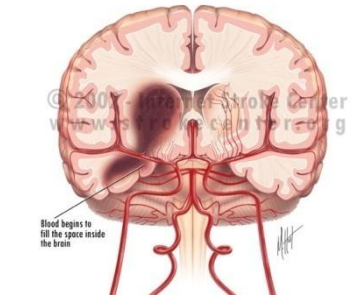
Cerebral Ischemia („stroke“)

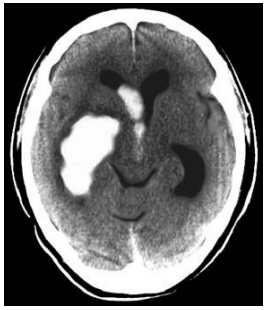




ca. 80%

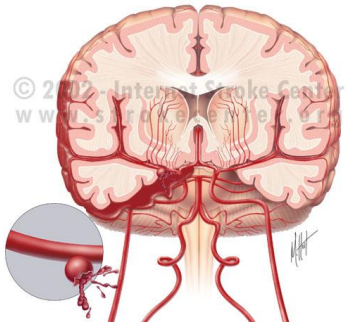
Intracerebral Hemorrhage (ICH)

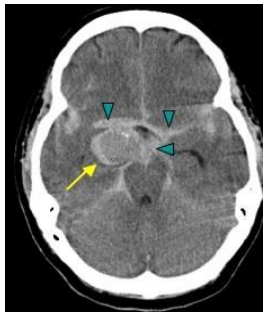




ca. 15%

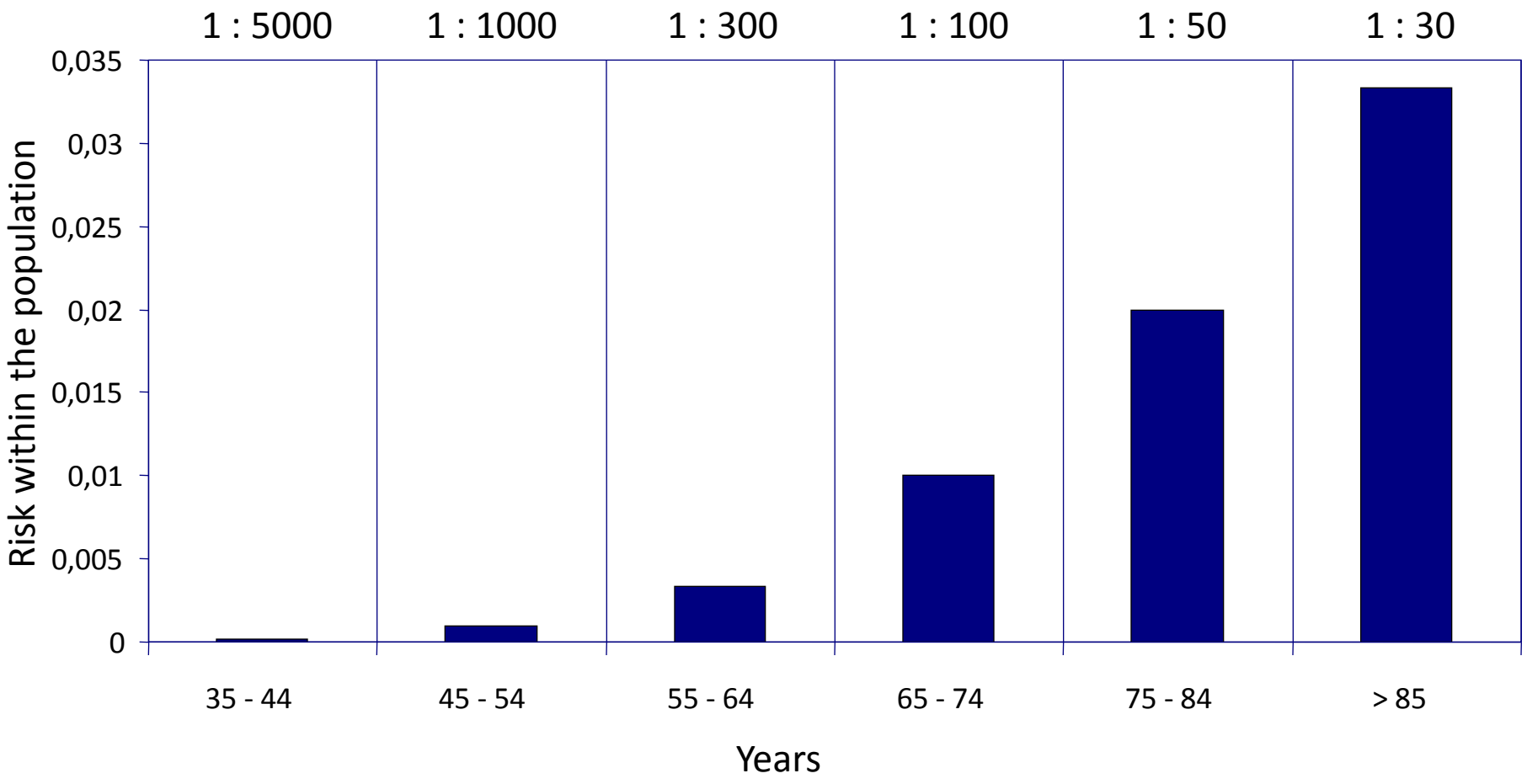
Subarachnoid Hemorrhage (SAH)





ca. 5%

Stroke Risk as a Function of Age

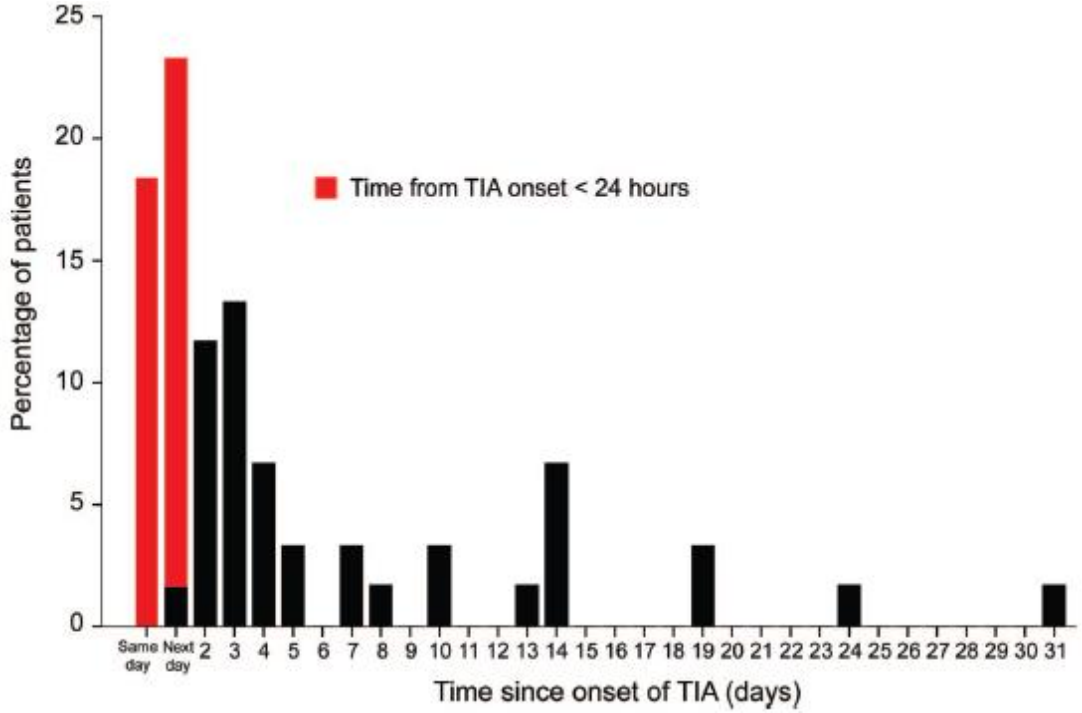


Anderson CS et al., Med J Aust 1993

Transient Ischemic Attacks as a Warning Sign of Stroke

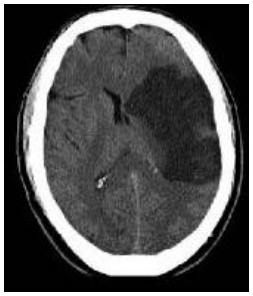
30-40 % of stroke patients hat a TIA prior to their stroke

90 day risk of stroke after a TIA: ca. 10 %, 50 % within the first two days



Rothwell et al., Lancet Neurol 2006
Chandratheva et al., Neurology 2009

Ischemic stroke: Infarkt patterns



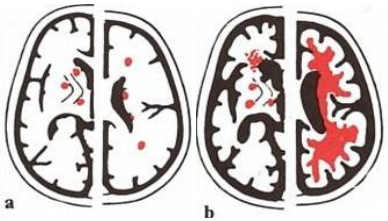
Territorial infarctions
(mostly embolic)

Occlusion of a large cerebral artery. Often cortical signs.

Lakunar Infarctions
(mostly microangiopathic)

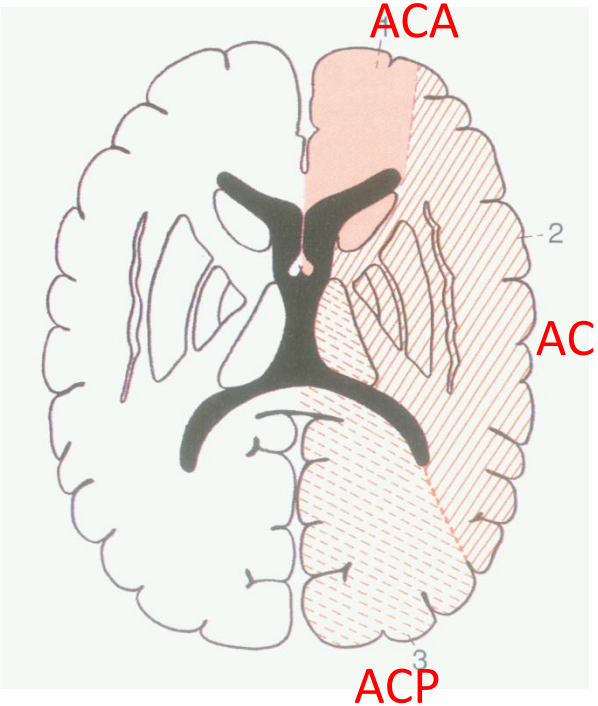
Occlusion of (tiny) Perforating arteries

Infarcted area < 1.5 cm (“lacune”)
subcortical zones, e.g. capsula interna, basal ganglia

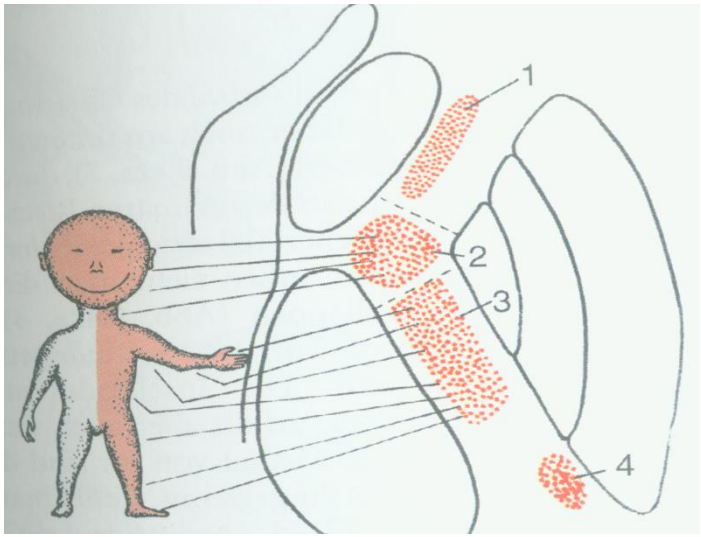


Strokes can be divided into cortical and subcortical („lacunar“) strokes by brain imaging and often clinically.

This important for the diagnostic workup and therapeutic recommendations!



Cortical signs involved
Gaze palsy, Aphasia, Neglect



No Cortical signs involved
Small size, big effect due to strategic location.

Acute Treatment: Recanalization!

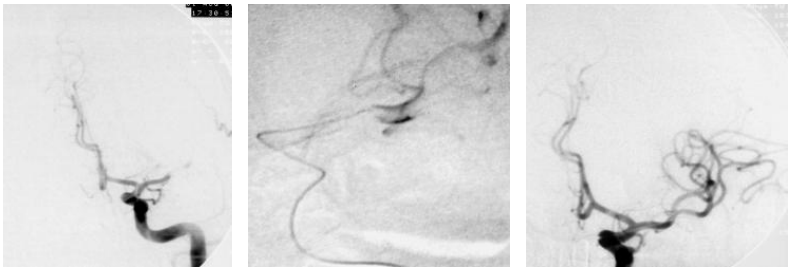
Systemic Thrombolysis (i.v.)

rtPA: recombinant tissue plasminogen inhibitor

10fold increased risk
of secondary hemorrhage
(6 % vs. 0,6 %)

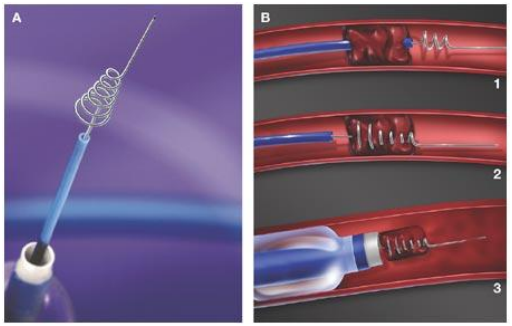
Local Thrombolysis (i.a.)

katheterbased Thrombolysis, selektive



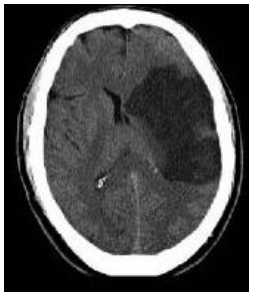
Mechanic Embolectomy

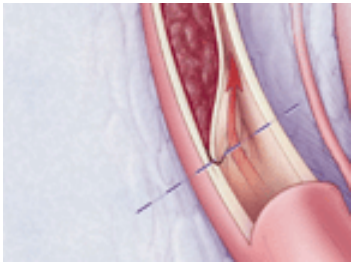
MERCI, multi-MERCI, Penumbra-Katheter
Solitaire-Stenting-system



R. du Mesnil, Neuroradiologie Ffm
Smith, Nat. Clin. Pract. Neurol. 2007

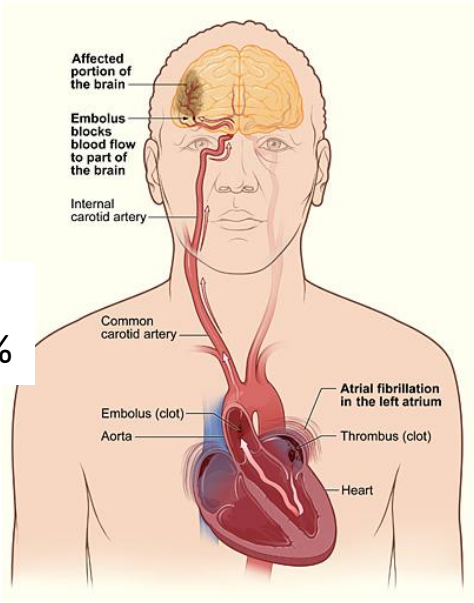
Causes of Cerebral ischemia



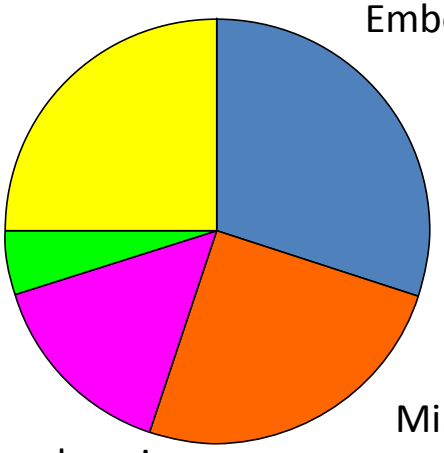


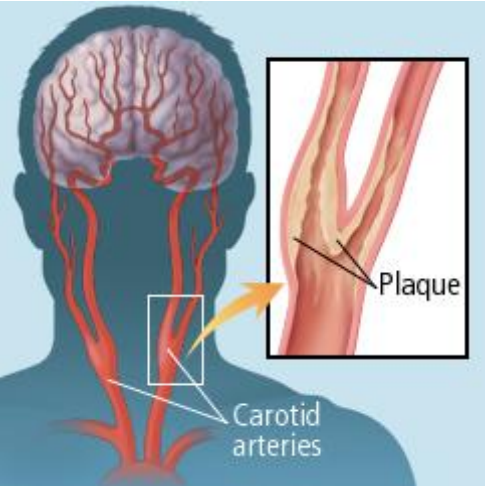
Unclear Origin 25 %

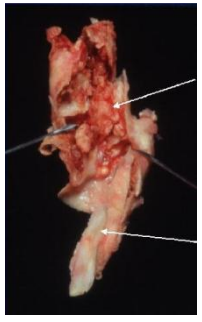
Cardio Embolism 26 %



andere 5%

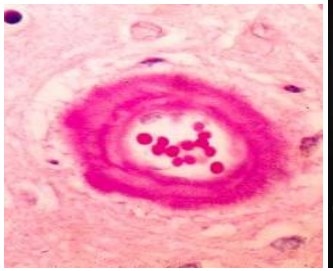


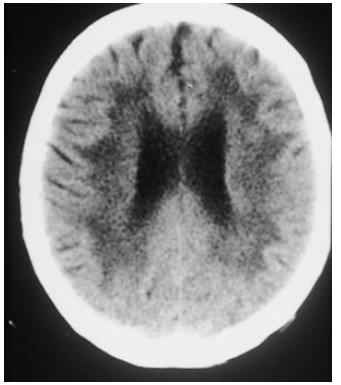




Atherosclerosis e.g. of Carotids 21 %

Mikroangiopathy 20 %





Risk factors of cerebral ischemia

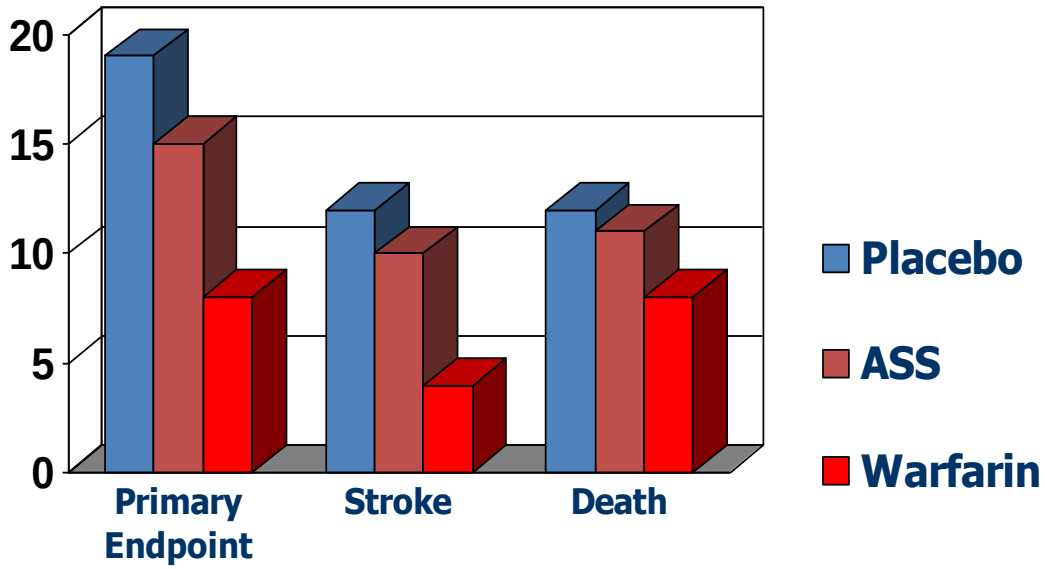
Atrial fibrillation (No. 1)
Large vessel atherosclerosis (e.g. Carotid artery)
Microangiopathy

Arterial Hypertension
Diabetes Mellitus
Hypercholesterolemia
Adipositas (esp. abdominal fat)
Physical inactivity

Smoking

Current treatment and further problems

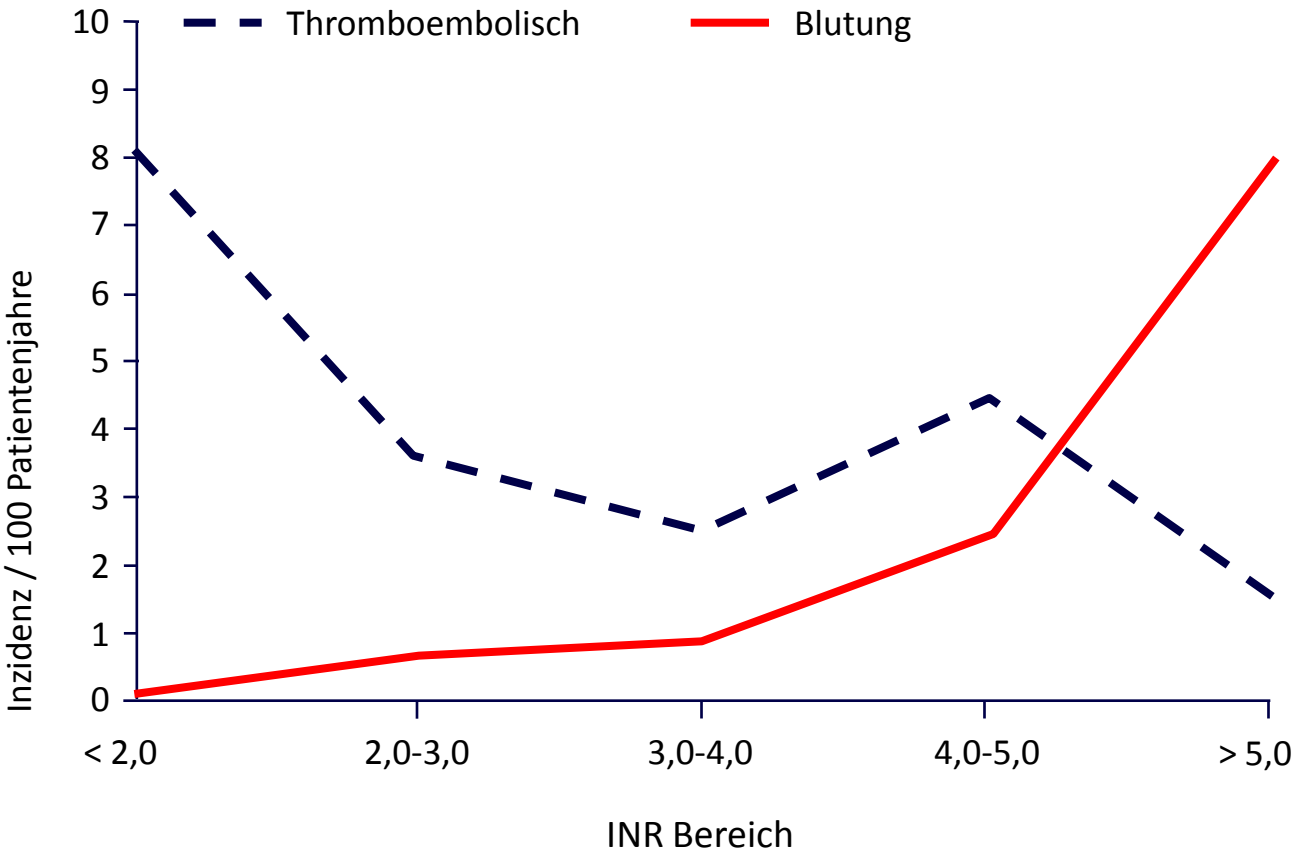
Atrial fibrillation:
Anticoagulation vs. Bleeding risk
Warfarin „Marcumar“ since 1950ies, ASS not sufficient
Newer drugs entering the market (direct thrombin inhibitors, factor Xa inhibitors)



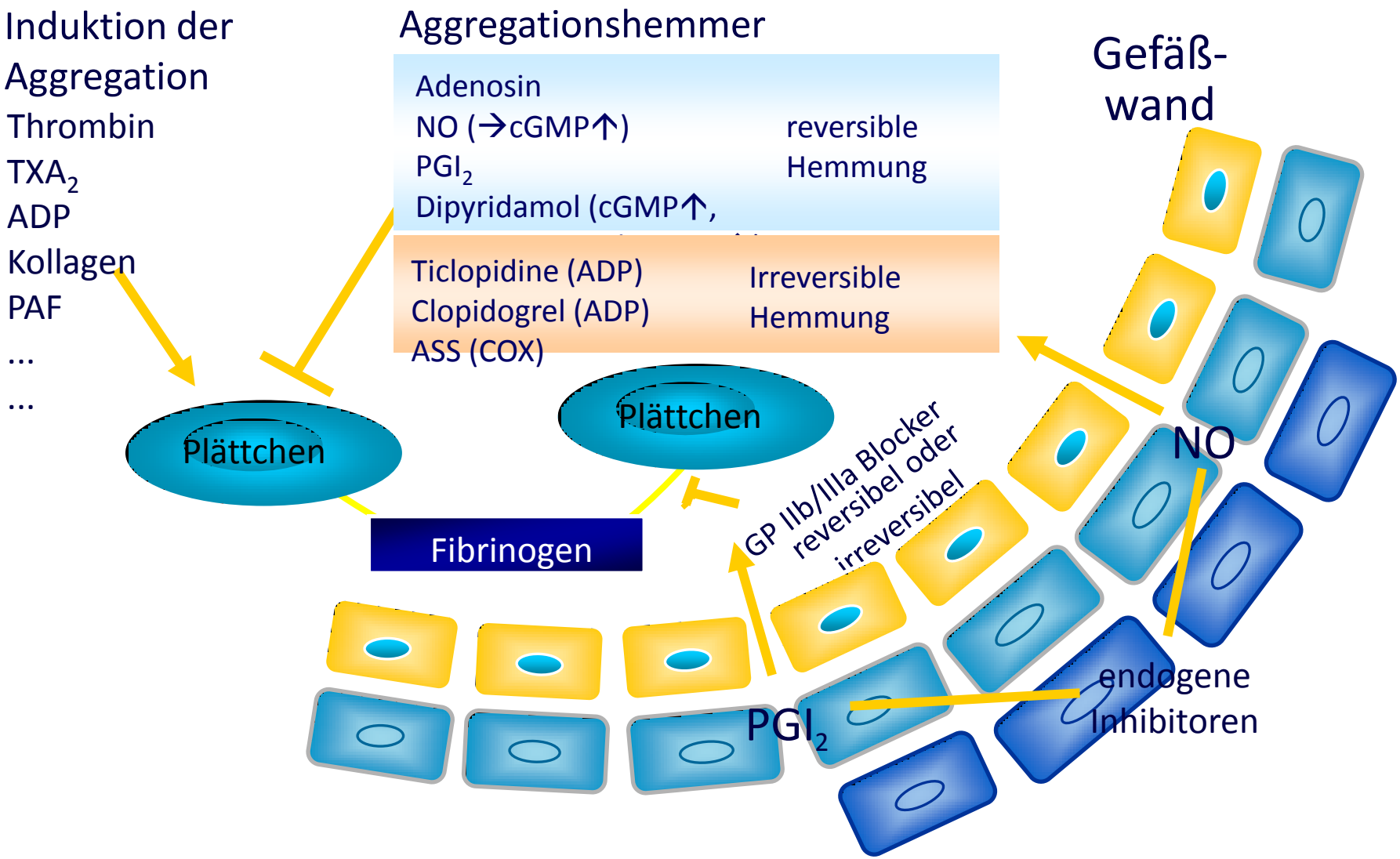
Oral antikoagulation in Afib:
Relative Risk Reduction: 67 %
NNT: 13

Protective effect of anticoagulation has to be weighed against bleeding risk

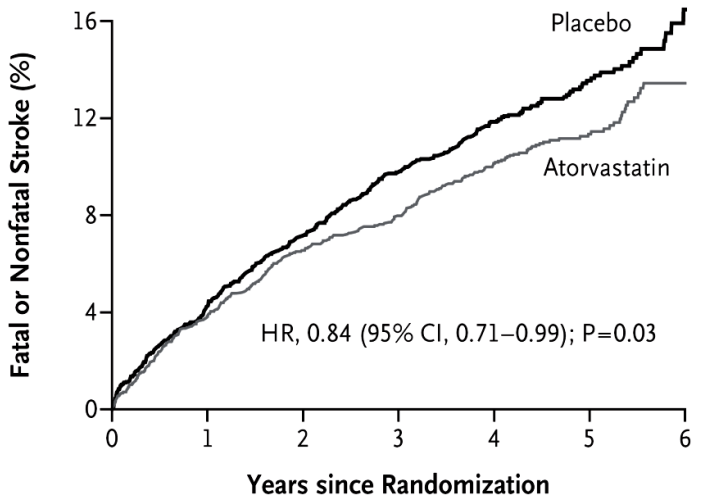
-> drugs with a better risk-to-benefit ratio than warfarin are needed



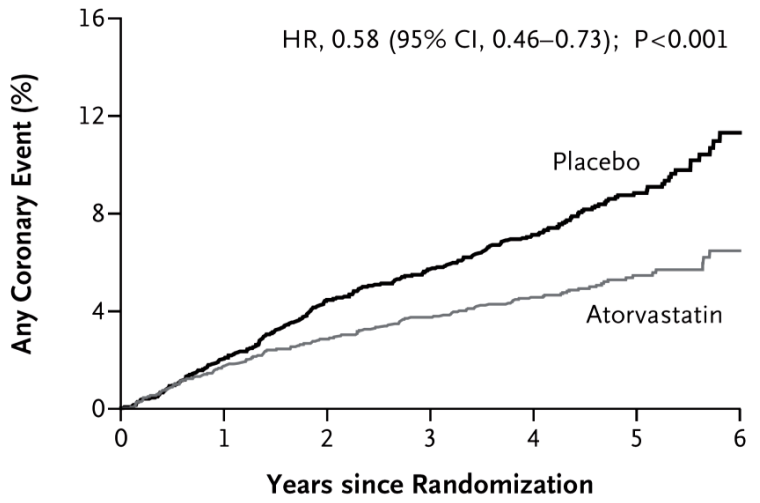
Micro- and Macroangiopathy:
Platelet-Inhibition
Warfarin does not have an additional protective effect, but higher bleeding risk.



Any stroke:
HMG-CoA-Reductase-Inhibitor (statin)
Lowers risk of second stroke or myocardial infarction
Independent of cholesterol level.



No. at Risk							
Atorvastatin	2365	2208	2106	2031	1935	922	126
Placebo	2366	2213	2115	2010	1926	887	137



No. at Risk							
Atorvastatin	2365	2261	2161	2029	2061	994	131
Placebo	2366	2260	2169	2086	2014	943	147

Current recommendations:

Platelet inhibitor (Macro- or Microangiopathy) **or**
Anticoagulant (Atrial fibrillation)
plus Statin

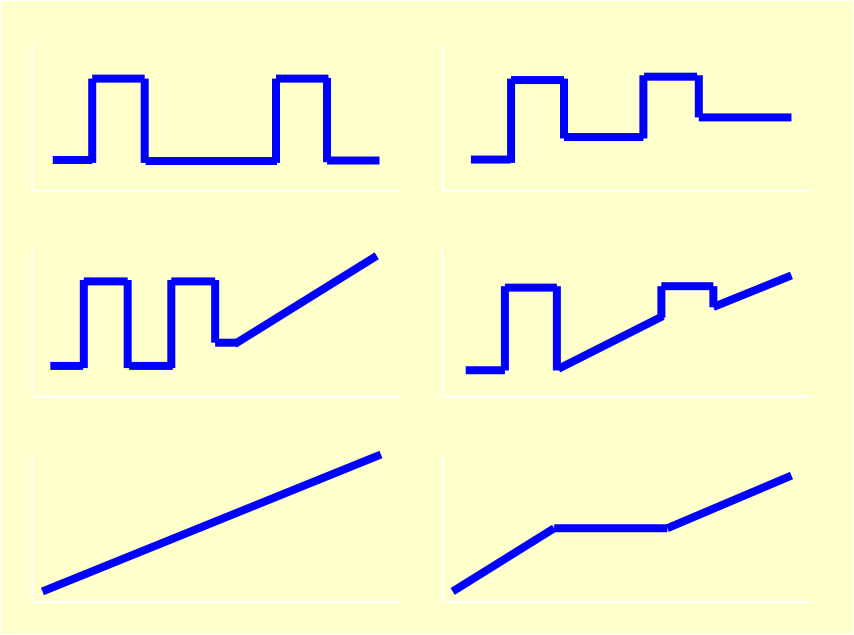
Treatment of Risk factors
- AHT
- Diabetes
- Inactivity
- Smoking
- Adipositas

Future Challenges:

- Find safer thrombolytics
  (thrombus specific, more selective protease activity)
- Improve the risk-to-benefit profile of platelet inhibitors and anticoagulants
- Establish additional treatments for the acute phase (neuroprotection)
- Find ways to fight the metabolic syndrome.

Multiple Sclerosis:

Autoimmune Encephalitis with focal demyeliniations of the Central Nervous System (Oligodendrocytes)

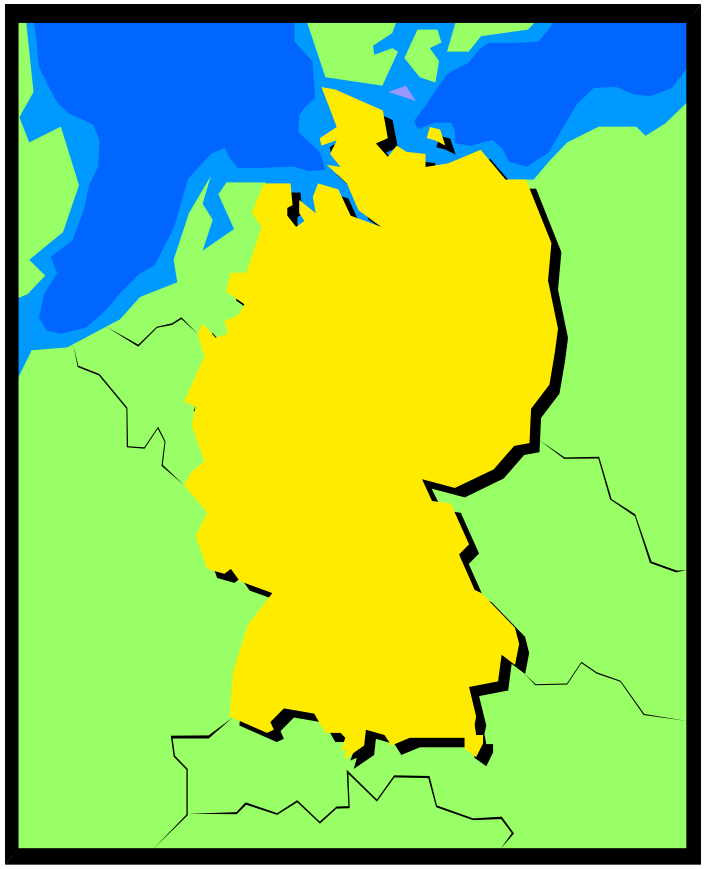


Relapsing-remitting

Secondary chronic progressive

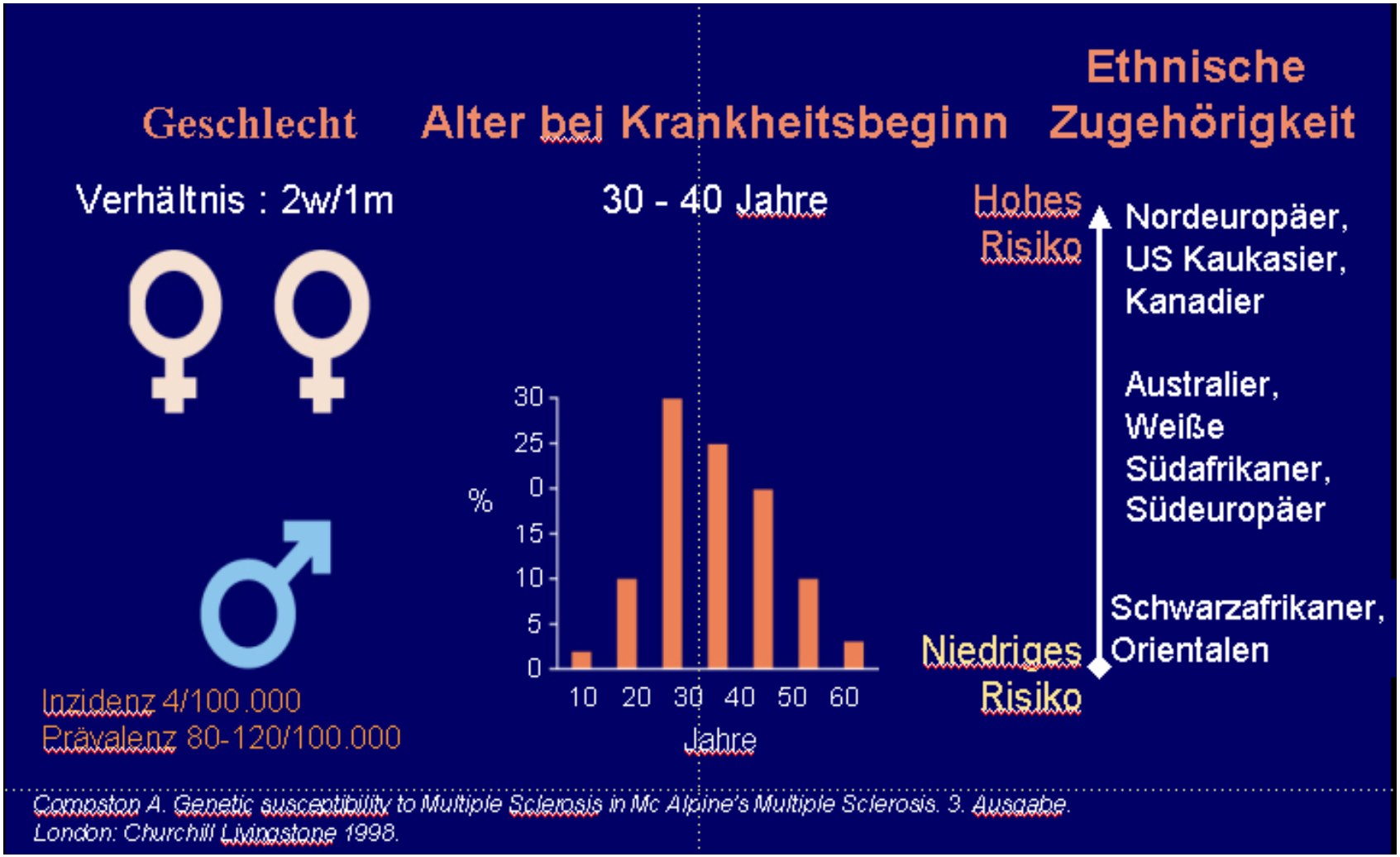
Primary chronic progressive

Epidemiology of MS in Germany

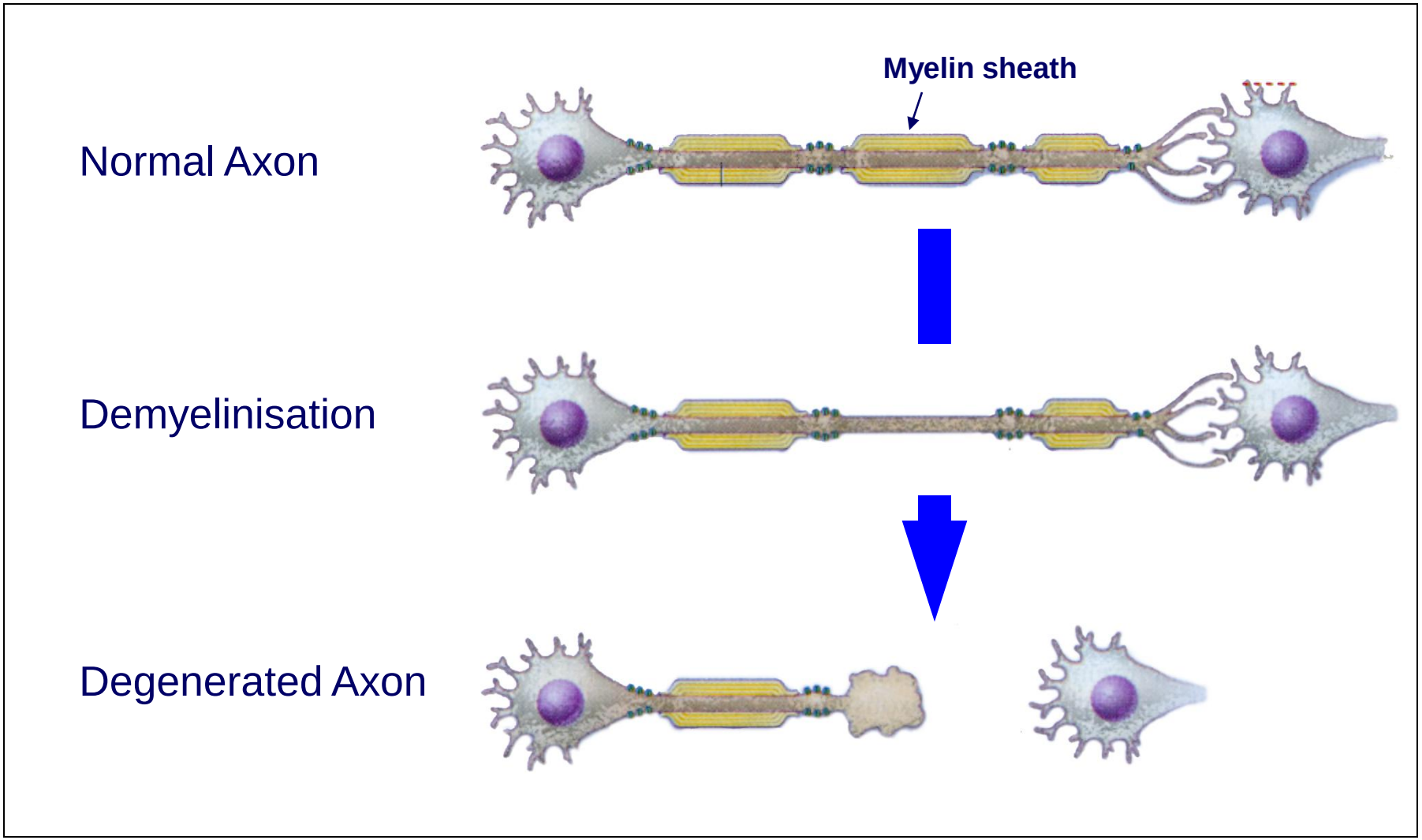


- Currently 80.000 -120.000 Patients
- Prevalence 100 – 150/100.000
- 3.000 - 5.000 new diagnoses/yr
- Incidence 4 – 6/100000/yr
- First signs mostly at 25-35 yrs
- female:male ratio 2 : 1

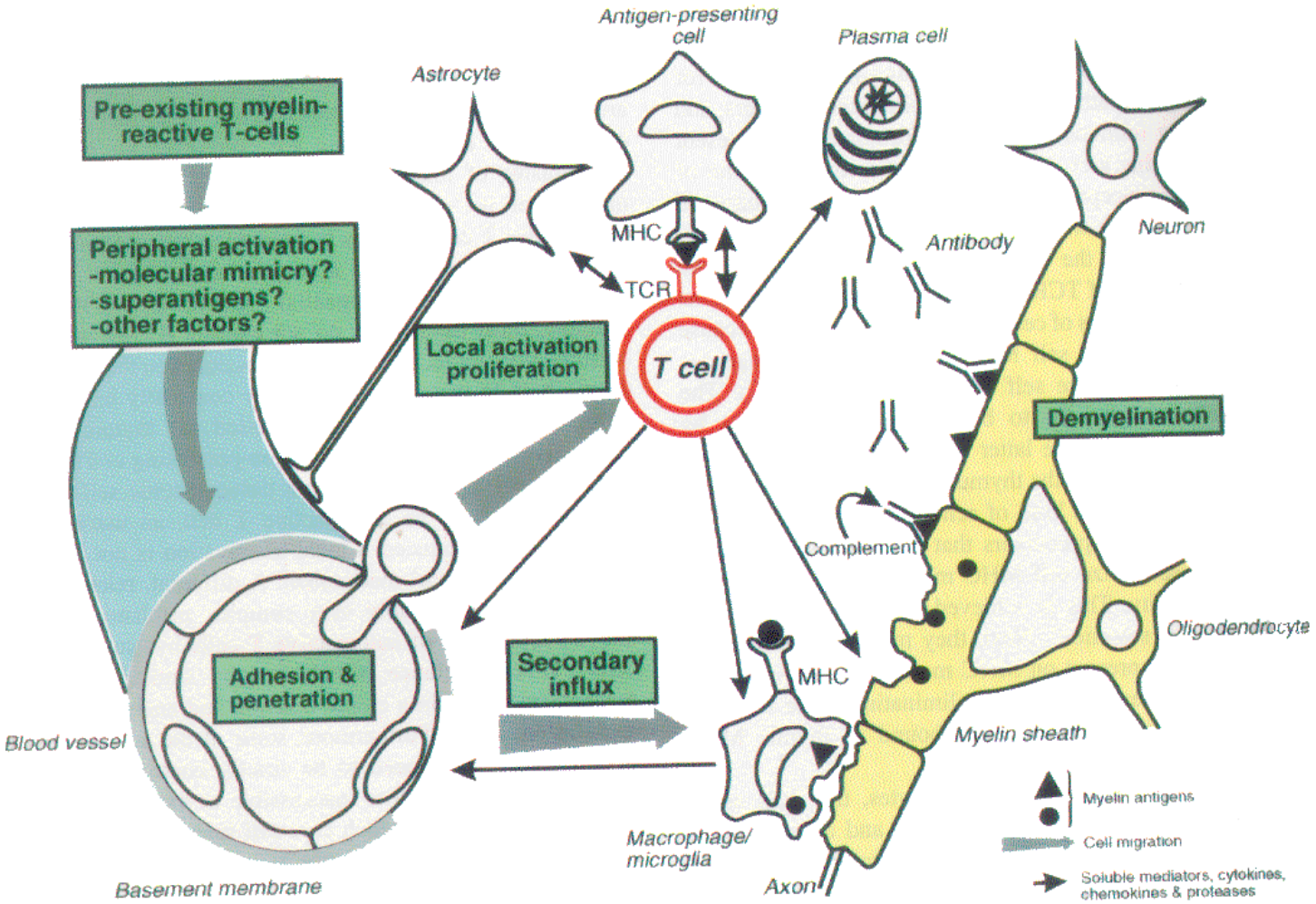
Multiple Sclerosis - Demography



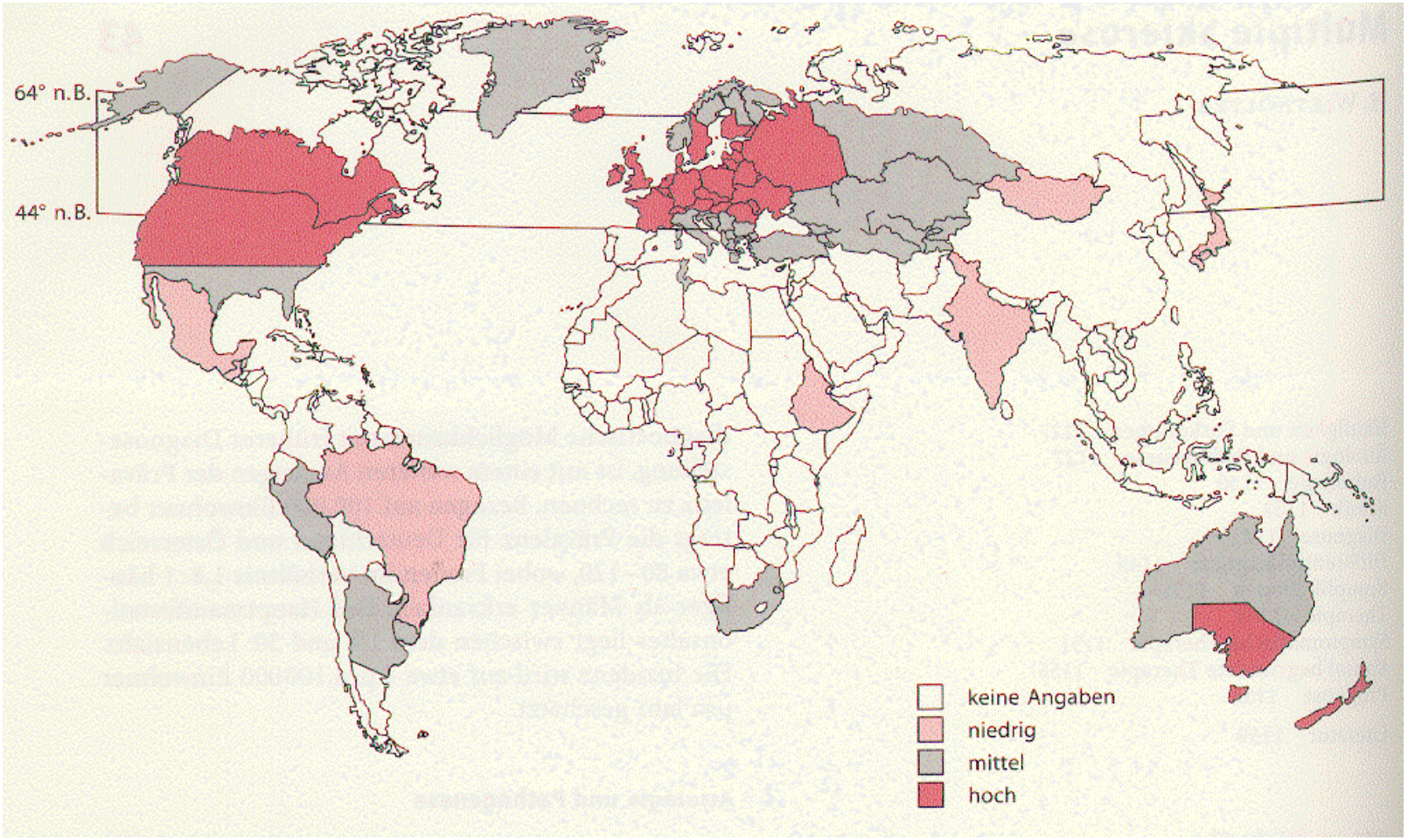
Multiple Sklerosis - Demyelinisation and Axonal Loss



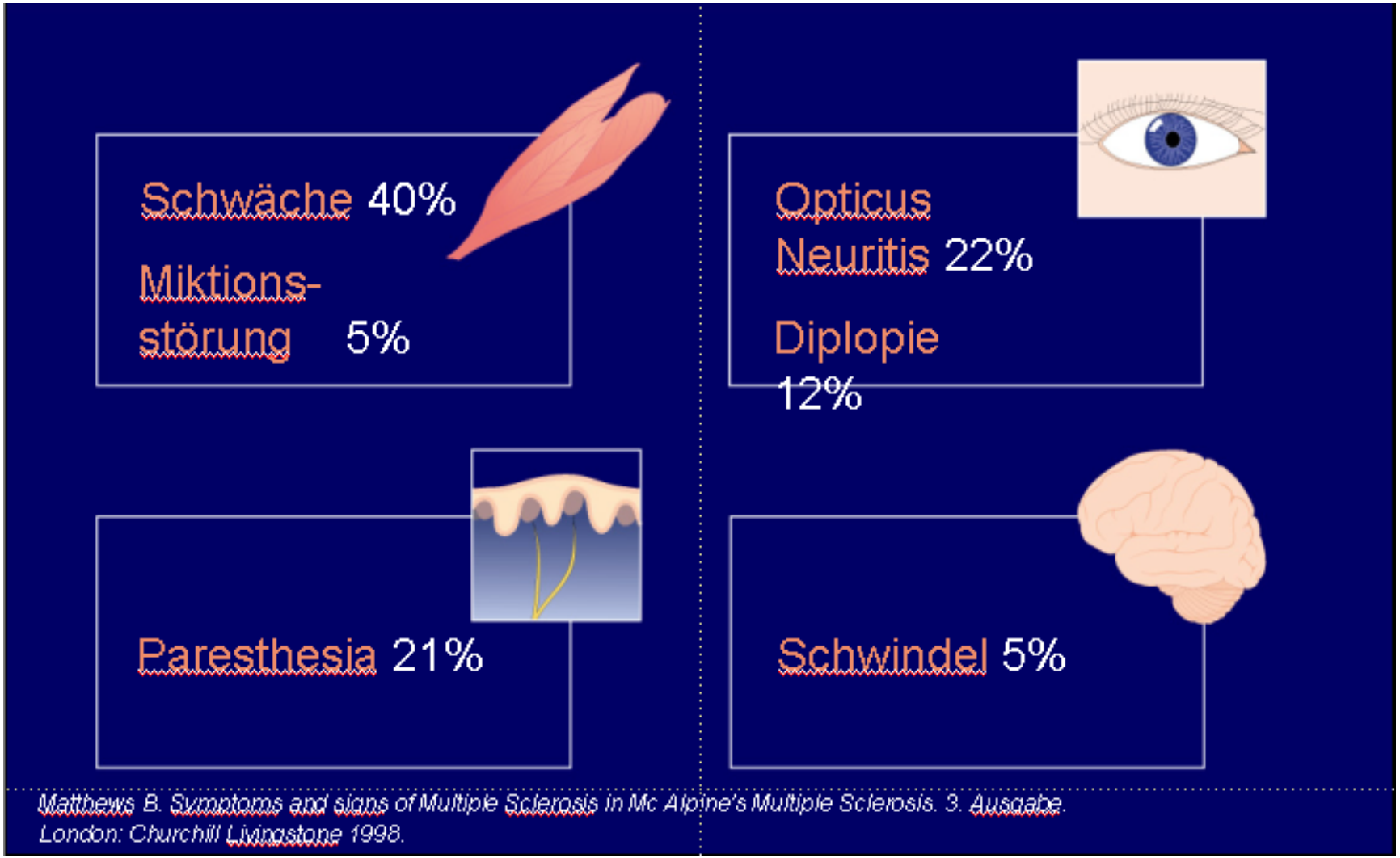
Waxman et al, New Engl. J. Med., 1998


Antigen-presenting cell
Plasma cell
Astrocyte
Pre-existing myelin-reactive T-cells
Peripheral activation
-molecular mimicry?
-superantigens?
-other factors?
MHC
TCR
Antibody
Neuron
Local activation proliferation
T cell
Demyelination
Complement
Oligodendrocyte
Adhesion & penetration
Secondary influx
MHC
Blood vessel
Myelin sheath
Myelin antigens
Cell migration
Soluble mediators, cytokines, chemokines & proteases
Macrophage/ microglia
Axon
Basement membrane

MS - Demography



Common initial Symptoms of MS



Common symptoms in the course of MS

Visual impairment

„Spastic“ gait disorder (Hypertonus of the muscles)

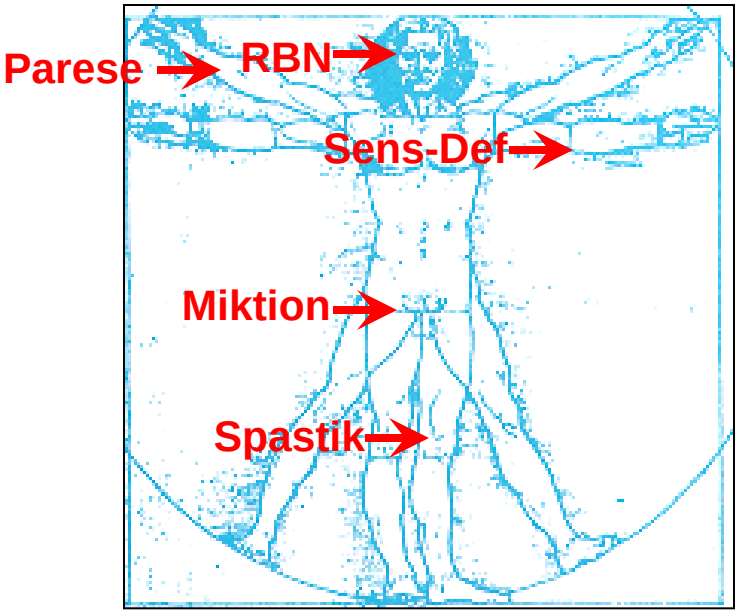
Sensory deficits or disturbances

Ataxie (lack of movement control)

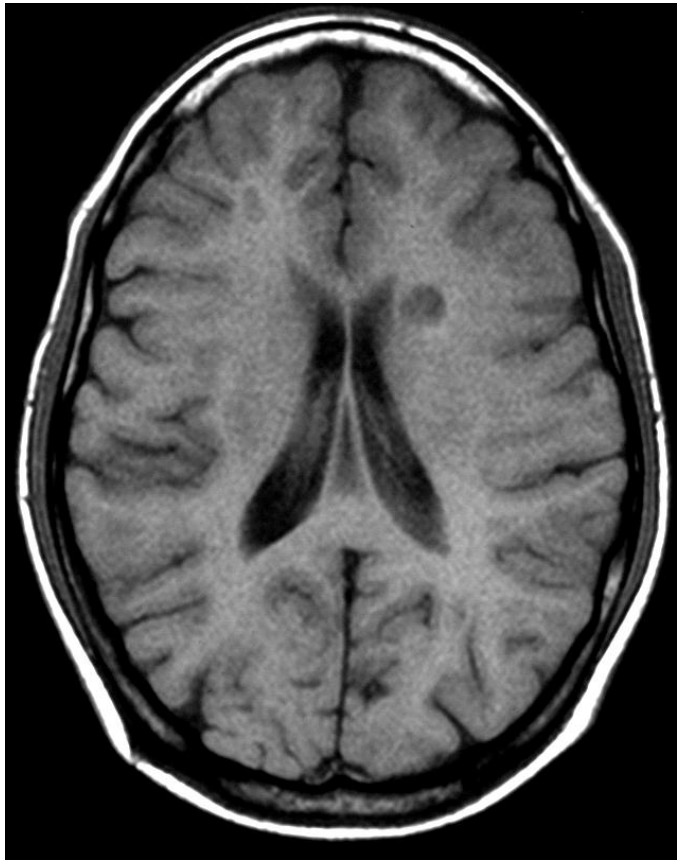
Urinary problems

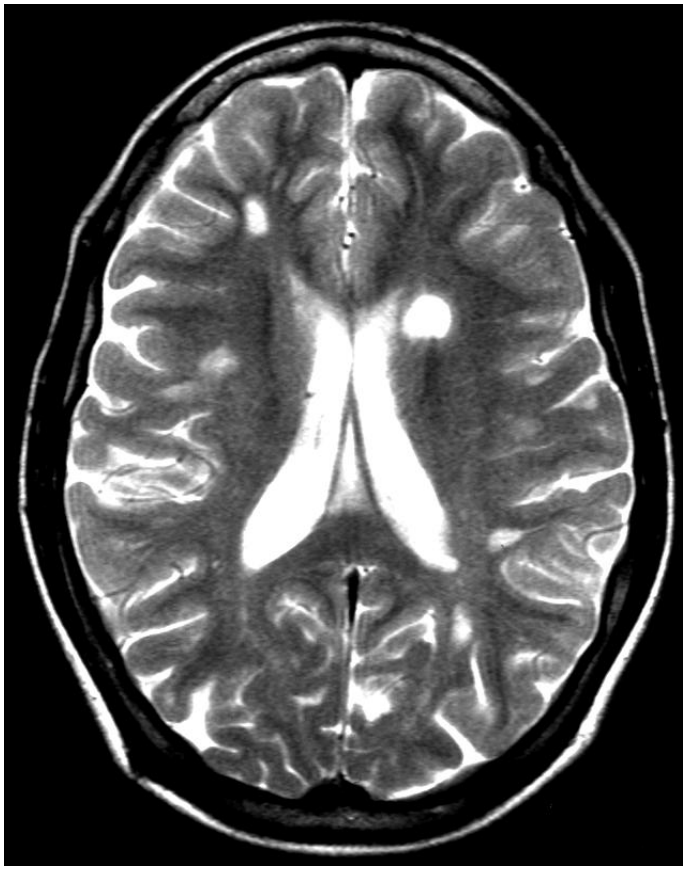
Visual impairment

An optic neuritis is a common presentation symptom of MS.



MS Brain imaging

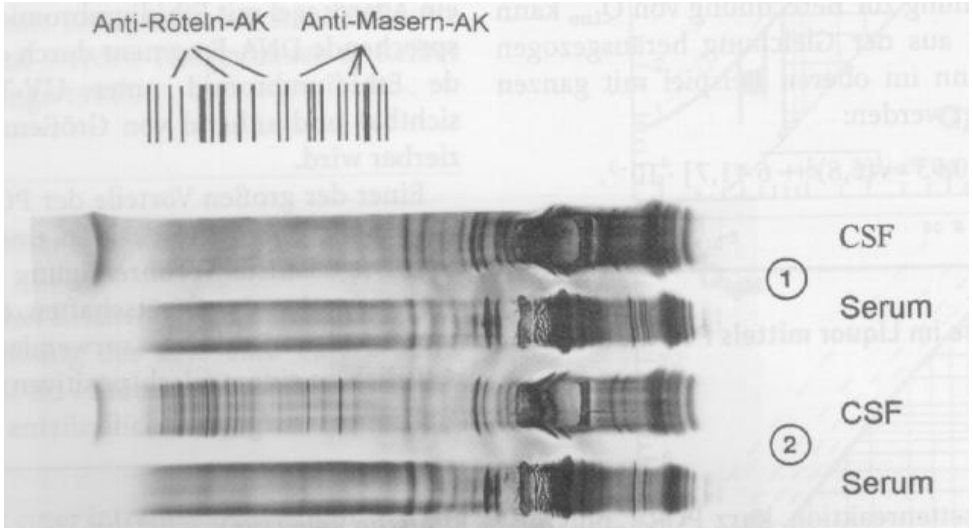


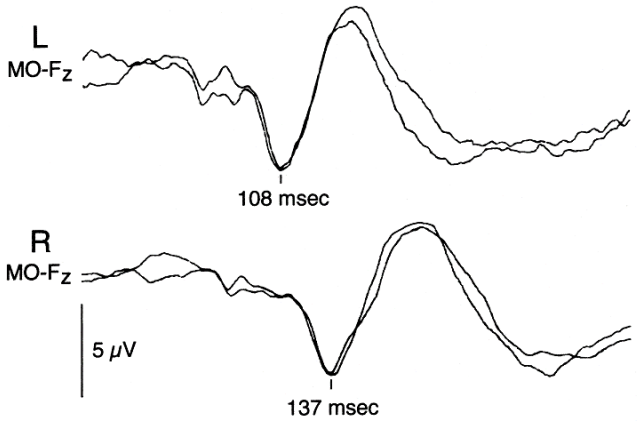


Diagnostic workup:

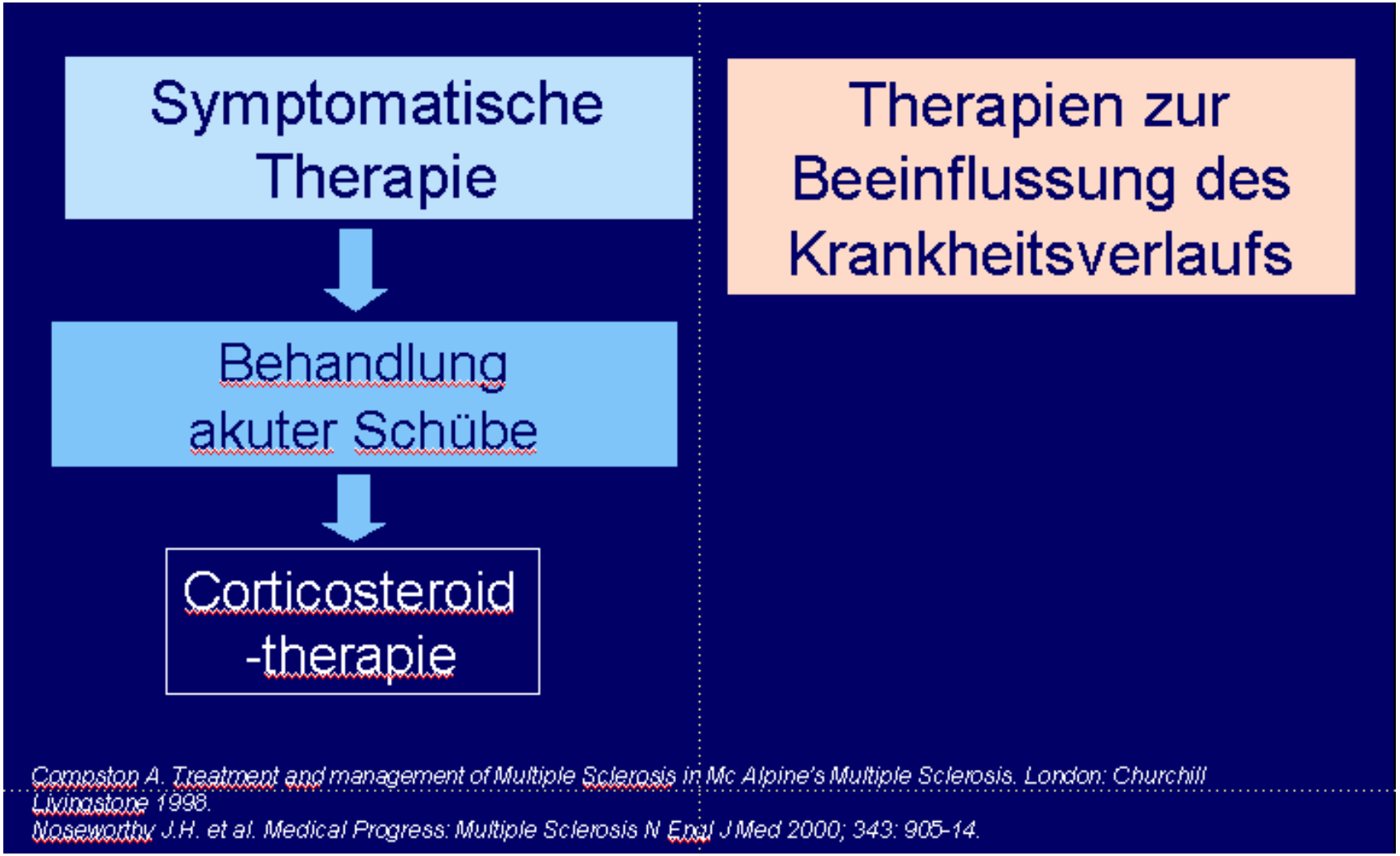
- Typical history – Young patient with subacute symptom onset
- MRI imaging
- Electrophysiological evidence of demyelinisation
- Cerebrospinal fluid analysis (evidence of intrathecal IgG formation)

Exclusion of concurrent diagnoses
(infections, vasculitis, malignancy)





Therapeutic approaches



Compston A. Treatment and management of Multiple Sclerosis in Mc Alpine's Multiple Sclerosis. London: Churchill Livingstone 1998.
Noseworthy J.H. et al. Medical Progress: Multiple Sclerosis N Engl J Med 2000; 343: 905-14.

Immunomodulatory therapy of RRMS

1. Immunomodulatory Therapy with β-Interferons or Glatiramer acetate (licensed)

IFN ß-1b (Betaferon®) 8 Mio. IE (250 µg) s.c. every 2nd day
IFNB Multiple Sclerosis Study Group (1993) Neurology 43: 655-661; Neurology 45: 1277-1285
IFN ß-1a (Avonex®) 6 Mio. IE (30 µg) i.m. 1 x / week
Jacobs et al. (1996) Ann Neurol 39: 285-294
IFN ß-1a (Rebif®) 3 x 6 Mio. IE oder 3 x 12 Mio. IE (22 / 44 µg) s.c. / week
PRISMS Study Group (1998) Lancet 352: 1498-1504
Glatirameracetat (Copaxone®) 20 mg s.c. daily
Comi et al. (2001) Ann Neurol 49: 290-297

2. Azathioprin (licensed since 2000, rarely in use)

3. IVIG (not licensed)

4. Mitoxantron (licensed for progressive RRMS)

5. Cyclophosphamid (not licensed)

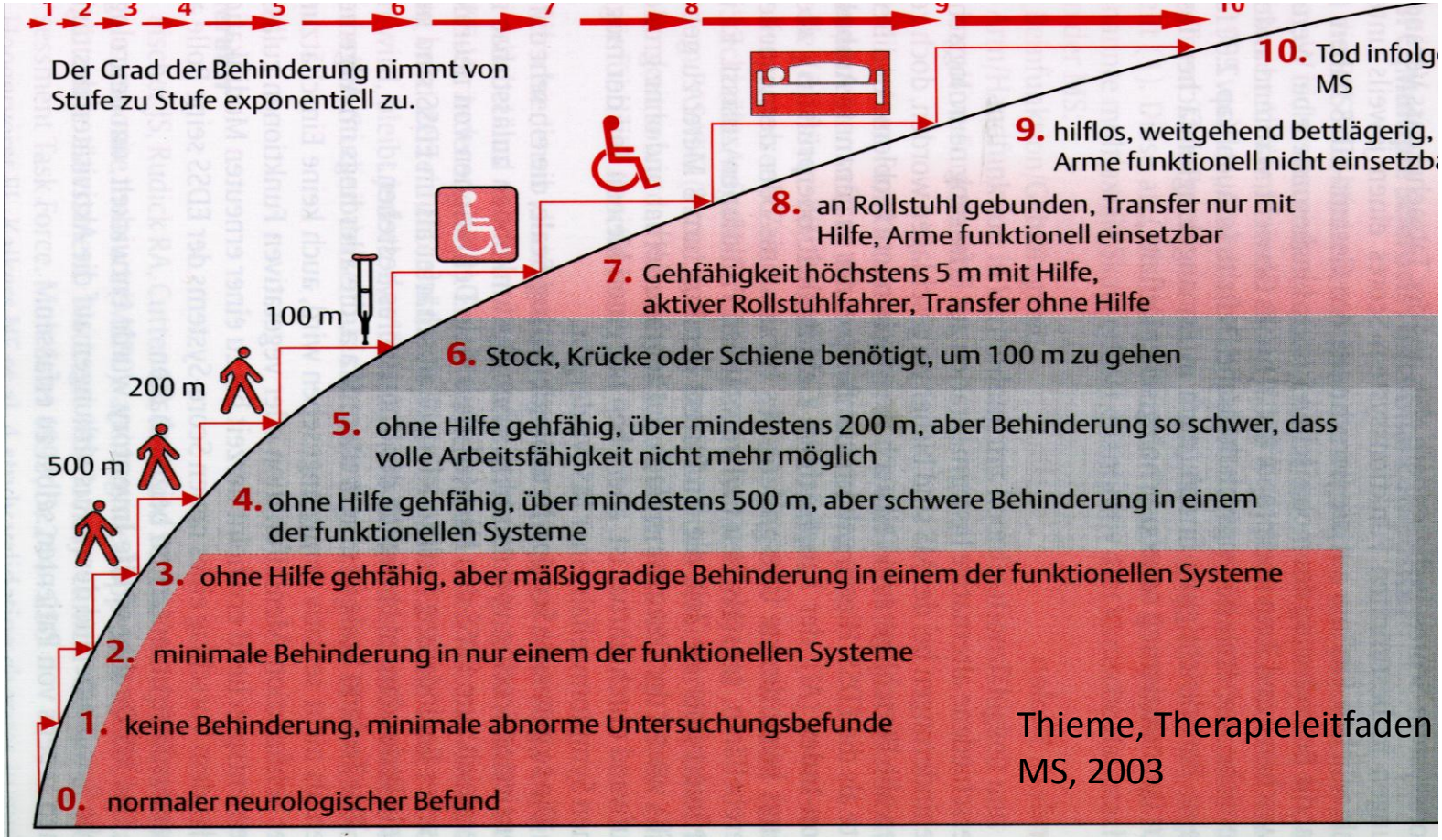
New:
Natalizumab
(Integrin Receptor antagonist)
Fingolimod
(S1P1 Receptor modulator)

When should an immunomodulatory treatment be initiated?

Clinical relapses	Lesions in Brain image	Additional criteria
≥ 2	≥ 2	• none, clinical evidence is sufficient (but additional evidence is desired)
≥ 2	1	• Spatial Dissemination of lesions in brain imaging ***or*** positive csf findings and 2 or more MR-Lesions ***or*** additional relapse
1	≥ 2	• Temporal Dissemination in brain imaging ***or*** second relapse
1 (mono-symptomatic)	1	• Spatial Dissemination of Lesions in brain imaging ***or*** positive csf findings and 2 or more MR-Lesions **AND** • Spatial Dissemination in brain imaging ***or*** second relapse
0 (chronic progression)	1	• Positive csf findings **AND** • Temporal Dissemination of lesions in brain imaging: ≥ 9 cerebral lesions ***or*** ≥ 2 spinal Lesions *oder* 4-8 brain lesions and 1 spinal Lesion ***or*** positive VEP with 4-8 cerebral esions ***or*** positive VEP with < 4 cerebral Lesions and 1 spinal Lesion **AND** • Temporal Dissemination in brain imaging ***or*** continuous Progression > 1 yr

Mc Donald et al Recommended diagnostic criteria for Multiple Sclerosis: Guidelines from the International Panel on the diagnosis of Multiple Sclerosis. Ann Neurol. 2001; 50: 121-127.

Course and prognosis...



Beurteilung des Ausmaßes der Behinderung bei MS (Skala 0-10): Extended Disability Status Scale (EDSS)

Prognosis

- after 25 years, 1/3 of patients is still able to work, and 2/3 of patients are still able to walk

- favourable prognostic factors:
  - initial RBN or sensitive syndrome,
  - female,
  - initially few lesions in MRT,
  - little contrast uptake,
  - remitting relapses, long remissions,
  - responsiveness towards steroids

Current recommendations:

- Steroid treatment of relapses
- Initiation of an immunomodulatory therapy as soon as the diagnosis is established.
- Physiotherapy, adaptation and treatment of complications.

Future Challenges:

- Find new immunomodulatory treatments (better efficacy, specificity: immunomodulation without risk of systemic infections, less side effects, oral route of administration)
- Develop diagnostic markers to predict the individual course of the disease (in order to weigh treatment risks and inconveniences against disease progression).
- Find ways to fight neurodegeneration/boost neuroregeneration in the course of MS.