# ZNS DEGENERATIONEN

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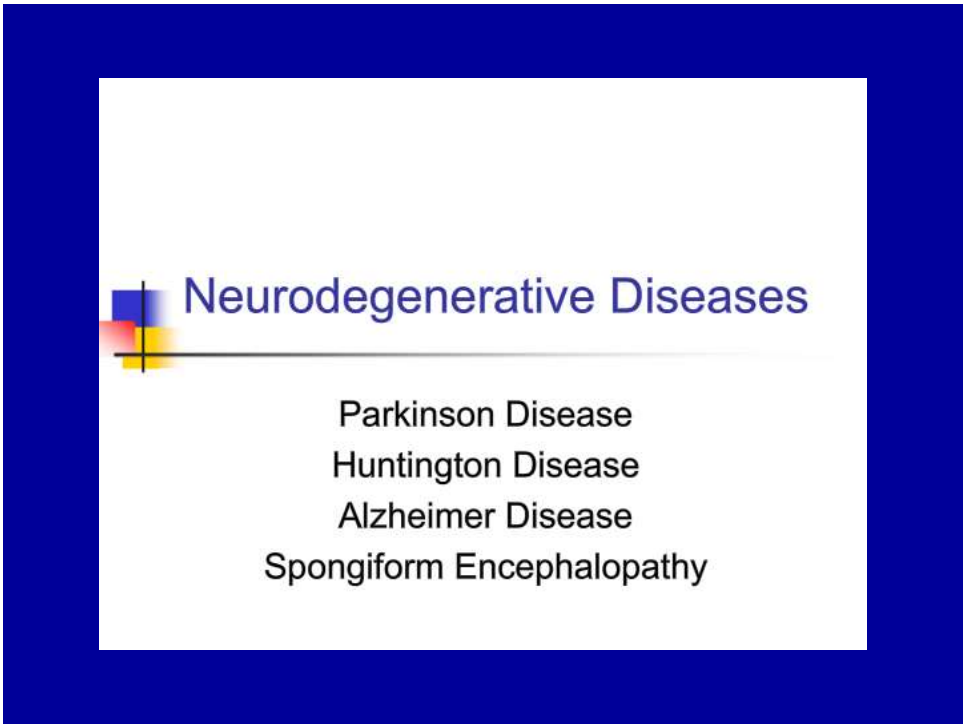
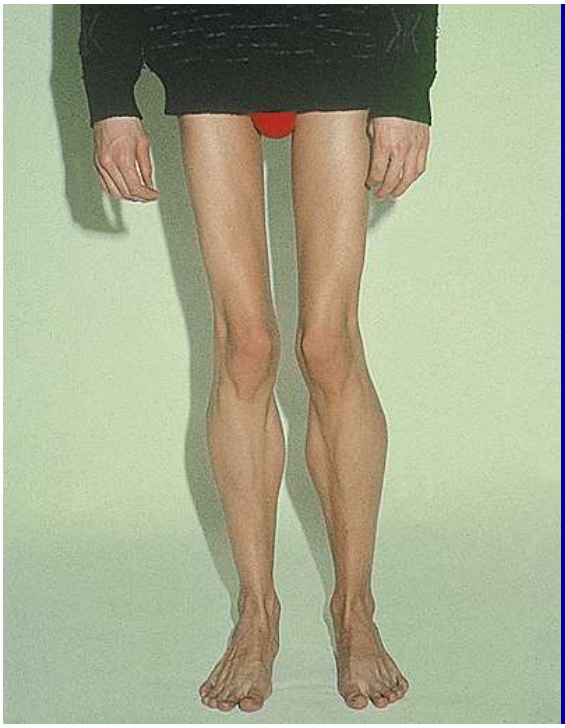
## ZNS DEGENERATIONEN

- Neuronale Degenerationen
- Demyelinisierende Krankheiten




# Neuronale Degeneration

- Krankheit der Neuronen berührt eine oder mehrere funktionelle Systeme (und es kann andere intakt lassen)
- In General, symmetrisch und progressiv
  Allg.: idiopathisch (Aber: Gen Mutationen!)
- Formen: Dementia (Kognitive Funktionen), motorische Funktionen
- Pathomechanismus ?, Anhaufung verschiedener abnormaler cytoskleletaler Proteine die Aggregate formen (Amyloid)

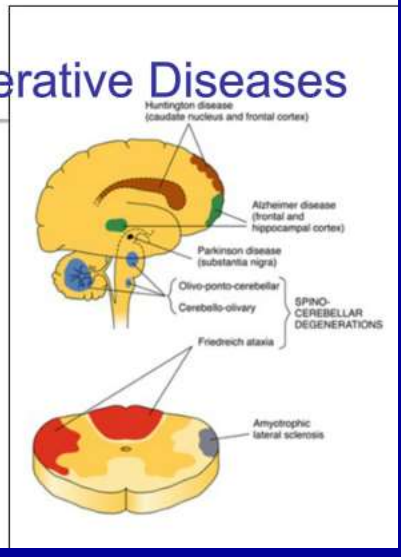


Muskelatrophie: Verminderung der Beckengürtel- und Oberschenkelmuskulatur

# Demenz (Schwachsinn)

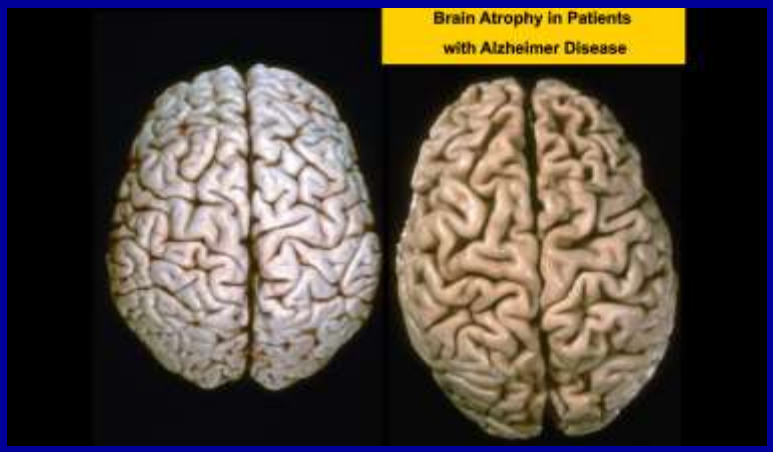
- Erworbener, persistenter Rückgang der intellektuellen Funktionen, hauptsachtlich:
  - Sprache, Memorie, Sehensfahigkeit, Emotion, Personalitat und Kognition (Erkennen)
- Schwergradige Demenz befallt 1-6% der Menschen über 65, milde bis massiger Demenz betrifft etwa 3-15%
- Haufigste Ursache:
  - Alzheimer's Krkht., multi-infarkt Demenz, alkoholische D., metabolische D., Hydrokephalus, Neoplasmen, Huntington's Krkht., usw.

## Neurodegenerative Diseases



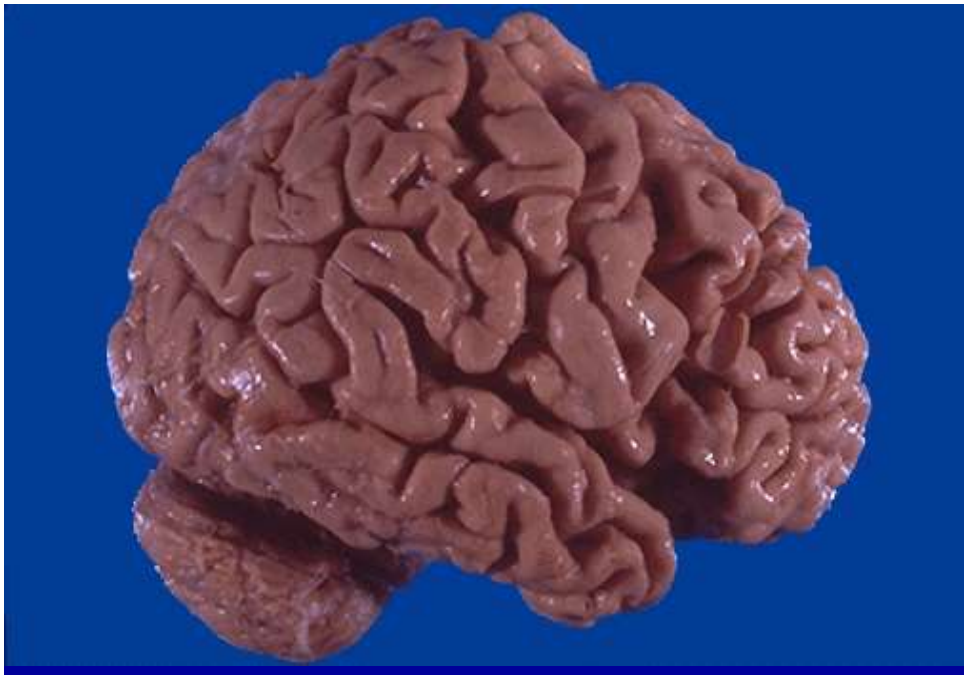

## Neuronale Degenerationen

| Krankheit | Lokalization | Wichtigste Symptomen |
|---|---|---|
| Alzheimer's<br>Pick's | Kortex | Demenz |
| ALS<br>(Amyotrophische Lateralsklerose) | Pyramydal motorisches System | Paralyse |
| Parkinson's Krkht.<br>Huntington's Krkht. | Basale Ganglia | Extrapyramidale Bewegungstörungen |
| Friedreich's | Spinozerebellar | Ataxia |

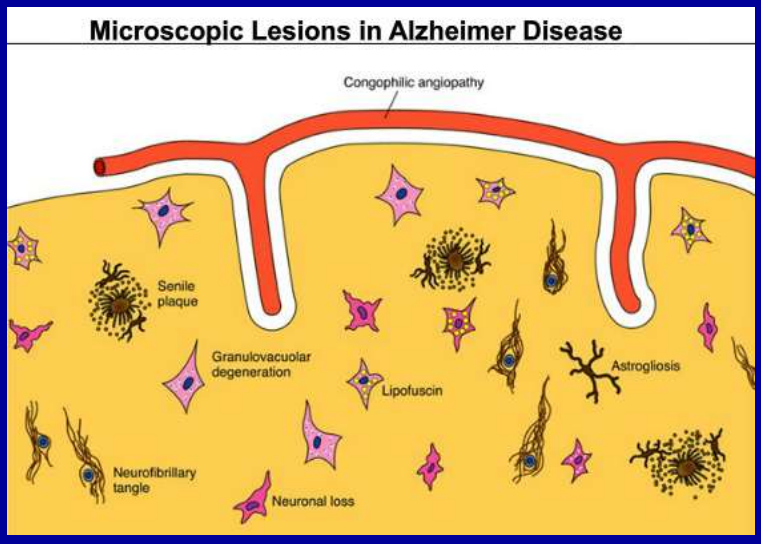



## Alzheimer's Krankheit

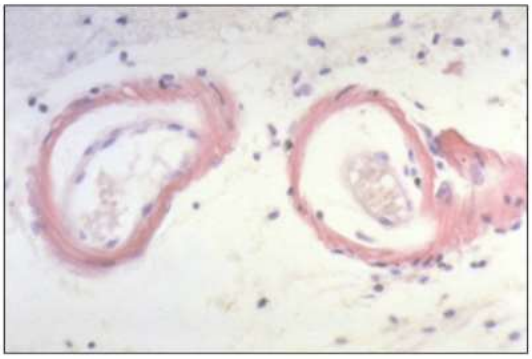
- Temporoparietal, frontotemporal
- Haufigste Demenz (50-75% der demenzierten alten Leuten: nachst haufigste ist Arteriosklerose verusachte Demenz)
- Formen: (1) sporadisch, spat, senile (2) familiar, spat (3) familiar, junge (4) Down-Krankheit (5) mit andere Krankheiten verbunden
- Ursache: ? Genetische Faktoren, Gen Mutationen (AD1,2,3,4)
- Neurochemie: verminderte Acetylcholine in Kortex
- Klinikum: progressive Demenz, Anfang kann schon in 40'Jahren oder 50'Jahren (prasenil): viel haufiger nach 65 (senile)
- Morfologie:
  - Makro: diffuse kortikale Atrophie,, Hydrocephalus ex vacuo,
  - Hist: senile Plaques (Amyloid core, umgearmt von degenerierenden Axon-Terminalen, reaktive Astrozyten), „Neurofibrillary tangles" (tau Proteine), dystrophische Neuriten, verlorene Neuronen



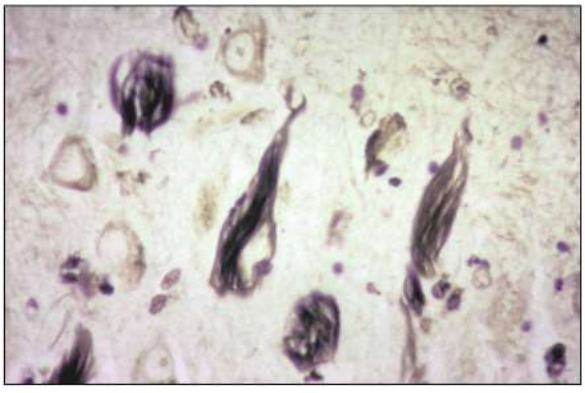
Alzheimer's Atrophie

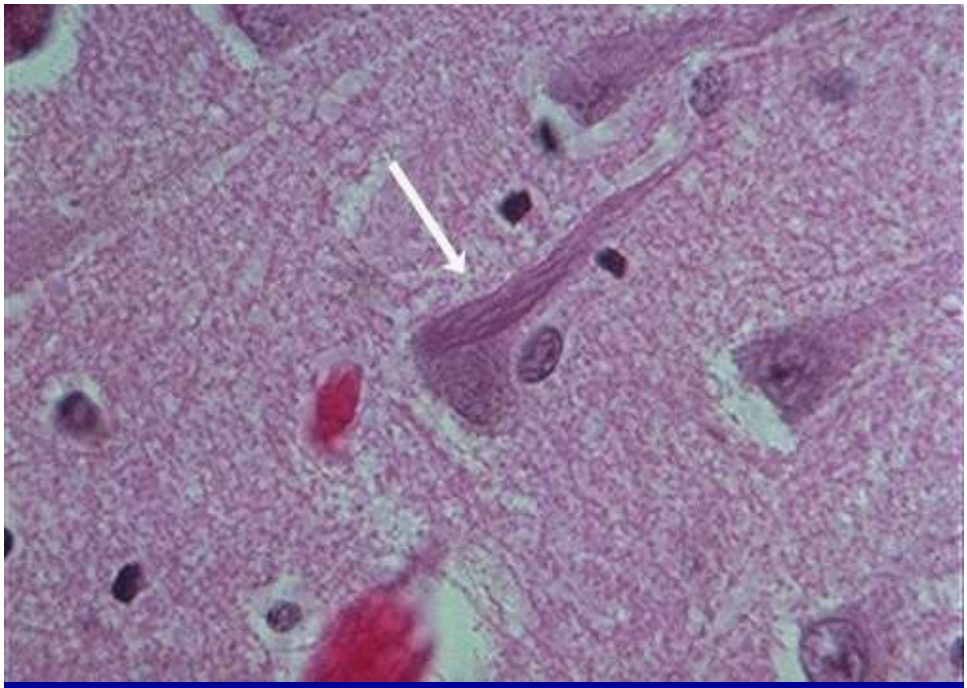


## Amyloid Surrounding Vessels



## Neurofibrillary Tangles in Patients with Alzheimer Disease





Neurofibrillum-Degeneration

# Alzheimer's Krankheit

- Amyloid β Protein – Depositum in der Kortex
- Senile Plaques:
  - core Aβ (abgeleitet von Proteolyse des grösseren prekursor Proteines (APP)
- Depositum ist nötig abet allein ist nicht genügend
- Neurofibrillary tangles (Gewirr) (NFT)
  - Helikale Filamente of abnorme MAP Proteine (microtubule associated protein) genannt tau (abnormale Phosphorilation) – microtubulares Aggregat
- Lewy Körperchen
- Presenilin – Gen assoziiert mit familiarer Alzheimer Krkht.
- Histologie:
  - Senile (neuritische) Plaques (Aβ protein)
  - Neurofibrillare Tangles (NFT)

**TABLE 28-4 Genetic Factors in Alzheimer Disease**

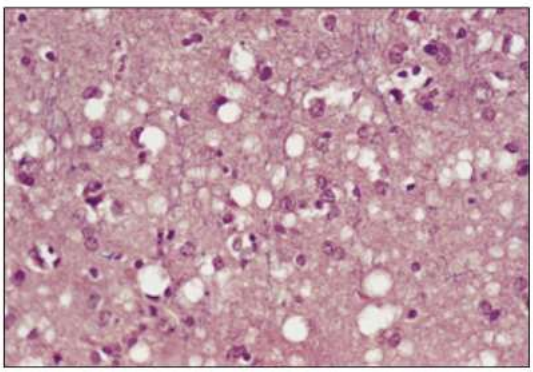
| Gene | Chromosome | Disease Association |
|---|---|---|
| Amyloid precursor protein (*APP*) | 21 | Mutations of the *APP* gene are associated with early-onset familial Alzheimer disease |
| Presenilin 1 (*PS1*) | 14 | Mutations of the *PS1* gene are associated with early-onset familial Alzheimer diseaseAD |
| Presenilin 2 (*PS2*) | 1 | Mutations of the *PS2* gene are associated with Volga German familial Alzheimer diseaseAD |
| Apolipoprotein E (*apoE*) | 19 | Presence of the ε4 allele is associated with increased risk and younger age of onset of both inherited and sporadic forms of late-onset Alzheimer disease |

# Pick-Krankheit – lobare Sklerose

- Frontotemporale (Stirn- und Schäfellappens), lobare Krankht. (selektive Atrophie), umschriebene Hirnatrophie, selektive Atrophie: Messerklinge Atrophie
  (Windungen sind verschmalert, Furchen sind breit !! )
- selten (2-5%), Demenz
- Anfang typisch vor 65 Jahren (prasenil)
- Morphologie:
  - Makro: fronto-temporale kortikale Atrophie
  - Histo: Pick-Körper (aggregierte basophile Neurofilamenten, argyrophile Vakuolen)
  - Klinikum: forrtschreitende Demenz, Persöhnlichkeitsverlust, Enthemmung

Pick-Atrophie

## Spongiform Degeneration in Prion Disease (Mad Cow)



## Amyotrophische Lateralsklerose (ALS)

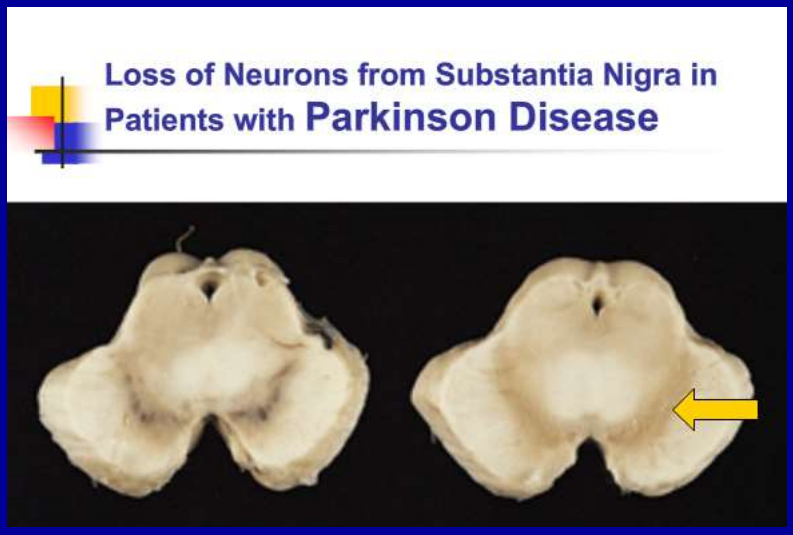
- Degeneration/Verlust der motor Neuronen des Gehirnes und des Rückenmarkes
- Ursache? Familiar (Gen 4 Mutation), sporadisch
- Klinikum:
  - Anfang: 40'-50' Jahre,
  - progressive Schwäche, Paralyse der willkürliche Muskelbewegungen erstmal die Extramitaten dann Respirationsmuskulatur
  - Übere Motor Neuron - erster Motoneuron, Pyramidbahnen (Hyperreflexie, Babinski), unterer Motor-Neuron – Atrophie der motorische Vorderhornzellen (Muskelatrophie, Faszikulationen, Störungen, Hindernisse)
  - Fatal in 2-6 Jahren (Pneumonie)
- Morphologie:
  - Makro: Atrophie der Vorderhornzellen des Rückenmarkes, Motorische Nuklei des Gehirnstammes, Atrophie des Gyrus praecentralis, Atrophie der überen motorischen Neuronen des Kortex
  - Hist: Verschwundene kortikospinale Fasern und Gliose, Abbau, Scwund der Neuuronen in der Nuklei des kranialen Nerven und Vorderhornes
  - Muskeln: gruppierte Atrophie

## Parkinson-Krankheit

- „Paralysis agitans"
- Idiopathisch
- 60 (50-80 Jahre) (Ablauf: 10-15 Jahre)
- Lewy Körperchen

# Krankheiten der Basalen Ganglia – Parkinson Krkht.

- extrapyramidales motorisches System
  - Subkortikales graues Material Strukturen nehmen in motor Regulation teil.
    - Basal Ganglia – Nucleus caudatus, Putamen, Pallidum
    - Substantia nigra
- Klinikum: „ Paralysis agitans"
  - 60 Jahre (50-80), Dauer: 10-15 Jahre
- (a) basale Ggl – subst.nigra- basal Ggl: Rigiditat, Bradykinesie, Akinesie, Mask ähnliches Gesicht
- , Dystonie, resting Tremor, (b) Kortex – basal Ggl-Thalamus-Kortex : Chorea, Athetosis (langsame, schlangelnde Bewegung)
- Parkinson-Krkht. (70-80%), Parkinson Syndrom **(20-30%)**
- Etioloige: idiopathisch (Paralysis agitans), Drogen, usw.
- Morf: Depigmentation der basalen Ganglia (Substantia nigra), Gliosis, Lewy Körperchen (runder, eosinophiler Kern, umfangen bei Halo, α-Synuclein – „α-Synucleinopathie" – Gehirn-spezifische Amyloidose)



## Basale Ganglia Krankheiten Huntington Krkht.

- Huntington-chorea (chorea hereditaria tarda)
  - Autosomal dominant Veerbt, Gen Mutation (HD Gen an Chr. 4., kodiert Huntingtin Protein), amyloid-ahnlich Aggregat von mutierten Proteine
  - 35-45 Jahre, progr. unwillkürliche Bewegungen (choreoathetosis), Demenz
  - Tod in 15 Jahre
  - Makroskopie: Atrophie des N. caudatus, Putamen, des frontalen Kortex
  - Histologie: Atrophie, Verlust der basal Ggl. und des frontalen Kortex

## Spinozerebellare Krankheiten (Ataxie)

- Selten, idiopathisch, spinocerebellar, progressiv
- Unpünktlichkeit der willkürlichen Bewegungen, benötigt mehrere Versüche den gewünschten Endziel zu treffen.
- Friedreich Ataxie
  - genetisch (Triplet's Repeate, Frataxin)
  - Anfang :10-15 Jahren,
  - Rigiditat, , Ataxie, progressive Paralyse, Tod in 15-20 Jahren
  - Assoziierte non-neurologische Befunde: pes cavus, Kyphoskoliose, Kardiomyopathie
- Huntington-chorea (chorea hereditaria tarda)
  - Autosomal, dominant, Gen Mutation
  - 35-45 Jahren, progr. Choreoathetosis, Demenz
  - Tod in 15 Jahren
  - Makro: Atrophie des N.caudatus, Putamen, des frontalen Kortex
  - Histo.: Atrophie, Verlust der basalen Ggl, des frontalen Kortex

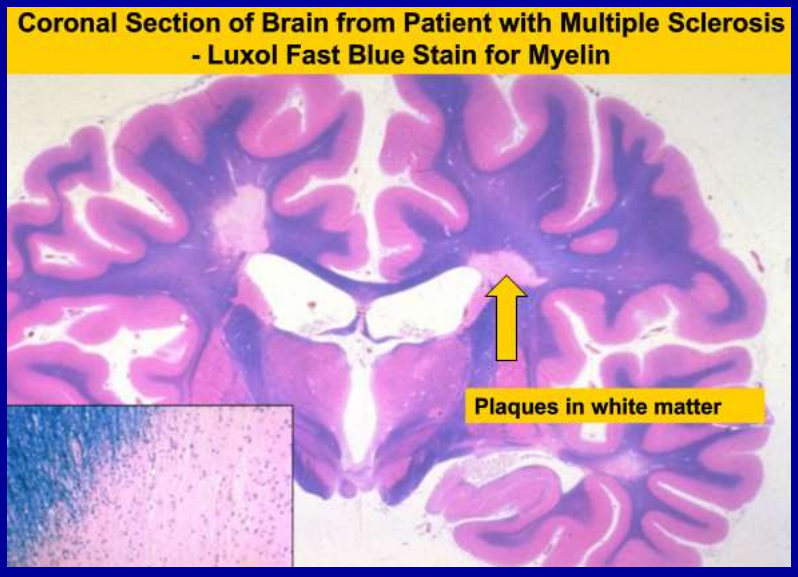
## Demyelinisierende Krankheiten

- Krankheit mit selektivem Verlust der Myelin (der Myelinscheide, der Markscheide)

- Encephalomyelitis disseminata – SM
- Para und postinfektiöse Enzephalomyelitiden
- Paraneoplastische Enzephalomyelitiden

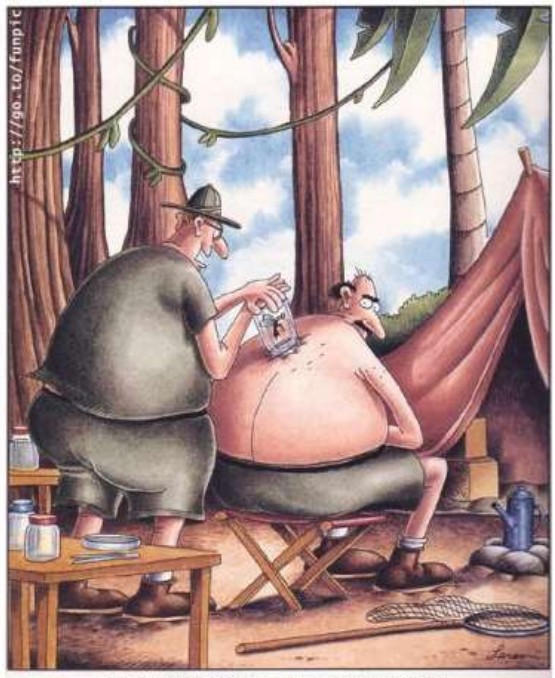
## Demyelinisierende Krankheiten

- Multiple sclerosis (Sclerosis multiplex), Encephalomyelitis disseminata
  - Klinikum: Anfang 20' und 30' Jahren
  - Defizit kann bei einem solitarer Lasion nicht erklart werden. Typisch: visuale Symptome, Schwäche, sensorisches Minus, Exazerbationen und Remissionen
  - Symptomen können mild bleiben oder progredieren (spastische Quadriplegie, Erblindung, Demenz)
  - Ung. jede zweite Patienten leben 25 Jahren nach der Diagnose
  - Makroskopie: graue, harte, opaleszierende Plaques sind breit gestreut in dem weissen und auch in grauen Material.
  - Histologie: Demyelinisierung, verloren gegangene Oligodendroglia Zellen, relativ gehaltene Axonen, reaktive Astrozytose




# Demyelinisierende Krankheiten

- Metachromatiscje Leukodystrophie (MLD)
  - Haufigste, autosomal rez. Krkht. der Myelin Metabolismus
  - Anhaufung der Zerebrosid (Galaktosyl Sulfatid) indem weissen Material und in der periferischen Nerven
  - Juvenile und Erwachsene Formen, lethal innerhalb von einigen Jahren
  - Ursache: Defizienz in der Aktivitat der Arylsulfatase A (lysosomales Enzym), Akkumulation der Sulphatiden in myelin-bildende Schwann Zellen und Oligodendrozyten)
  - Histo.: zytoplasmische Granula, verfarbt sich metachromatisch
- Krabbe Krkht.
  - Rapid, progressiv, fatal, autosomal rezessiv
  - Globoid Zell Leukodystrophie (Galaktocerebroside)
- Adrenoleukodystrophie
  - X-verbundene, vererbte Krankheit
  - Dysfunktion des adrenalen Kortex und Demyelinierung der ZNS, hohe Werte der sehr-lange Kette Fettsauren
- Alexander Krkht.
  - Selten, Neugeborene, Kinder, Mutation
  - Verlust der Myelin, Fasern (Rosenthal Fasern)




"Got him, Byron! It's something in the *Vespula* genus, all right—and coooweeeee does he look mad!"

# KURU

The Nobel Prize in Physiology or Medicine 1976
Baruch S. Blumberg, D. Carleton Gajdusek

# Autobiography

My scientific interests started before my school years, when as a boy of five years I wandered through gardens, fields and woods with my mother's entomologist sister, Tante Irene, as we overturned rocks and sought to find how many different plant and animal species of previously hidden life lay before us. We cut open galls to find the insects responsible for the tumors, and collected strange hardening gumme masses on twigs which hatched indoors to fill the curtains with tiny praying mantises, and discovered wasps with long ovipositors laying their eggs into the larvae of wood-boring beetles. In petri dishes we watched some leaf-eating insects succumb to insecticide poison while others survived, and on exciting excursions visited the laboratories and experimental greenhouses of the Boyce Thompson Institute for Plant Research in my hometown of Yonkers, New York, where my aunt, Irene Dobroscky, worked, studying in the 1920's virus inclusions in the cells of leaf-hoppers.

In my first years at school I had problems with my teachers for carrying to school insect-killing jars, correctly labeled "Poison: potassium cyanide". As a grade schoolboy, I met at the Boyce Thompson Institute laboratories the quiet, amused, watchful and guiding eyes of the mathematician and physical chemist, Dr. William J. Youden, who enjoyed letting me play with his hand crank desk calculator, with his circular or cylindrical slide rules, and with models of crystal lattice structure, and on his laboratory bench where he taught me to prepare colloidal gold solution time color reactions and to manufacture mercuric thiocianate snake-generating tablets. Before I was ten years old I knew that I wanted to be a scientist like my aunt and my quiet mathematician tutor. I rejected completely, as did my younger brother, Robert, who is now a poet and critic, the interests of our father and maternal grandfather in business, which had made our life style possible.

My life and outlook were greatly influenced be the polyglot immigrant Eastern European communities, adjacent and unwillingly interfaced, living in the carpet, elevator and copper wire manufacturing and sugar refining city of Yonkers, just upstream on the Hudson River from the New York megalopolis and possessing a schoolbook history of a Seventeenth Century Royal Dutch land grant of Indian land to Johnig Heer (hence Yonkers) Adrian van der Donck. The confusion in our living room, beside the piano, Romanian and Hungarian gypsies who fiddled the czardas and Nagyatos at our family festivities and camped in the empty store adjacent to my father's butcher shop, an uninterrupted flow of loud conversation in many tongues, rarely English, and kitchen odors of many Habsburg cuisines filling our crowded expanded-family-filled home, gave me an orthodox and optimistic view of America as a land of change and possibility which I never lost. Below our almost rural hilltop home - our family had "risen" - clustered the factories, churches, shops and two to four family houses of immigrant factory workers and tradesmen in the valleys of the almost obliterated Nepperhan and Tackanoe Indian-named creeks. In the hollow stood Hungarian, Slovak and Polish Catholic and Russian Orthodox churches and a Presbyterian mission to the factory workers. (This exciting conglomeration of Eastern Europeans has been later displaced by Mediterranean and Caribbean and, still later, Black Americans, all enclaves "melting".)

My father, Karl Gajdusek, was a Slovak farm boy from a small village near Senica, who had left home at an adventurous [illegible] before World War I, spoke and learned, speaking English, to become a butcher in the immigrant communities of Yonkers, where he met and married my mother, Ottilia Dobroczki. Her parents had also come, each alone, as youthful immigrants from Debrecen, Hungary to America. On my father's side we were a family of farmers and tradesmen, vocations which never interested me brother or myself, but my father's temperament for laughter and stupid fun, lust for life in work and play, music, song, dance and food, and above all, conversation, affected us strongly. On my mother's side were the more somber academic and aesthetic aspirations of four universally educated first generation American siblings and a heroic interest in fantasy and inquiry, in the classics and culture, nature, nurture and process. Because of my mother's unquenchable interest in literature and folklore, my brother and I were reared listening to Homer, Hesiod, Sophocles, Plutarch and Virgil long before we learned to read.

I was born on September 9, 1923 in the family home we still own, while my maternal grandparents and my mother's youngest sister shared the home. My brother arrived nineteen months later. We and I grew up closely together, for every move I made further into mathematics and the sciences, he moved farther into poetry, music and the other arts. In 1930 we traveled to Europe to visit our relatives, mostly those of my father's large family, which he had abandoned twenty years earlier. My brother and I were left for months in my father's birthplace with his old father and the huge remaining family (the square had sired some twenty five children), while our parents toured European capitals.

Back in America, my early school years were those of great happiness. I liked school and the enchanting family excursions up the Hudson valley were frequent. My Tante Irene was working on problems of economic entomology in the Philippines and South East Asia, and exotic artifacts and natural history specimens, particularly the beautiful giant leafhoppers clad in batteline patterns, arrived to fascinate me. On her return from the Orient she took me on ever broader excursions to collect insects, to watch the emergence of the seventeen-year cicadas and to attend scientific meetings in the American Museum of Natural History. I became an early habitué of New York city's museums, attending courses on Egyptology at the Metropolitan Museum of Art on schoolday afternoons after my fifth grade classes and at weekend and evening lectures on entomology, geology and botany at the Museum of Natural History.

Today, I and my large family of adopted sons from New Guinea and Micronesia still occupy, on our frequent visits to New York city, our family home in which I was born fifty-three years ago. Here, the boys recently discovered, while installing new attic insulation, daguerreotypes and tintypes of the family taken in towns east of the Danube and in turn of the century New York city

From him and from Marcel Ballazard of the Institut Pasteur of Teheran, where I worked in 1952 and 1953 on rabies, plague, arbovirus infections, scurvy and other epidemic disease in Iran, Afghanistan and Turkey, I learned of the excitement and challenge offered by urgent opportunistic investigations of epidemiological problems in exotic and isolated populations. My quest for medical problems in primitive population isolates took me to valleys of the Hindu Kush, the jungles of South America, the coast and inland ranges of New Britain, and the swamps and high valleys of Papua New Guinea and Malaysia, but always with a base for quiet contemplation and exciting laboratory studies with John Enders in Boston, Joe Smadel in Washington, and Frank Burnet in Melbourne. To these teachers I am indebted for guidance and inspiration and for years of encouragement and friendship.

To Joe Smadel I also owe the debt of further sponsorship and encouragement, and recognition of my scientific potential for productive research which led him to create for me several years later a then unique position as an American visiting scientist at the National Institutes of Health, in the National Institute of Neurological Diseases and Blindness, under Dr. Richard Masland, wherein I could nurture my diverse interests in a settled Study of Child Growth and Development and Disease Patterns in Primitive Cultures. Our Laboratory of Slow, Latent and Temperate Virus Infections grew out of the elucidation of one of our "disease patterns", kuru, and blossomed into a new field of medicine. For about two decades I have enjoyed at the National Institutes of Health the base and haven for our diverse studies in remote parts of the world together with a small group of students and coworkers and many visiting colleagues who have formed the strong team of our endeavor. Here, Marion Poms, Joe Gibbs, Paul Brown, Vin Zigas, Michael Alpers, David Asher and Nancy Rogers have shared these adventures with me through almost two decades.

My boyhood reading, first in Homer, Virgil, and Plutarch, on which we were nurtured by our Classicist-Romanticist Hungarian mother, led, upon the instigation of my poet brother, to my more thorough return to the classics as a young, too-ardent scientist-cum-physician, and to the modern literature of European authors and philosophers, which I had missed in my university days devoted too exclusively to mathematics and the sciences. This reading changed greatly my way of thinking. Particularly, I would have to credit Dostoevsky, Chekhov and Tolstoy; Montaigne, Baudelaire, Rimbaud, Valery and Gide; Shakespeare, Wordsworth, Yeats and Lawrence; Poe, Whitman and Melville; Ibsen, Goethe, Schiller, Kant, Nietzsche; Kafka and Mann; Saadi and Hafiz.

In 1954 I took off for Australia to work as a visiting investigator with Frank Burnet at the Walter and Eliza Hall Institute of Medical Research in Melbourne from where, between periods of bench work in immunology and virology, I launched studies on child development and disease patterns with Australian aboriginal and New Guinean populations.

In eighteen volumes of some five thousand pages of published personal journals on my explorations and expeditions to primitive cultures, I have told far more about myself and my work since 1957, when I first saw kuru, under the guidance of Vincent Zigas, than one should in a lifetime ... I do not see how I can précis that here.

02 JANUARY 2009

## Kuru pioneer Gajdusek dies at 85

The controversial scientist Carleton Gajdusek, whose research into kuru led to important insights into brain disease, has died in Norway.

When Gajdusek was taken to an Amsterdam hospital two years ago for a check up, the young doctor who examined him identified his long-term congestive heart failure, obesity and diabetes and also concluded he must be psychotic. Asked why, the doctor replied: "He claimed he was a Nobel laureate, that he is one of the world's greatest neuroscientists, has trained many of the best in the world and says he must leave tomorrow to fly to Siberia where a conference is being held in his honour."

It was all true, and so, too, was his imprisonment on a paedophilia charge a decade ago, which overshadowed his pioneering work into a new class of diseases known initially as slow viruses, and his lifelong study of child development in primitive cultures.

Daniel Carleton Gajdusek was born in New York and his experiments and early work on viruses helped lay the foundations of spongy brain infections - or prion diseases - that have latency periods lasting decades.

After working briefly with Sir Macfarlane Burnet at the Walter and Eliza Hall Institute in Melbourne in 1956, Gajdusek was returning to the US by way of PNG when he decided to find out more about a strange disease called *kuru* in the Eastern Highlands. With none of the usual markers of infectious disease, and many siblings dying within families, often years apart, the condition was threatening to wipe out the 12,000 strong Fore tribe.

*Kuru* (Fore for shivering) was thought by the locals to be caused by sorcery and was incurable and untreatable with symptoms including staggering and body tremors. It led to certain death, from what Europeans referred to grimly as 'laughing sickness', within 18 months.

Gajdusek alerted the world to *kuru* in November 1957 and his blatant takeover irked Burnet. A flurry of uncomplimentary correspondence followed.

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Gajdusek alerted the world to *kuru* in November 1957 and his blatant takeover irked Burnet. A flurry of uncomplimentary correspondence followed.

Gajdusek and colleagues proved that *kuru* and related diseases are transmissible. In 1967 his Australian colleague Michael Alpers showed that the Fore's cannibalism - eating dead relatives as a mourning ritual - had spread *kuru* to epidemic proportions. After the practice ceased around 1960 the incidence of *kuru* decreased.

In 1976, Gajdusek was awarded the 1976 Nobel Prize in medicine, which he shared with Baruch Blumberg.

He returned regularly to PNG from where he adopted more than 50 children, educating them in the US where he headed the laboratory for brain studies at the National Institute of Neurological Disorders and Stroke for more than 25 years.

In 1997 he served a year in prison for the sexual abuse of one of his adopted children and lived the rest of his life in exile, splitting his time between Amsterdam, Paris and Norway. In 2007 he attended the 'end of *kuru*' conference - held in Pidgin and English - at the Royal Society in London. It marked the end of the disease - the last autopsy being in 2003.