CONDITION - state of your health

SYMPTOMS - the subject’s (patient's) PERCEPTIONS of their condition.

When seeking medical attention, these are elicited in the patient's own words for the HISTORY OF PRESENT ILLNESS.

SIGNs - medical FINDINGS noted and documented by a qualified observer.

SYNDROME - a group of symptoms and signs that MIGHT NOT ALWAYS HAVE A DEFINED CAUSE;
symptoms & signs may be clustered in a pattern that suggests association as a manifestation of a disease.

DISEASE - usually has a DEFINING CAUSE, presents with DISTINGUISHING SYMPTOMS and treatments exist by which to alter its natural course.
Alzheimer disease (AD) & “Type III Diabetes Mellitus”

Dementia with Lewy Bodies (DLB)

Fronto-temporal Dementia (FTD)

Alcoholic Related Dementia (ARD)

Dementia of Unknown Etiology (DUE) and mixed etiology

What Is Dementia? Symptoms, Types, and Diagnosis

VENTRICLES \equiv Four \text{ CEREBRAL SPINAL FLUID (CSF)-filled spaces:}
LATERAL VENTRICLES (largest) in \textit{cerebrum}
THIRD ventricle is in the diencephalon of the forebrain between the right and left thalamus
FOURTH ventricle at the back of the pons and upper half of medulla oblongata of hindbrain
\textit{Ependymal cells in CHOROID PLEXUS lining ventricles produce Cerebral Spinal Fluid (CSF).}
\textit{CSF is absorbed by ARACHNOID GRANULATIONS after circulating through ventricles}

By BruceBlaus - Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28761845
GLIA CELLS (glia or neuroglia - all NEUROECTODERM DERIVATIVES) ≡ non-neuronal cells in the central nervous system (brain and spinal cord) and peripheral nervous system.
- maintain homeostasis, form myelin, provide support and protection for neurons.

Oligodendrocytes ≡ myelinating cells of the central nervous system (CNS). They are the end product of a cell lineage which has to undergo a complex and precisely timed program of proliferation, migration, differentiation, and myelination to finally produce the insulating sheath of axons. Due to this complex differentiation program & unique metabolism/physiology among the most vulnerable cells of the CNS.

Astrocytes - varied types & the most numerous cell type within central nervous system. TASKS: from axon guidance and synaptic support; control of the blood brain barrier and blood flow; role in maintaining homeostasis at synapse, regulating neuronal signalling; protect neurons from oxidative damage; determining the fate of endogenous neural precursors – also have a role in motor neuron disease.

***MICROGLIA*** (10–15% of all brain cells) ≡ resident macrophage cells, act as the first and main form of active immune defence in the central nervous system (CNS).
DEMENTIA ≡ SYNDROME consisting of a LOSS of several separable but overlapping INTELLECTUAL ABILITIES and presents in a number of different combinations.

CONSTELLATIONS OF INTELLECTUAL DEFICITS constitute the pre-eminent clinical abnormalities and are sometimes virtually the only abnormalities.

What Is Dementia? Symptoms, Types, and Diagnosis
Dementia is a major illness and cause of disability among the elderly.

Categorically, CEREBRO-VASCULAR DISEASE or MULTI-INFARCT DEMENTIA is the second leading cause of dementing illness.

ALZHEIMER’S disease is number 1.

What Is Dementia? Symptoms, Types, and Diagnosis

## DEMENTING DISEASE (most common ETIOLOGIES or CAUSES of DEMENTIA)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEREBRAL ATROPHY, mainly Alzheimer, but including Lewy-body Dementia, Parkinsons, Frontotemporal, and Picks diseases</td>
<td>50 %</td>
</tr>
<tr>
<td>Multi-Infarct Dementia (Vascular Dementia)</td>
<td>10 %</td>
</tr>
<tr>
<td>Alcoholic Dementia (Wernicke-Korsakoff Amnesia Syndrome)</td>
<td>7 %</td>
</tr>
<tr>
<td>Intracranial tumors</td>
<td>5 %</td>
</tr>
<tr>
<td>Normal Pressure HYDROCEPHLUS</td>
<td>5 %</td>
</tr>
<tr>
<td>Huntington Chorea</td>
<td>2 %</td>
</tr>
<tr>
<td>Chronic Drug Intoxications</td>
<td>3 %</td>
</tr>
<tr>
<td>MISCELLANEOUS: hepatic (liver) failure; pernicious anemia (Vit B-12 deficiency); hypo- or hyper-thyroidism; amyloid angiopathy; dementias with Amyothropic Lateral Sclerosis (ALS / Lou Gerig’s Disease), neurosyphilis, Creutzfeldt Jacob Disease; multiple sclerosis; chronic epilepsy</td>
<td>6 %</td>
</tr>
<tr>
<td>Cerebral Trauma</td>
<td>2 %</td>
</tr>
<tr>
<td>AIDS Dementia (can be accelerated by methamphetimine abuse)</td>
<td>2 %</td>
</tr>
<tr>
<td>Pseudodementias: depression; hypomania; schizophrenia; hysteria; undiagnosed</td>
<td>8 %</td>
</tr>
</tbody>
</table>
FRONTOTEMPORAL DEMENTIA (FTD) ≡ clinical syndrome associated with shrinking of the frontal and temporal anterior lobes of the brain. Originally known as Pick’s disease PICK’S DISEASE.

- current designation of the syndrome groups together PICK’S DISEASE PRIMARY PROGRESSIVE APHASIA, and SEMANTIC DEMENTIA

Some authorities propose adding CORTICO-BASILAR DEGENERATION and PROGRESSIVE SUPRANUCLEAR PALSY to FTD and calling the group PICK COMPLEX.

- These designations will continue to be debated.

Frontotemporal Dementia Information Page - What research is being done?
The National Institute of Neurological Disorders and Stroke (NINDS) and other institutes of the National Institutes of Health (NIH) conduct and fund research on FTD.

https://www.ninds.nih.gov/Disorders/All-Disorders/Frontotemporal-Dementia-Information-Page
In symbols one observes an advantage in discovery which is greatest when they express the exact nature of a thing briefly and, as it were, picture it; then indeed the labour of thought is wonderfully diminished.

— Gottfried Wilhelm Leibniz

DEFINITION

NOSOLOGY

1: a classification or list of diseases
2: a branch of medical science that deals with classification of diseases

adjective form = NOSOLOGIC

etymology:
Greek “nosos” = disease + “logy” = study of
FRONTOTEMPORAL DEMENTIA (FTD) ≡ clinical syndrome associated with shrinking of the frontal and temporal anterior lobes of the brain. Originally known as PICK’S DISEASE.

SEMANTIC DEMENTIA
progressive, relatively FOCAL, BRAIN ATROPHY, most prominently affecting the anterior, inferior temporal lobes of the brain.

The principal cognitive consequence of this condition is a deterioration of SEMANTIC MEMORY, or CONCEPTUAL KNOWLEDGE

Frontotemporal Dementia Information Page - What research is being done? The National Institute of Neurological Disorders and Stroke (NINDS) and other institutes of the National Institutes of Health (NIH) conduct and fund research on FTD. https://www.ninds.nih.gov/Disorders/All-Disorders/Frontotemporal-Dementia-Information-Page
Brain MRI of a female 65 y.o. white patient with Pick's disease. Cortex and white matter atrophy of the frontal lobes is clearly visible.

- MRI was done without contrast enhancement utilizing Magnetom Vision 1.5 Tesla with superconductive magnet.
FRONTO-TEMPORAL DEMENTIA (FTD)
by current definitions falls into two clinical patterns that involve either
(1) changes in BEHAVIOUR
can be either impulsive (DISINHIBITED) or bored and listless (APATHETIC)
and includes inappropriate social behaviour; lack of social tact; lack of
empathy; distractibility; loss of insight into the behaviours of oneself and
others; an increased interest in sex; changes in food preferences; agitation
or, conversely, blunted emotions; neglect of personal hygiene; repetitive or
compulsive behaviour, and decreased energy and motivation.

(2) problems with LANGUAGE
primarily features symptoms of LANGUAGE DISTURBANCE, including
difficulty making or understanding speech, often in conjunction with the
behavioural type’s symptoms.
  - Spatial skills and memory remain intact
  - strong genetic component; FTD often runs in families.

The Face of Dementia 
Robert A. Hendrix, M.D. 
Science Circle 
10 – 11:00 AM PDT 
21 September 2019

Frontotemporal Dementia Information Page - What research is being done?
The National Institute of Neurological Disorders and Stroke (NINDS) and other institutes of the National
Institutes of Health (NIH) conduct and fund research on FTD.

https://www.ninds.nih.gov/Disorders/All-Disorders/Frontotemporal-Dementia-Information-Page
LEWY BODY DEMENTIA (LBD) ≡ disease associated with abnormal deposits in clusters of a protein called alpha-synuclein in the brain.

These deposits, called Lewy bodies, disrupt chemical processes in the brain whose changes, in turn, can lead to problems with thinking, movement, behaviour, and mood.

LBD affects about 1.3 million Americans - (0.4% prevalence)
LEWY BODY DEMENTIA (LBD) - Photomicrograph of regions of SUBSTANTIA NIGRA of midbrain in a PARKINSON’S patient showing LEWY BODIES and LEWY NEURITES in various magnifications.

**Legend:**

*top panels (60x): alpha synuclein*
Intra-neuronal inclusions aggregated to form Lewy bodies.

*bottom panels (20×): strand-like Lewy neurites and rounded Lewy bodies of various sizes.

Neuromelanin laden cells of the substantia nigra are visible in the background

Stains used:
mouse monoclonal alpha-synuclein antibody
Counter-stained with Mayer's haematoxylin.

---

File:Substantia nigra with Lewy body pathology.svg 12.May 2012
Suraj Rajan [CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0)]
https://commons.wikimedia.org/wiki/File:Substantia_nigra_with_Lewy_body_pathology.svg
**SNCA gene** provides instructions for making a small protein called **alpha-synuclein**. Abundant in the brain, found mainly at the tips of nerve cells (neurons) in specialized structures called presynaptic terminals.

- Smaller amounts are found in heart, muscle, and other tissues.

Studies ⇒ important role maintaining an adequate supply of pre-synaptic vesicles in **presynaptic terminals**.

It may also help regulate the release of dopamine, a neurotransmitter that is critical for controlling the start and stop of voluntary and involuntary movements.

May also play a role in the movement of structures called **microtubules** that help cells maintain their shape.

Cytogenetic Location in Homo sapiens: 4q22.1, which is the long (q) arm of Chromosome 4 at position 22.1

---

**SNCA gene** - synuclein alpha

Alcohol Related Dementia (ARD)  
‘alcohol-related brain damage’ (ARBD)  
‘alcohol-related brain injury’  
‘alcoholic amnesia syndrome’  
Wernicke-Korsakoff (or Korsakoff) Syndrome

1 & 2 below are SALIENT FEATURES that are always conjoined:

1) RETROGRADE AMNESIA - Impaired ability to recall events and other information that had been firmly established before the onset of the illness.  
   - Ribot’s law can be observed:  
     like Union workers in factories, 1st memories are last to go.

1) ANTEROGRADE AMNESIA – impaired ability to acquire new information - i.e., to learn or to form new memories.

   This duality inspired the WHITE QUEEN character of Lewis Carroll to quip:  
   „It’s a poor sort of memory that works only backwards.“

PRINCIPLE: FUNCTIONS OF MEMORY & LEARNING ARE INSEPARABLE
   - derangement of these can occur in isolation of other impairment of mentation and behaviour.
Alcohol Related Dementia (ARD)  ‘alcohol-related brain damage’ (ARBD)
‘alcohol-related brain injury’
‘alcoholic amnesia syndrome’
Wernicke-Korsakoff (or Korsakoff) Syndrome

1 & 2 below are SALIENT FEATURES that are always conjoined:

1) RETROGRADE AMNESIA - Impaired ability to recall events and other information that had been firmly established before the onset of the illness.

- Ribot’s law can be observed: like Union workers in factories, LAST IN, FIRST OUT!
  1st memories are last to go.

2) ANTEROGRADE AMNESIA – impaired ability to acquire new information
  - i.e., to learn or to form new memories.

3) impaired temporal localization of past experience.
Alcohol Related Dementia (ARD)

‘alcohol-related brain damage’ (ARBD)
‘alcohol-related brain injury’
‘alcoholic amnesia syndrome’
Wernicke-Korsakoff (or Korsakoff) Syndrome

1) RETROGRADE AMNESIA
2) ANTEROGRADE AMNESIA
3) impaired temporal localization of past experience

„IT’S ALL THE SAME DAY, MAN!
It’s all the same day...“
- Janis Joplin (1943 – 1970)
Rock Megastar
<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>Sources</th>
<th>Symptom of DEFICIENCY affecting NERVOUS SYSTEM</th>
<th>SPECIFIC RISK FACTORS FOR DEFICIENCY</th>
<th>RDA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 THIAMINE pyrophosphate</td>
<td>Whole grains, Brown rice, Green leafy veggies, Soy beans, nuts, peas, eggs, or kill mammals and eat their livers</td>
<td>BERI-BERI incl peripheral neuropathy &amp; weakness. Wernicke-Korsakoff Syndrome = neurodegeneration within medial thalamus MEDIAL THALAMUS and CEREBELLUM; ataxia, abnormal motor function &amp; eye movement, AMNESIA, APATHY, CONFABULATION</td>
<td>Alcohol Abuse, Obesity, Severe malnutrition, IF YOU DON’T B1, YOU’LL BE STUMBLING AND NUMB with risk of dying of heart failure!</td>
<td>1.2</td>
</tr>
<tr>
<td>VITAMIN</td>
<td>Sources</td>
<td>Symptom of DEFICIENCY affecting NERVOUS SYSTEM</td>
<td>SPECIFIC RISK FACTORS FOR DEFICIENCY</td>
<td>RDA (mg)</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>B2 riboflavin</td>
<td>Flavoproteins: flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) (redox reactions)</td>
<td>Fatigue, personality change, brain dysfunction</td>
<td>inherited riboflavin malabsorption and utilisation (10%–15% prevalence)</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Dairy, leafy VEGGIES, legumes / beans, yeast, mushrooms, or kill and eat sentient creatures and eat their livers or kidneys</td>
<td>More generally: Weakness, oral pain/tenderness, burning or itching of the eyes, dermatitis, Anaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>Sources</th>
<th>Symptom of DEFICIENCY affecting NERVOUS SYSTEM</th>
<th>SPECIFIC RISK FACTORS FOR DEFICIENCY</th>
<th>RDA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3 NIACIN</td>
<td>nicotinic acid (pyridine-3-carboxylic acid), nicotinamide (niacinamide or pyridine-3-carboxamide), and related derivatives, such as nicotinamide riboside</td>
<td>Depression, anxiety, progressing to vertigo, memory loss, paranoia, psychotic symptoms, aggression (Pellagrous insanity)</td>
<td>Alcohol abuse</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Whole grains / cereals, legumes / beans, mushrooms, nuts, or kill and eat sentient creatures including mammals and fish</td>
<td>generally, Pellagra entails: dermatitis/photo dermatitis, alopecia, muscle weakness, twitching burning in the extremities, altered gait, diarrhoea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VITAMIN Sources</th>
<th>Symptom of DEFICIENCY affecting NERVOUS SYSTEM</th>
<th>SPECIFIC RISK FACTORS FOR DEFICIENCY</th>
<th>RDA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B5 PANTHOTHENIC ACID Co-enzyme A (CoA) (acyl activation and transfer)</td>
<td>Encephalopathy, behaviour change, Demyelination</td>
<td>starvation</td>
<td>5</td>
</tr>
<tr>
<td>Whole grains / cereals, broccoli, or kill and eat sentient mammals</td>
<td>Numbness or burning sensations in extremities, dermatitis, diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VITAMIN Sources</td>
<td>Symptom of DEFICIENCY affecting NERVOUS SYSTEM</td>
<td>SPECIFIC RISK FACTORS FOR DEFICIENCY</td>
<td>RDA (mg)</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>B6 pyridoxine</td>
<td>Irritability, impaired alertness, depression, cognitive decline, dementia, autonomic dysfunction, convulsions</td>
<td>Alcohol abuse, age-related malabsorption, contraceptive medications</td>
<td>1.2</td>
</tr>
<tr>
<td>Legumes / beans, nuts, bananas, potatoes, Or kill sentient animals to eat meat &amp; fish</td>
<td>More generally: Anaemia</td>
<td>NOTE: neuropathy at intakes of 1000 mg per day or more, which is about 800 times the daily intake from foods. There have also been occasional reports of toxicity at intakes of 100-300 mg per day.</td>
<td></td>
</tr>
</tbody>
</table>
### Vitamin B7: Biotin

**Sources**
- Eggs, liver, leafy VEGGIES or pork

**Symptom of Deficiency Affecting Nervous System**
- Depression, lethargy, hallucinations, seizures
- Generally: Seborrheic eczematous rash, tingling and/or burning of the extremities

**Specific Risk Factors for Deficiency**
- Type II diabetes, poor gluco-regulation

**RDA (µg)**
- 30 µg

---

**Some creatures were born as pigs. For humans, it's a choice.**

- Robert Hendrix

---

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review

<table>
<thead>
<tr>
<th>VITAMIN Sources</th>
<th>Symptom of DEFICIENCY affecting NERVOUS SYSTEM</th>
<th>SPECIFIC RISK FACTORS FOR DEFICIENCY</th>
<th>RDA (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B9 FOLIC ACID Tetrahydrofolates including methyltetrahydrofolate</td>
<td>Affective disorders, behaviour changes, psychosis, cognitive impairment/decline, dementia including Alzheimer’s disease and vascular dementia</td>
<td>Common genetic polymorphisms including MTHFR C667T Low Riboflavin and B12</td>
<td>400 µg</td>
</tr>
</tbody>
</table>
### Vitamin Sources

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Sources</th>
<th>Symptom of Deficiency Affecting Nervous System</th>
<th>Specific Risk Factors for Deficiency</th>
<th>RDA (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12 Cobalamins</td>
<td>Methylcobalamin, Adenosylcobalamin</td>
<td>Affective disorders, behaviour changes, psychosis, cognitive impairment/decline, dementia including Alzheimer’s disease and vascular dementia</td>
<td>age-related malabsorption, vegetarians, vegans, genetic polymorphisms</td>
<td>2.4 µg</td>
</tr>
<tr>
<td></td>
<td>Eggs, dairy, fortified cereal, nutritional yeast, nori (seaweed), shiitake mushroom, or you can kill and eat sentient animal victims like meat &amp; fish</td>
<td>Generally: megaloblastic anaemia, peripheral neuropathy, spinal cord lesions, metabolic abnormalities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pyridoxine (vitamin B6) neurotoxicity: enhancement by protein-deficient diet.


<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>TOXICITY affecting NERVOUS SYSTEM</th>
<th>TOP LIMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6 pyridoxine</td>
<td>a well-known cause of primary sensory, length-dependent, axonal polyneuropathy.</td>
<td>&lt;&lt; 100 mg</td>
</tr>
<tr>
<td>Legumes / beans, nuts, bananas, potatoes, or kill sentient animals including meat &amp; fish</td>
<td>Large doses of pyridoxine cause injury to primary sensory neurons in trigeminal and dorsal root ganglia of animals and patients subjected to megavitamin therapy. Increased hazard with reduced renal excretory function.</td>
<td>Max usu 35</td>
</tr>
<tr>
<td></td>
<td>Neuropathy at intakes of 1000 mg per day or more, which is about 800 times the daily intake from foods. There have also been occasional reports of toxicity at intakes of 100-300 mg per day.</td>
<td></td>
</tr>
</tbody>
</table>
EIGHT B-COMPLEX VITAMINS

<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>Caveat</th>
<th>TOP LIMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3 NIACIN</td>
<td>EXCESSIVE DOSAGES CAN DAMAGE HEPATOCYTES (Liver cells). This hepatotoxicity may be manifested by JAUNDICE. In rare cases, the liver damage can be fatal or require a liver transplant</td>
<td>35</td>
</tr>
</tbody>
</table>

“Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioural abilities to such an extent that it interferes with a person's daily life and activities.”

Dysfunction reflecting deviation from expected, human neurological norms;

Some cannot control their emotions, and their personalities may change.

Dementia ranges in severity
- from the mildest stage, when it is just beginning to affect a person's functioning,
- to the most severe stage, when the person must depend completely on others for basic activities of living.”

What Is Dementia? Symptoms, Types, and Diagnosis

Dementia - loss of cognitive function
- thinking
  - language skills
  - problem solving
  - visual perception
- problem solving
- memory & remembering
- reasoning
- behavioural abilities
  - self-management
- ability to focus and pay attention

What Is Dementia? Symptoms, Types, and Diagnosis
MMSE: Mini-Mental State Exam
a.k.a., the Folstein test

- 30-point questionnaire
- used extensively in clinical and research settings to measure cognitive impairment

- commonly used in medicine and allied health to screen for dementia.

NCBI: The National Center for Biotechnology Information is part of the United States National Library of Medicine, a branch of the National Institutes of Health

**MMSE: Mini-Mental State Exam**

_**assessment must take into account:**_
- Illiteracy or low education
- Not fluent in English
- Handicaps and disabilities (e.g., poor vision or hearing)
- Paralysis / physical impairment
- Depression / possible Depression
- Aphasia / dysphagia
- Parkinsonism or neurological impairment
- Coma

---

Mini-Mental State Exam (MMSE)  Tech- Administered

Hanns Hippius, MD, Psychiatrische Klinik der LMU, Munich:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181715/
A FUN READ!!!
On November 3, 1906, a clinical psychiatrist and neuroanatomist, Alois Alzheimer of Frankfurt Psychiatric Hospital, reported

“A peculiar severe disease process of the cerebral cortex”

to the 37th Meeting of South-West German Psychiatrists in Tubingen, He described a 50-year-old woman whom he had followed from her admission for paranoia, progressive sleep and memory disturbance, aggression, and confusion, until her death 5 years later.

His report noted *distinctive plaques and neurofibrillary tangles* in the brain histology. It excited little interest...

Hanns Hippius, MD, Psychiatrische Klinik der LMU, Munich:


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181715/

A FUN READ!!!
In 1906, Dr. Alois Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness: symptoms included:
   memory loss,
   language problems
   unpredictable behaviour.

PLAQUES & TANGLES on autopsy with microscopic exam:
   abnormal clumps (beta-amyloid plaques)
   tangled bundles of fibers (NFT):
      (neurofibrillary, or tau-tangles)

Another feature = LOSS OF SYNAPTIC CONNECTIONS between nerve cells (neurons) in the brain with eventual cell death (& atrophy = loss of brain volume)
original 1984 clinical criteria for Alzheimer's disease required the presence of a dementia syndrome and were based exclusively on clinical symptoms: **MEMORY LOSS** was the first and only major symptom.

According to a literal interpretation of these 1984 criteria, people free of dementia did not have Alzheimer's disease.

In 1984, Alzheimer’s Disease was a diagnosis confirmed by autopsy...most often still is...

Now we have BIOMARKERS...**watch this space**!


Z.S. Khachaturian / Alzheimer’s & Dementia 7 (2011) 253–256
In 2011, clinical diagnostic criteria for Alzheimer’s disease dementia were REVISED, and research guidelines for earlier stages of the disease were characterized to reflect a deeper understanding of the disorder.

*Development of the new guidelines was led by the National Institutes of Health and the Alzheimer’s Association.*

Alzheimer’s disease progresses on a spectrum with *three stages*
- early, preclinical stage with NO symptoms;
- middle stage of mild cognitive impairment;
- final stage marked by symptoms of dementia.

The 1984 criteria addressed only one stage of Alzheimer’s disease—the final stage of dementia.

MEMORY LOSS was the 1st and only major symptom in the 1984 criteria for Alzheimer’s dementia.

The 2011 criteria recognized that other aspects of cognition, such as word-finding ability or judgment, may become impaired first.

---

Alzheimer’s disease progresses on a spectrum with three stages
- early, preclinical stage with NO symptoms;
- middle stage of mild cognitive impairment;
- final stage marked by symptoms of dementia.

**OTHER FEATURES OF 2011 CRITERIA**
- distinctions and associations between Alzheimer’s and non-Alzheimer’s dementias, as well as between Alzheimer’s and disorders that may influence its development, such as vascular disease.

- noted potential for diagnostic use of **BIOMARKERS** as indicators of underlying brain disease.

However, the guidelines state that biomarkers are almost exclusively to be used in **RESEARCH** rather than in a clinical setting.

Summary - updated diagnostic guidelines describe three stages of AD

**Preclinical**—Brain changes, including amyloid / tau build-up and other nerve cell changes, may already be in progress, but significant clinical symptoms are not yet evident.

**Mild cognitive impairment (MCI)**—A stage marked by symptoms of memory and/or other thinking problems that are greater than normal for a person’s age and education, but that do not interfere with his or her independence.

- People with MCI may or may not progress to Alzheimer’s dementia.

**Alzheimer’s dementia** —The final stage of the disease in which symptoms of Alzheimer’s, such as memory loss, word-finding difficulties, and visual/spatial problems, are significant enough to impair a person’s ability to function independently.

role of genetic testing in the revised guidelines?  

A rare type of familial Alzheimer’s disease, called Early-Onset Alzheimer’s Disease (EOAD) caused by mutations in the amyloid precursor protein, presenilin 1, or presenilin 2 genes.

A person who inherits any of these mutations from a parent will almost surely develop Alzheimer’s dementia before age 65.

Genetic testing for the disease is common in families with a history of EOAD.

The major genetic risk factor for the more common, sporadic form of the disease, or Late-Onset Alzheimer’s disease (LOAD), is the ε4 allele of the APOE gene. NOTE: carrying this allele by itself does not mean a person has or will develop Alzheimer’s dementia,

- genetic testing for APOE ε4 is NOT recommended outside of a research setting.

IMAGING TECHNIQUES

Computerized Tomography (CT SCAN) with or without iodinated contrast

Magnetic Resonance Imaging (MRI SCAN) with or without Gadolinium-ligand (coordination dative bonding)

Functional MRI scanning (f-MRI)

NUCLEAR MEDICINE IMAGING TECHNIQUES

- Positron Emission Tomography (PET scan)

- SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)
**IMAGING TECHNIQUES**

**Computerized Tomography** (CT SCAN) with or without Iodinated contrast

1979 Nobel Prize in Physiology or Medicine was awarded jointly to Allan M. Cormack and Godfrey N. Hounsfield

"for the development of computer assisted tomography."

**Magnetic Resonance Imaging** (MRI SCAN) with or without Gadolinium-ligand (coordination dative bonding)

First reported in 1971 by Raymond Damadian who achieved the 1st first whole-body MR images in 1977-78.

2003 Nobel Prize in Physiology or Medicine went to competing scientists: Paul Christian Lauterbur and Peter Mansfield for developmental work making Magnetic Resonance Imaging possible, ignoring Damadian.

1952 **Nobel Prize** in physics was awarded two American scientists: Felix Bloch and Edward M. Purcell, for their work in development of **Nuclear magnetic resonance (NMR)** in 1945

Paul Dreizen - The Nobel prize for MRI: a wonderful discovery and a sad controversy

Published: January 03, 2004DOI: [https://doi.org/10.1016/S0140-6736(03)15182-3](https://doi.org/10.1016/S0140-6736(03)15182-3)
Functional MRI scanning (f-MRI) is a methodology for detecting dynamic patterns of activity in the working human brain.

- **Blood oxygenation level dependent (BOLD) effect**
- To detect changes in brain activity.

Biophysical basis in magnetic properties of deoxyhemoglobin,

Physiological basis
- In the way blood flow increases more than oxygen metabolism when local neural activity increases.

Discovered in 1990 by Seiji Ogawa

Richard B. Buxton
The physics of functional magnetic resonance imaging (fMRI)

NUCLEAR MEDICINE IMAGING TECHNIQUES using radioactive tracers (radiopharmaceuticals) to assess bodily functions and to diagnose and treat disease

Positron Emission Tomography (PET scan) an imaging technology in which substances containing positron-emitting isotopes are introduced into the body, allowing the precise location of physiological processes by detection of the gamma rays produced by the isotopes.

- can be used with CT scan (e.g., PET-CT) or even MRI imaging to better define anatomical relationships

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) gamma camera detectors that can detect the gamma ray emissions from the tracers that have been (usually) injected into the patient.

Nuclear Medicine - National Institute of Biomedical Imaging and Bioengineering
NUCLEAR MEDICINE IMAGING TECHNIQUES

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

gamma camera detectors that can detect the gamma ray emissions from the tracers that have been (usually) injected into the patient.

This simulated image shows how an inexpensive adapter for a SPECT camera could provide higher resolution images of the part of the brain affected in Parkinson’s disease.
PET or single-photon emission computed tomography (SPECT)?

PET has many advantages sensitivity by approximately two to three order of magnitude over that of SPECT

Also PET imaging allows one to obtain quantitative 2D and 3D biochemical and physiological information through the use of positron emitting radioelements such as $^{11}\text{C}$, $^{13}\text{N}$, $^{15}\text{O}$, and $^{18}\text{F}$

Each have relative low molecular weights and can label molecules of interest with little or no change in biological activity from their non-labeled counterparts.

Radiosyntheses using Fluorine-18: the Art and Science of Late Stage Fluorination

Erin L. Cole, Megan N. Stewart, Ryan Littich, Raphael Hoareau, Peter J.H. Scott

PET radionuclides decay by **positron emission**
- in the case of fluorine-18, it decays to oxygen-18 releasing a **neutrino** ($\nu$) and a **positron** ($\beta^+$).

Each positron then travels through surrounding tissue up to 1 mm, where it can encounter its antiparticle, the electron ($e^-$), thus causing an **ANNIHILATION EVENT**.

The event produces **two gamma ray photons** ($\gamma$) of 511 keV each, which progress away from the annihilation at 180° in opposite directions.

Detectors are set in rings that encircle the patient can identify the photon pair simultaneously in a coincidence event and allow determination of location of the radiopharmaceutical.

---

Radiosyntheses using Fluorine-18: the Art and Science of Late Stage Fluorination

Erin L. Cole, Megan N. Stewart, Ryan Littich, Raphael Hoareau, Peter J.H. Scott

PET imaging detector.

Positron emission followed by an annihilation event and detection of photons.

Radiosyntheses using Fluorine-18: the Art and Science of Late Stage Fluorination
Erin L. Cole, Megan N. Stewart, Ryan Littich, Raphael Hoareau, Peter J.H. Scott
MAKING TRACERS FOR IMAGING BY POSITRON (\(\beta^+\)) EMISSION TOMOGRAPHY (PET SCAN)

OXYGEN, \(Z = 8\) Standard atomic weight = 15.999

naturally occurring (stable) isotopes:
- \(^{18}\text{O}\) abundance \(\approx 0.2\\%\) 10 neutrons with isotope mass = 17.9991610 u
- \(^{17}\text{O}\) abundance \(\approx 0.04\%\) 9 neutrons with isotope mass = 17.9991610 u
- \(^{16}\text{O}\) abundance \(\approx 99.76\%\) 8 neutrons with isotope mass = 17.9991610 u

FLUORINE produced is in the form of a water solution of \([^{18}\text{F}]\)fluoride, which is then used in a rapid chemical synthesis of radiopharmaceutical.

The organic oxygen-\(^{18}\) pharmaceutical molecule is not made before the production of the radiopharmaceutical, as high energy protons destroy such molecules.

Radiosyntheses using Fluorine-18: the Art and Science of Late Stage Fluorination
Erin L. Cole, Megan N. Stewart, Ryan Littich, Raphael Hoareau, Peter J.H. Scott

POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

The Acetylcholine Neurotransmitter idea

Pathological Neurofibrillary Tangles of beta amyloid & tau polypeptides

gum disease – herpes infection

INFLAMMATION
microglia weakening TREM2 mutation

Updates to Diagnostic Guidelines for Alzheimer's Disease
Roy Yaari, MD, MAS,  Adam S. Fleisher, MD, MAS, and Pierre N. Tariot, MD

*Prim Care Companion CNS Disord*. 2011; 13(5): PCC.11f01262
POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

The “Cholinergic theory”

- Cholinergic neurons located in the basal forebrain, including the neurons that form the nucleus basalis of Meynert, are SEVERELY LOST in Alzheimer’s disease (AD) –

⇒ treatment of AD with drugs that act on the cholinergic system...
   (e.g., acetylcholine esterase inhibitors to slow degradation or depletion of acetylcholine neurotransmitter at the synapse)

   did NOT pan out

------------------------------------------------------------------------------------------------------------------------

Alzheimer's Disease: Targeting the Cholinergic System
Talita H. Ferreira-Vieira, Isabella M. Guimaraes, et. al.
POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

Beta-amyloid is a degradation product of a larger protein called “amyloid precursor protein” (APP)

Amyloid precursor protein (APP) = integral membrane protein expressed in many tissues & concentrated in synapses of neurons.

Its primary function is NOT KNOWN, though it has been implicated as a regulator of synapse formation and neural plasticity

AD ⇒ progressive neuronal dysfunction, reactive gliosis, and the deposition of amyloid-β (Aβ) plaques in the brain
⇒ synaptic dysfunction is a critical element in the pathogenesis of AD

amyloid plaques (Aβ) & neurofibrillary tangles (NFT) = pathological HALLMARK

Synapse Formation and Function Is Modulated by the Amyloid Precursor Protein
Christina Priller, Thomas Bauer, Gerda Mitteregger, Bjarne Krebs, Hans A. Kretzschmar and Jochen Herms: Journal of Neuroscience 5 July 2006, 26 (27) 7212-7221

https://www.jneurosci.org/content/26/27/7212
Histopathogic image: SENILE PLAQUES seen in cerebral cortex in a patient with Alzheimer disease of PRE-SENILE ONSET. Silver impregnation

Feingeweblicher Schnitt mit Alzheimer-typischen senilen Plaques, Versilberung

Very high magnification micrograph of brain, showing normal white matter and normal grey matter. HPS stain.  Brain biopsy.

File:Grey matter and white matter - very high mag.jpg
https://commons.wikimedia.org/wiki/File:Grey_matter_and_white_matter_-_very_high_mag.jpg
Neurofibrillary tangles in the Hippocampus of an old person with Alzheimer-related pathology.

Alzheimer-Fibrille in der HE-Färbung

Neurofibrillary tangles in the Hippocampus of an old person with Alzheimer-related pathology.

Alzheimer-Fibrillen in der Versilberung (Gallyas)  
Von Patho - Eigenes Werk, CC BY-SA 3.0,  
https://commons.wikimedia.org/w/index.php?curid=20016547
POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

Beta-amyloid (Aβ)
- family of polypeptides with 37 to 49 amino acids (esp. 40 & 42) –
- degradation product of a larger protein
  “amyloid precursor protein” (APP)

APP is delivered to the surface membrane in which it is subjected to proteolytic processing by α-secretase.

APP molecules that fail to be cleaved by α-secretase can be internalized into endocytic compartments and subsequently cleaved by β-secretase and γ-secretase to generate beta-Amyloid (Aβ).

- A fraction of Aβ peptides is also generated in the Golgi apparatus and, to a lesser extent, the endoplasmic reticulum.

- Aβ peptides generated in the Golgi and in recycling compartments are secreted into the extracellular space

Synapse Formation and Function Is Modulated by the Amyloid Precursor Protein
Christina Priller, Thomas Bauer, Gerda Mitteregger, Bjarne Krebs, Hans A. Kretzschmar and Jochen Herms: Journal of Neuroscience 5 July 2006, 26 (27) 7212-7221

https://www.jneurosci.org/content/26/27/7212
THERE IS VERY ACTIVE RESEARCH ON NEW PET LIGANDS for BETA AMYLOID: ⇒ more specific and more sensitive

∃ Three FDA-approved PET ligands on the market for detecting Aβ by brain imaging,
- flurbetapir  flurbetaben  flutemetamol - but arguably with shortcomings
  - bind non-specifically to white matter
  - they are blind to diffuse plaques, which may occur earlier in the disease than the dense-core variety.

All use the $^{18}$F radioisotope

POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

“**Tau** represents the subunit protein of one of the major hallmarks of Alzheimer disease (AD), the neurofibrillar tangles, and is therefore of major interest as an indicator of disease mechanisms.”

tau ⊂ MICROTUBULE-ASSOCIATED PROTEINS (MAPs)

Tau = stabilizer of tubulin in microtubules (tubulin-binding protein)
- natively unfolded protein (hydrophilic)
  - large number of structural conformations and biochemical modifications (phosphorylation, proteolysis, glycosylation, etc.)
  - varied interaction with other biomolecules & structures (e.g., microtubules)
- high solubility
- aggregation of Tau is toxic in cell and animal models, but can be reversed by suppressing expression or by aggregation inhibitors
- POTENTIAL diagnostic marker and therapeutic target


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3385935/
POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

τ ∈ MICROTUBULE-ASSOCIATED PROTEINS (MAPs) - Marc Kirschner 1975

- Tau has 6 isoforms – NFT do not appear to be pure
- Human Tau is encoded on chromosome 17q21
- 40 mutations have been discovered that might cause TAUOPATHY = Fibrillar aggregates of tau characteristic hallmarks of several neurodegenerative diseases

THEORY IN A NUT SHELL

- various kinases activated (by oxidative stress?)
- ⇒ HYPERPHOSPHORYLATION of the MAP, tau protein IN AXONS
  - ⇒ grouping in aggregations, in an insoluble form.
    - these aggregations of tau are called PAIRED HELICAL FILAMENTS (PHF)
  - ⇒ Neurofibrillary tangles are formed
    - ⇒ MICROTUBULE STABILIZATION BY TAU AFFEKTED
      ⇒ MICROTUBULE DYSFUNCTION
    - ⇒ IMPAIRED DELIVERY SYSTEMS & METABOLISM ⇒ CELL DEATH


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882247/
\textbf{18F-flortaucipir} has shown early promise as a marker of tau pathology in AD.

**Tau PET Imaging Using 18F-AV-1451**

Tau is a protein that accumulates abnormally in the brains of people with Alzheimer's disease and other neurodegenerative disorders.

National Institute of Aging announcement recruiting patients (80 enrolled so far) for study of Tau PET Imaging using $^{18}$F-flortaucipir (formerly $^{18}$F-AV1451 or $^{18}$F-T807) in identifying tau tangles in positron emission tomography (PET) scans.

Study location is Washington University in St. Louis, Missouri, USA

-----------------------------------------------

Tau PET Imaging Using 18F-AV-1451
Tau PET Imaging using 18F-flortaucipir (formerly 18F-AV1451 or 18F-T807)

NOTE: pyridine 1 N; recall ∃ 1,2- or 1,4-diAZINE & Pyrimidine = 1,3 diAZINE

Pyrrole is a heterocyclic aromatic organic compound, a five-membered ring with the formula C₄H₄NH.

← Indole is an aromatic heterocyclic organic compound with formula C₈H₇N. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered pyrrole ring.

Carbazole (right) is an aromatic heterocyclic organic compound. It has a tricyclic structure, consisting of two six-membered benzene rings fused on either side of a five-membered nitrogen-containing ring – one step more complex than a hydrocarbon FLUORENE (13 C: 6 fused 5 fused 6) from coal tar.

------------------------------------------------------------------------------------------------------------------------

Tau PET Imaging Using 18F-AV-1451

POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

Cholinergic Theory
degenerative processes leading to
    Neurofibrillary Tangles of beta amyloid & tau

Other ideas:
gum disease
herpes infection
INFLAMMATION
    predisposed by microglia weakening TREM2 mutation

DISRUPTION OF INSULIN SIGNALING IN THE BRAIN ***
POSSIBLE CAUSES OF ALZHEIMER’S DISEASE (AD)

Diabetes Mellitus
and the notion of Type III DM

Below is a reference about this idea:

Suzanne M. de la Monte, M.D., M.P.H. and Jack R. Wands, M.D.
Alzheimer's Disease Is Type 3 Diabetes—Evidence Reviewed
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769828/
Traditionally, the view on INSULIN was fairly limited to:

1. **Insulin facilitates entry of glucose into muscle, adipose and several other tissues**

2. **Insulin stimulates the liver to store glucose in the form of glycogen**

3. **A well-known effect of insulin is to decrease the concentration of glucose in blood**

Nowadays:

the **BRAIN** is recognized as an **INSULIN-SENSITIVE ORGAN** that is responsible for physiologic changes in altered metabolic disorders such as obesity and type 2 diabetes

- **EXCELLENT ARTICLE – RECOMMENDED READING**

  Seung-Hwan Lee, Janice M. Zabolotny, Hu Huang, Hyon Lee, Young-Bum Kim

  [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021669/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021669/)
HISTORY OF INSULIN IN MEDICAL SCIENCE

In mid 19th century, a link between PANCREAS PATHOLOGY & DIABETES MELLITUS was suspected based on autopsies:
Pancreas damage <=> Diabetic Patient

In 1869 during his studies for his doctorate at the Berlin Pathological Institute, 22-year-old Paul Langerhans (1847-1888) discovered two systems of cells in the pancreas:

ACINAR cells – secreted pancreatic juice with enzymes such as Trypsin into the duodenum

very vascular “ISLETS of LANGERHANS” clumps of cells of unknown function dispersed among the acini in the tail of the pancreas.

Nicolas Paulescu Diabetes and Metabolic Disease Paul R. Earl Facultad de Ciencias Biológicas Universidad Autónoma de Nuevo León San Nicolás, NL 66450,
Published by Lynette Morris
HISTORY OF INSULIN IN MEDICAL SCIENCE
CELL TYPES OF ISLETS OF LANGERHANS

α-cells (glucagon)
β-cells (insulin)
Δ-cells (somatostatin)
ε-cells (grehlin „hunger hormone“)
PP-cells (a.k.a., f-cells or γ-cells
(pancreatic polypeptide)

self regulates pancreatic endocrine & exocrine function
**HISTORY OF INSULIN IN MEDICAL SCIENCE**

**CELL TYPES OF ISLETS OF LANGERHANS**

- α-cells (glucagon)
- β-cells (insulin)
- Δ-cells (somatostatin)
- ε-cells (grehlin „hunger hormone“)
- PP- (f-, γ-)cells (pancreatic polypeptide)

Endogenous ghrelin in islets restrict glucose-induced insulin release via the following mechanism:

ghrelin directly acts on the β-cell Growth Hormone (GH) secretagogue receptor... attenuates glucose-induced \([\text{Ca}^{2+}]_i\) signalling partly through enhancement delayed outward \(K^+\) currents. This insulinostatic action of ghrelin of islet origin, possibly together with that of circulating ghrelin, UPWARDLY controls blood glucose levels. This function of ghrelin in regulating glucose metabolism, together with inducing GH release and feeding, suggests that ghrelin underlies the integrative regulation of energy homeostasis.

Endogenous Ghrelin in Pancreatic Islets Restricts Insulin Release by Attenuating \(\text{Ca}^{2+}\) Signaling in β-Cells;

PORTION OF ISLET GREATLY MAGNIFIED (X 1200); GOMORI'S ALDEHYDE FUCHSIN AND PONCEAU STAIN

(BNOTE: DELTA CELLS ARE NOT DIFFERENTIATED BY THIS STAIN)
The Nobel Prize committee in 1923 credited the practical extraction of insulin to a team at the University of Toronto and awarded the Nobel Prize to two men: Frederick Banting and J.J.R. Macleod.

They were awarded the Nobel Prize in Physiology or Medicine in 1923 for the discovery of insulin.

Banting, incensed that Best was not mentioned, shared his prize with him, and Macleod immediately shared his with James Collip. The patent for insulin was sold to the University of Toronto for one dollar.
HISTORY OF INSULIN IN MEDICAL SCIENCE

Figure 10. License 6254. Pancreine

Nicolas Paulescu Diabetes and Metabolic Disease Paul R. Earl Facultad de Ciencias Biológicas Universidad Autónoma de Nuevo León San Nicolás, NL 66450,

Published by Lynette Morris
HISTORY OF INSULIN IN MEDICAL SCIENCE

British Biological Chemist DOROTHY MARY CROWFOOT HODGKIN, OM FRS HonFRSC
b. May 12, 1910 in Cairo, Egypt – d. July 29, 1994, Ilmington, UK
determined the three-dimensional structure of insulin
by the X-ray crystallographic method (1969), thus making a
fundamental contribution to our understanding
of the hormone’s chemical and biological properties.
Her achievements rested on extraordinary experimental
skills in X-ray crystallography and a genius for applying
and developing its methods.

She also solved the physical structures of
cholesterol (1937)
penicillin (on VE Day in 1945)
vitamin B12 (1954)
- which she cracked with the help of Alan Turing’s PilotACE Computer,

Accomplishments for which she was awarded the Nobel Prize 1964

This post was written by Rachel Boon, Content Developer for
Churchill’s Scientists, a 2015 exhibition at the Science Museum
Exhibition Road, South Kensington, London SW7 2DD

https://www.diapedia.org/introduction-to-diabetes-mellitus/1104105146/dorothy-hodgkin#targetText=Dorothy%20Hodgkin%20was%20one%20of%0Ahormone's%20chemical%20and%20biological%20properties.
HISTORY OF INSULIN IN MEDICAL SCIENCE

British Biological Chemist DOROTHY MARY CROWFOOT HODGKIN, OM FRS HonFRSC
b. May 12, 1910 in Cairo, Egypt – d. July 29, 1994, Ilmington, UK

Molecular model of 3-dimensional structure of penicillin by Dorothy Hodgkin, c.1945.
Image credit:
- Science Museum / SSPL

This post was written by Rachel Boon, Content Developer for Churchill’s Scientists, a 2015 exhibition at the Science Museum
Exhibition Road, South Kensington, London SW7 2DD

https://www.diapedia.org/introduction-to-diabetes-mellitus/1104105146/dorothy-hodgkin#targetText=Dorothy%20Hodgkin%20was%20one%20of,hormone's%20chemical%20and%20biological%20properties.
British molecular biologist Frederick Sanger (13 August 1918 – 19 November 2013) determined the primary structure of insulin in 1955, making it the first protein to be sequenced. Sanger was awarded the 1958 Nobel Prize in Chemistry for this work.

American medical physicist Rosalyn Sussman Yalow (19 July 1921 – 30 May 2011) received the 1977 Nobel Prize in Medicine for the Development of the radioimmunoassay for insulin.
Body of Michigan Man Deported to Iraq Is Returned to the U.S.

41-year-old Jimmy Aldaoud died in Baghdad of a "diabetic crisis".

Jimmy Aldaoud was found dead in a Baghdad apartment on Aug. 6 after days of vomiting blood and begging to return to Michigan in the United States of America where he had lived since infancy.

He spoke only English – no Arabic – and was unable to get insulin in IRAQ after his deportation by ICE. His body was brought home for his funeral.

by Mariel Padilla  The New York Times
Published Aug. 31, 2019
the BRAIN is recognized as an INSULIN-SENSITIVE ORGAN that is responsible for physiologic changes in altered metabolic disorders such as obesity and type 2 diabetes.

In the brain, the INSULIN RECEPTOR is broadly expressed in regions including the hypothalamus, hippocampus, and cerebral cortex, all of which are involved in the metabolic control of insulin action, including feeding behaviour, body weight homeostasis, neuronal development and cognitive function.

Insulin also plays important roles in neuronal circuitry formation, synaptic maintenance, neuronal survival, dendritic arborisation, as well as LEARNING and MEMORY.

likely that DEFECTIVE INSULIN SIGNALLING in the brain is one of the key features in the pathogenesis of insulin resistance that is found in obesity, type 2 diabetes, memory impairment, cognitive dysfunction, and mood disorders.

- EXCELLENT ARTICLE – RECOMMENDED READING

Seung-Hwan Lee, Janice M. Zabolotny, Hu Huang, Hyon Lee, Young-Bum Kim
Besides regulating neural circuits involved in maintaining energy homeostasis, insulin also influences cognitive functions through its actions on synaptic plasticity and long-term potentiation in the hippocampus and other brain regions involved in learning and memory.

Recent studies also have indicated strong association between Alzheimer's disease & CNS insulin resistance

**INSULIN RESISTANCE**- associated with progressive atrophy in cortical regions affected by Alzheimer's disease, and this corresponded to worse cognitive performance in asymptomatic, late middle-aged adults.

**DIET** may play an important part in the development of **INSULIN RESISTANCE IN THE BRAIN**.

In hamsters, a diet high in FRUCTOSE induces peripheral as well as NEURAL INSULIN RESISTANCE

Seung-Hwan Lee, Janice M. Zabolotny, Hu Huang, Hyon Lee, Young-Bum Kim

# Table 2

Intranasal insulin treatment outcomes.

<table>
<thead>
<tr>
<th>CNS function</th>
<th>Clinical subjects</th>
<th>Intranasal insulin</th>
<th>Phenotype</th>
<th>Treatment outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Amnestic MCI or early AD or healthy</td>
<td>single dose (20 IU or 40 IU)</td>
<td>Verbal memory</td>
<td>Facilitated recall on two measures of verbal memory in memory-impaired APOE-e4 adults. These effects were stronger for memory-impaired APOE-e4- subjects than for memory-impaired APOE-e4+ subjects and normal adults.</td>
</tr>
<tr>
<td></td>
<td>Amnestic MCI or early AD</td>
<td>3 weeks (20 IU)</td>
<td>Verbal memory</td>
<td>Enhanced verbal memory, selective attention, and functional status.</td>
</tr>
<tr>
<td></td>
<td>Amnestic MCI or AD or healthy subjects</td>
<td>5 days (10, 20, 40, or 60 IU)</td>
<td>Verbal memory</td>
<td>Facilitated recall on two measures of verbal memory in memory-impaired APOE-e4 adults.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Differentially modulated plasma amyloid-β for memory-impaired subjects and normal controls, with effects that differed by APOE genotype.</td>
</tr>
</tbody>
</table>

|              | Amnestic MCI or mild to moderate AD | 4 months (20 or 40 IU) | Dementia Testing | Improved delayed memory with 20 IU intranasal insulin. |
|              | APOE-e4 carriers with mild-moderate AD | Single dose (40 IU) | Memory | Preserved cognition and functional abilities with 20 and 40 IU insulin. |
|              |                      |                    | Correlation between effects on memory and function with CSF Aβ42 and tau/Aβ42. | No impact on cognition; serum insulin levels dropped post treatment, but peripheral glucose levels were unchanged. |

---

Seung-Hwan Lee, Janice M. Zabolotny, Hu Huang, Hyon Lee, Young-Bum Kim

Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021669/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021669/)
TYPE III DIABETES MELLITUS
The brains of patients with Alzheimer’s disease (AD) show the evidence of reduced expression of insulin and neuronal insulin receptors, as compared with those of age-matched controls.

New tracers to probe disorders of neural metabolism and cell biology are on the way.

Deeper insight into the degenerative processes of cellular dysfunction and DEMENTIA are coming soon.

“WRAP it up!”
- Comedian, Dave Chappelle
IMAGINING WHAT ADVICE POLONIUS MIGHT HAVE OFFERED
TO HIS SON, LAERTES, HAD HE LIVED...

The Brain is a complex and arcane entity, but it’s up there where you live. Guard yourself with the best of all possible choices from moment to moment.

Be careful of what you breathe, eat, drink and above all, choose carefully those things with which you have contact because all will weigh in to the outcome of your life’s journey.

Just saying, on behalf of your liver, microbiome, and the integrity and function of your nervous system...

Enjoy learning and sharing and being part of the scientific culture of humanity but don’t worry about wealth or fame – life is rarely fair but really, it doesn’t matter.

The End