The Face of Dementia

Robert A. Hendrix, M.D. *Science Circle* *10 – 11:00 AM PDT* *21 September 2019*

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 DEFINIED 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*"

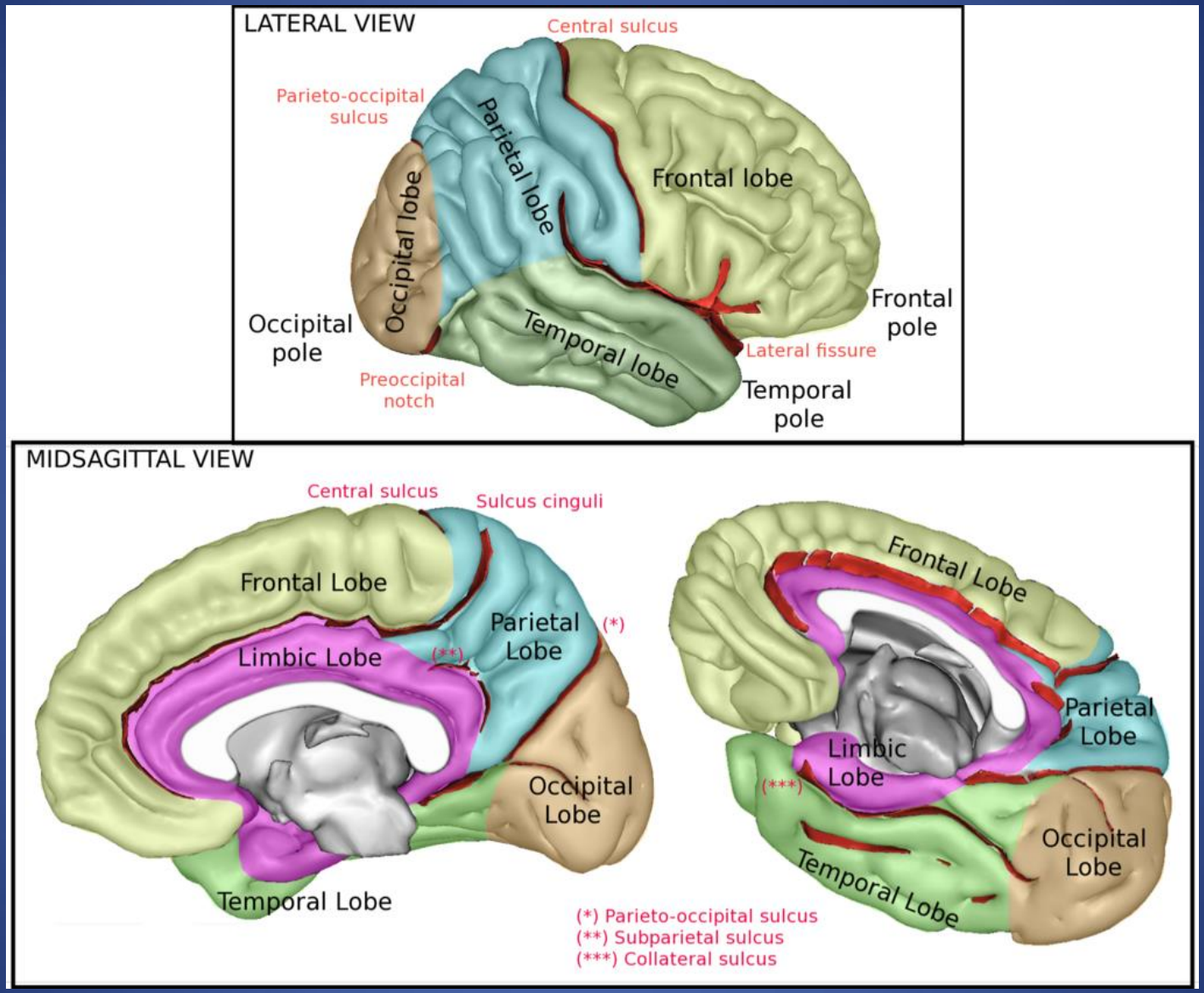
Dementia with Lewy Bodies (DLB)

Fronto-temporal Dementia (FTD

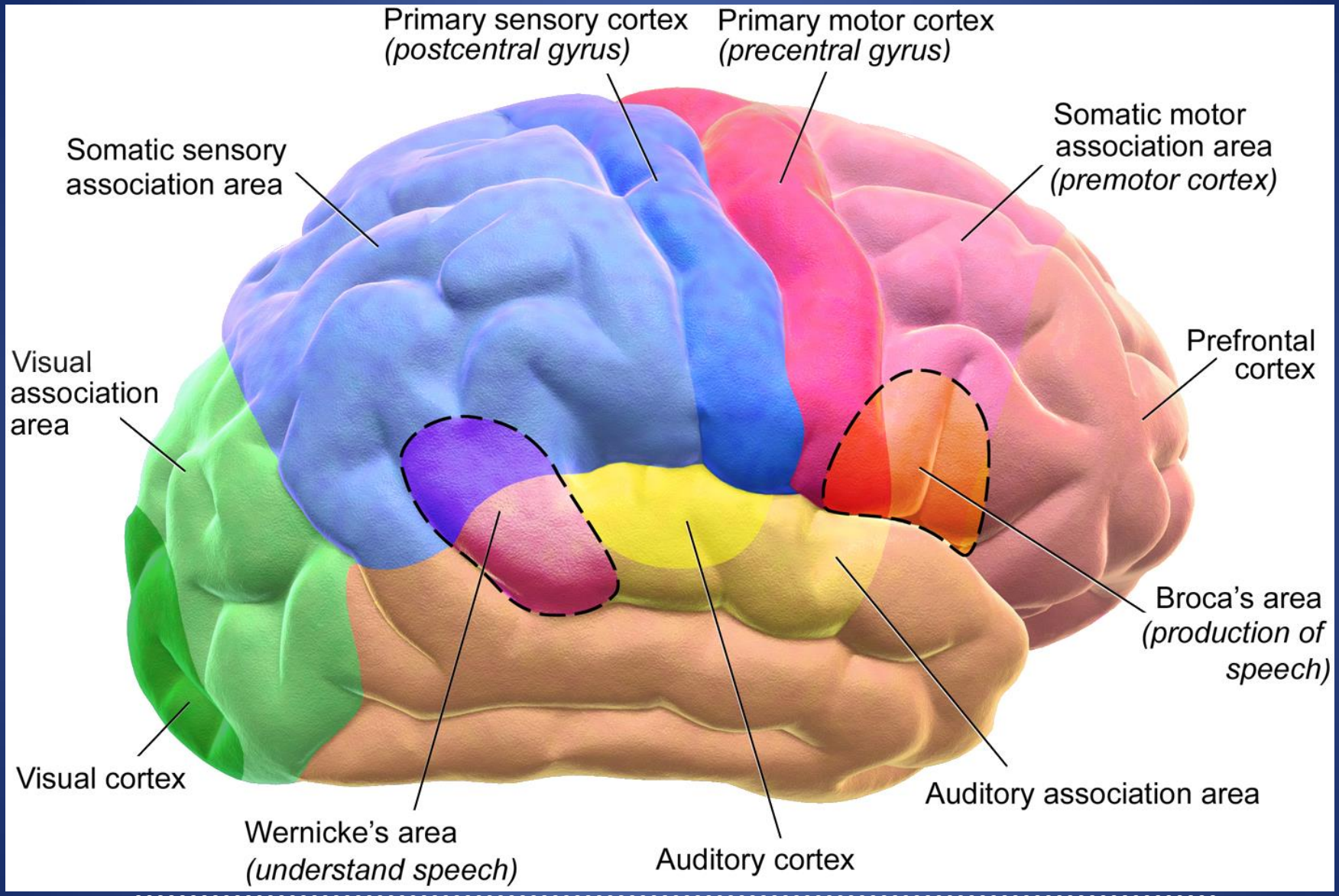
Alcoholic Related Dementia (ARD)

Dementia of Unknown Etiology (DUE)
and *mixed etiology*

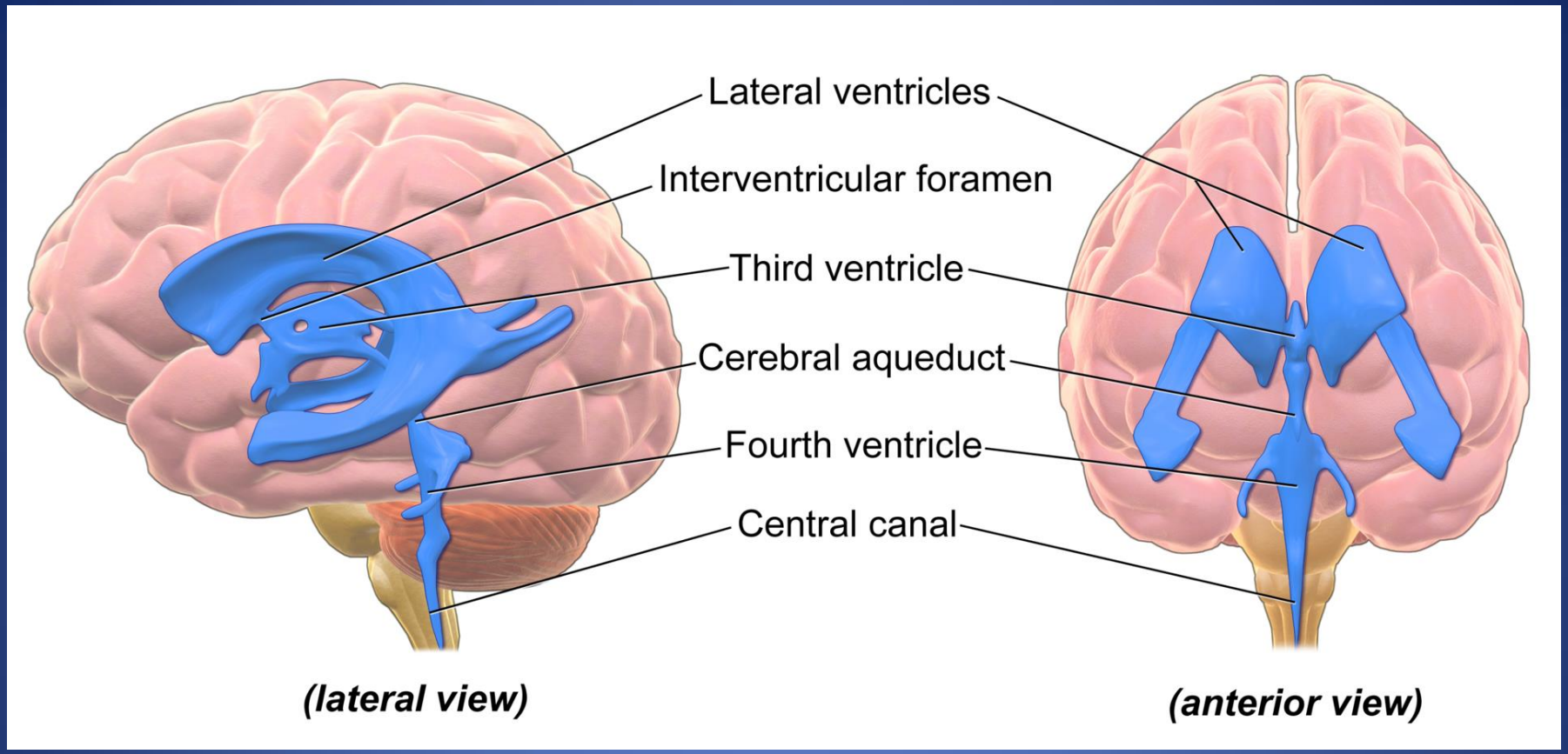
What Is Dementia? Symptoms, Types, and Diagnosis
https://www.nia.nih.gov/health/what-dementia-symptoms-types-and-diagnosis



By Sebastian023 - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=16137447



Functional areas of the human brain . Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". *WikiJournal of Medicine* **1** (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. - Own work



VENTRICLES ≡ Four CEREBRAL SPINAL FLUID (CSF)-filled spaces:

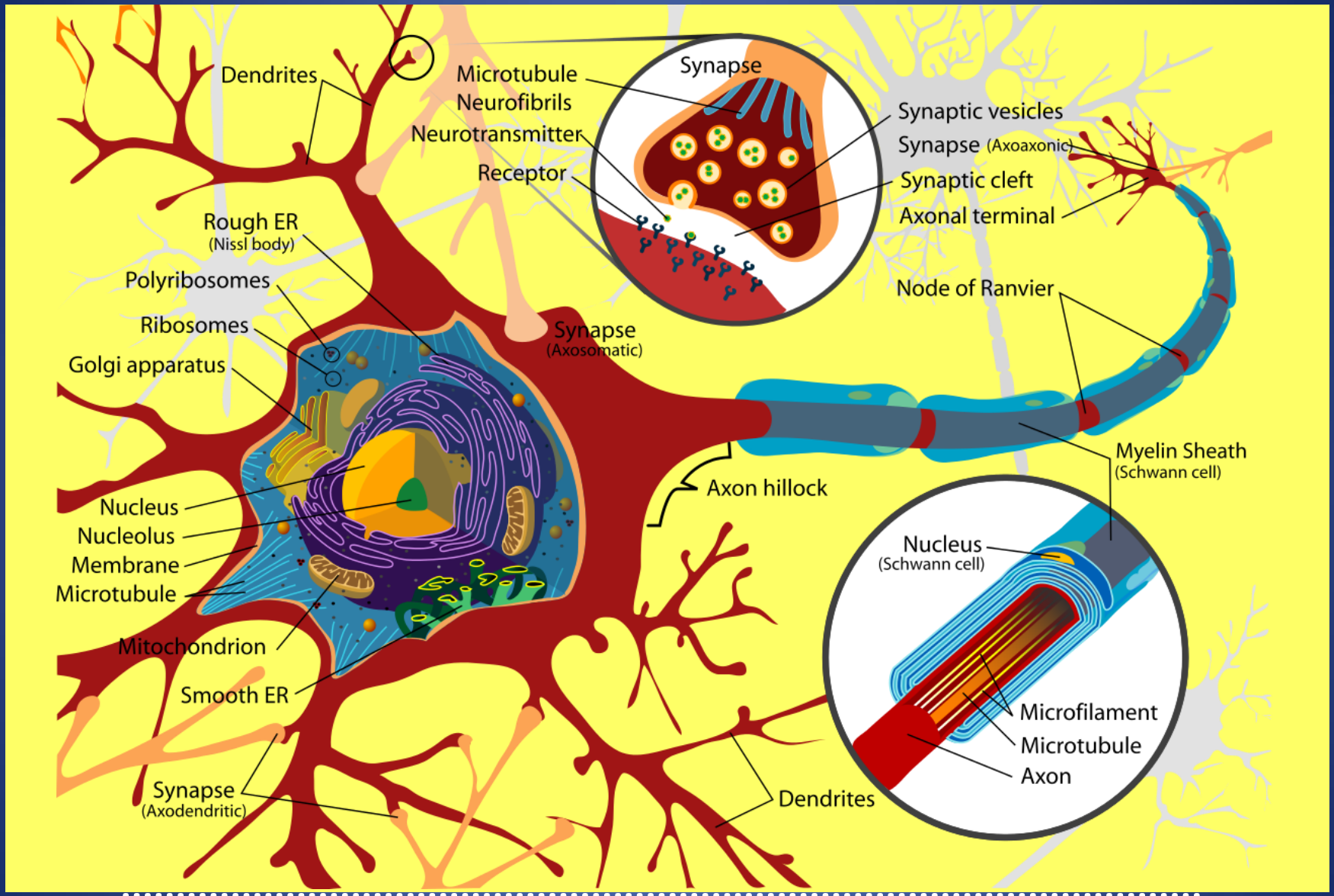
LATERAL VENTRICLES (largest) in **cerebrum**

THIRD ventricle is in the diencephalon of the forebrain between the right and left thalamus

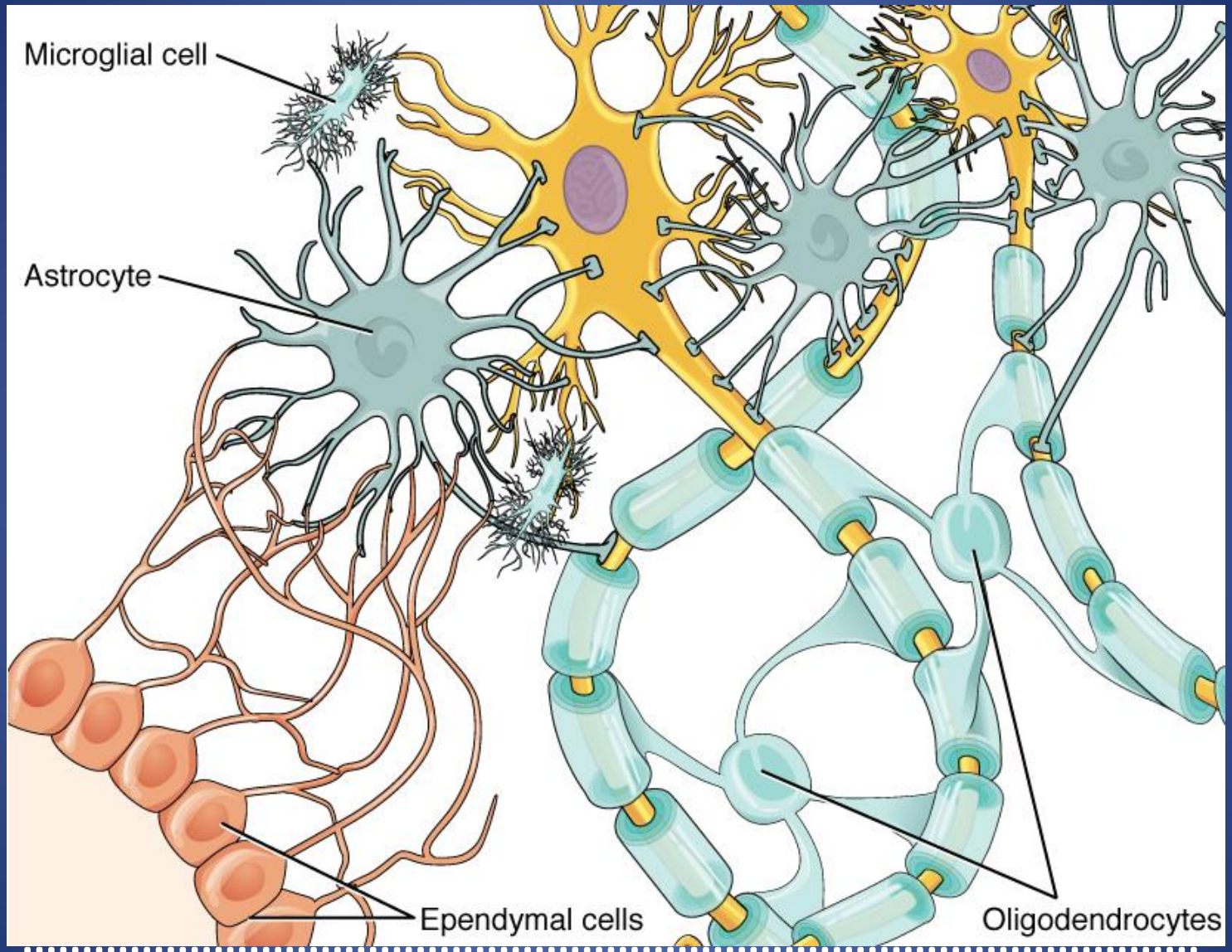
FOURTH ventricle at the back of the pons and upper half of medulla oblongata of hindbrain

Ependymal cells in CHOROID PLEXUS lining ventricles produce Cerebral Spinal Fluid (CSF).

CSF is absorbed by ARACHNOID GRANULATIONS after circulating through ventricles



File:Complete neuron cell diagram en.svg - This work released into **public domain** by its author, **LadyofHats** 12.July 2007 https://en.wikipedia.org/wiki/File:Complete_neuron_cell_diagram_en.svg



File:1209 Glial Cells of the CNS-02.jpg Version 8.25 from the Textbook
OpenStax Anatomy and Physiology - Published May 18, 2016
https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface

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.

<u>MICROGLIA</u> **(**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).

.....

Definitions for File:1209 Glial Cells of the CNS-02.jpg Version 8.25 from the Textbook
OpenStax Anatomy and Physiology - Published May 18, 2016
https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface

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
https://www.nia.nih.gov/health/what-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.

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DEMENTING DISEASE (*most common ETIOLOGIES or CAUSES of DEMENTIA*)	**Relative Frequency**
CEREBRAL ATROPHY, mainly Alzheimer, but including **Lewy-body** Dementia, Parkinsons, **Frontotemporal**, and **Picks** diseases	50 %
Multi-Infarct Dementia (**Vascular** Dementia)	10 %
Alcoholic Dementia (***Wernicke-Korsakoff Amnesia Syndrome***)	7 %
Intracranial tumors	5 %
Normal Pressure HYDROCEPHLUS	5 %
Huntington Chorea	2 %
Chronic Drug Intoxications	3 %
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), neurosyphillis, Creutzfeldt Jacob Disease; multiple sclerosis; chronic epilepsy	6 %
Cerebral Trauma	2 %
AIDS Dementia (can be accelerated by methamphetimine abuse)	2 %
Pseudodementias: depression; hypomania; schizophrenia; hysteria; undiagnosed	8%

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

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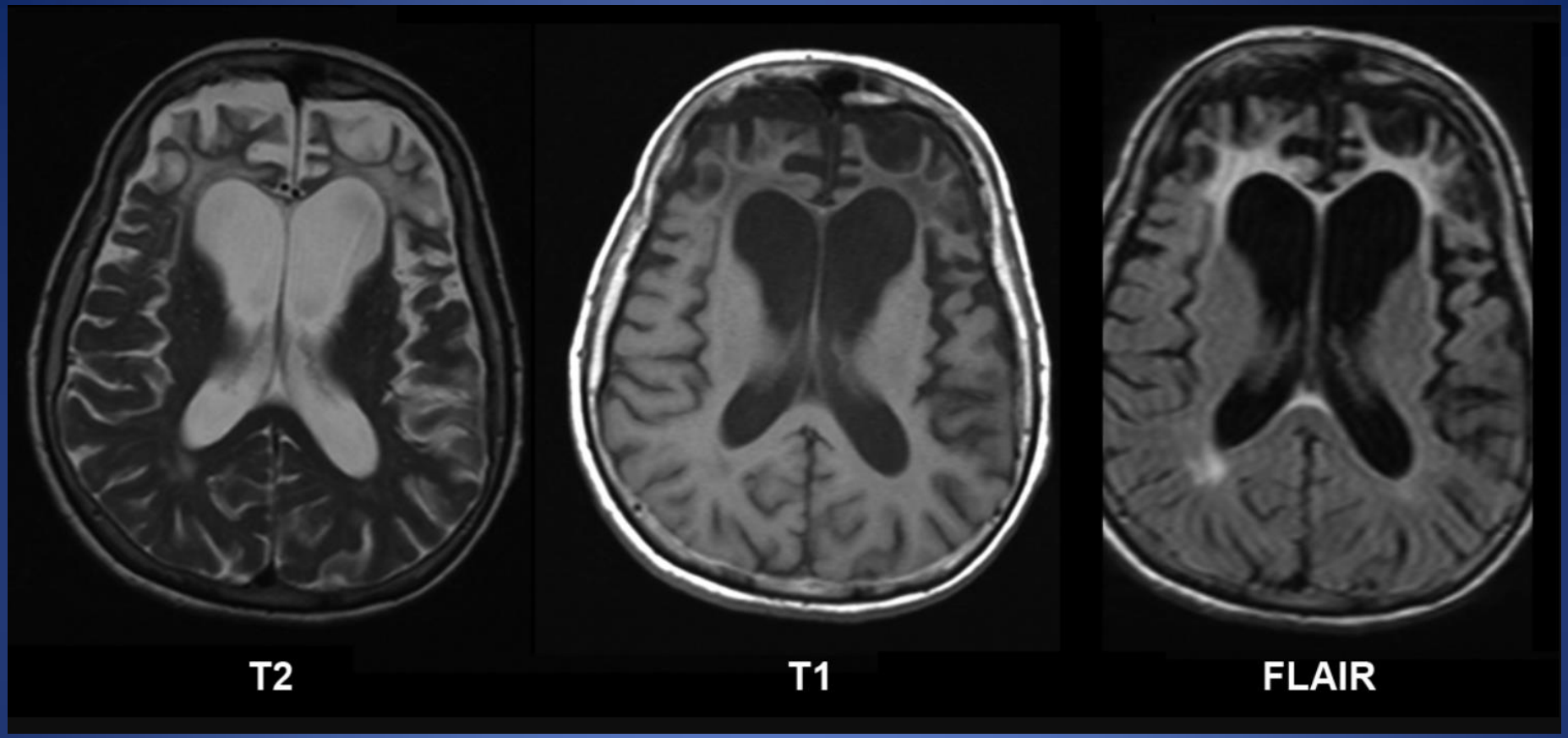

Brain MRI of a female 65 y.o. white patient with Pick's disease.
Cortex and white matter atrophy of the frontal lobes is clearly visible.

- MRI was done without contrast enhancement utilizing Magnetom Vision 1.5 Tesla with superconductive magnet.

Mikhail Kalinin 9.July 2009 File:Pick's disease.png
https://commons.wikimedia.org/wiki/File:Pick%27s_disease.png

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.

Frontotemporal Dementia Information Page - What research is being done?

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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)

National Institute on Aging - What Is Lewy Body Dementia?

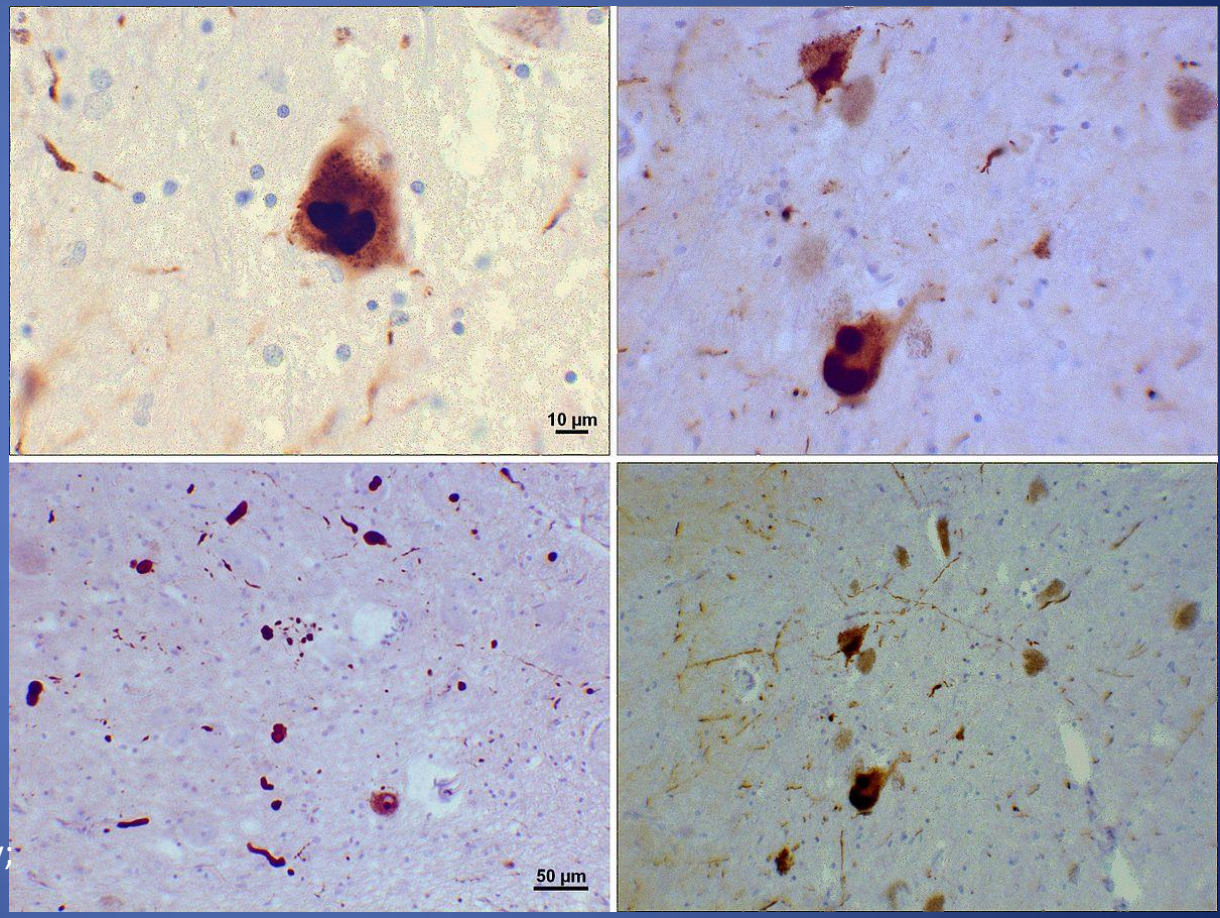
https://www.nia.nih.gov/health/what-lewy-body-dementia

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.

<u>*Legend*</u>:
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

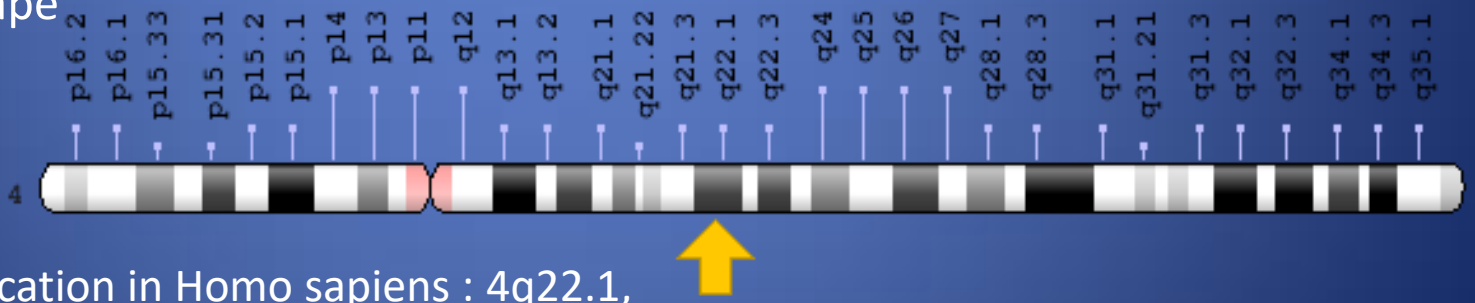
***SNCA* gene** provides instructions for making a small protein called **alpha-synuclein**. abundant in the brain, found mainly at the tips of nerve cells (neurons) in specialized structures called presynaptic terminals.

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

Studies ⇒ important role maintaining an adequate
SUPPLY OF PRE-SYNAPTIC VESICELS 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 **MICROTUBLES** 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

https://ghr.nlm.nih.gov/gene/SNCA#location

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 abilitiy 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.**

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- 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 abilitiy 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

VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (mg)
B1 THIAMINE pyrophosphate Whole grains, Brown rice Green leafy veggies, Soy beans, nuts, peas, eggs, or kill mammals and eat their livers	BERI-BERI incl peripheral neuropathy & weakness. Wernicke.Korsakoff Syndrome = neurodegeneration within medial thalamus MEDIAL THALAMUS and CEREBELLUM; ataxia, abnormal motor function & eye movement, AMNESIA, APATHY, CONFABULATION	Alcohol Abuse Obesity Severe malnutrition NOTE: EXCESS COFFEE OR TEA CAN DEPLETE B1 IF YOU DON'T B1, YOU'LL BE STUMBLING AND NUMB *with risk of dying of heart failure!*	1.2

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (mg)
B2 riboflavin Flavoproteins: flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) (redox reactions) Dairy, leafy VEGGIES, legumes / beans, yeast, mushrooms, or kill and eat sentient creatures and eat their livers or kidneys	Fatigue, personality change, brain dysfunction More generally: Weakness, oral pain/tenderness, burning or itching of the eyes, dermatitis, Anaemia	inherited riboflavin malabsorption and utilisation (10%–15% prevalence)	1.3

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

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

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (mg)
B5 PANTHOTHENIC ACID Co-enzyme A (CoA) (acyl activation and transfer) Whole grains / cereals, broccoli, or kill and eat sentient mammals	Encephalopathy, behaviour change, Demyelination Numbness or burning sensations in extremities, dermatitis, diarrhoea	starvation	5

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (mg)
B6 pyridoxine Legumes / beans, nuts, bananas, potatoes, Or kill sentient animals to eat meat & fish	Irritability, impaired alertness, ***depression,*** ***cognitive decline,*** ***dementia***, autonomic dysfunction, convulsions More generally: Anaemia	Alcohol abuse, age-related malabsorption, contraceptive medications 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.	1.2

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (µg)
B7 BIOTIN for carboxylation reactions Eggs, liver, leafy VEGGIES or pork	Depression, lethargy, hallucinations, seizures Generally: Seborrheic eczematous rash, tingling and/or burning of the extremities	Type II diabetes, poor gluco-regulation	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 Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (µg)
B9 FOLIC ACID Tetrahydrofolates including methyltetrahydrofolate Leafy VEGGIES, legumes / beans, citrus fruits	Affective disorders , behaviour changes, psychosis, cognitive impairment/decline, ***dementia*** including Alzheimer's disease and vascular dementia Generally: megaloblastic anaemia, peripheral neuropathy , spinal cord lesions, metabolic abnormalities	Common genetic polymorphisms including MTHFR C667T Low Riboflavin and B12	400 µg

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VITAMIN Sources	Symptom of DEFICIENCY affecting NERVOUS SYSTEM	SPECIFIC RISK FACTORS FOR DEFICIENCY	RDA (µg)
B12 COBALAMINS Methylcobalamin Adneosylcobalamin Eggs, dairy, fortified cereal, nurtritional yeast, nori (seaweed), Shitake mushroom, or you can kill and eat SENTIENT ANIMAL VICTIMS like meat & fish	Affective disorders , behaviour changes, psychosis, cognitive impairment/decline, ***dementia*** including Alzheimer's disease and vascular dementia Generally: megaloblastic anaemia, peripheral neuropathy , spinal cord lesions, metabolic abnormalities	age-related malabsorption, Vegetarians, vegans, Genetic polymorphisms	2.4 µg

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

VITAMIN	TOXICITY affecting NERVOUS SYSTEM	TOP LIMIT
B6 pyridoxine Legumes / beans, nuts, bananas, potatoes, or kill sentient animals íncluding meat & fish 	a well-known cause of primary sensory, length-dependent, axonal polyneuropathy. 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 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.	<< 100 mg Max usu 35

Levine S, Saltzman A.: **Pyridoxine (vitamin B6) neurotoxicity: enhancement by protein-deficient diet.** J Appl Toxicol. 2004 Nov-Dec;24(6):497-500.

EIGHT B-COMPLEX VITAMINS

thiamine (**B1**) riboflavin (**B2**) niacin (**B3**)

pantothenic acid (B5) pyridoxine (**B6**), biotin (**B7**)

folate (**B9**) cobalamin (**B12**)

VITAMIN	Caveat	TOP LIMIT
B3 NIACIN	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	35

David O. Kennedy: B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review Nutrients. 2016 Feb; 8(2): 68. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

”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

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"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

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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

https://www.ncbi.nlm.nih.gov/

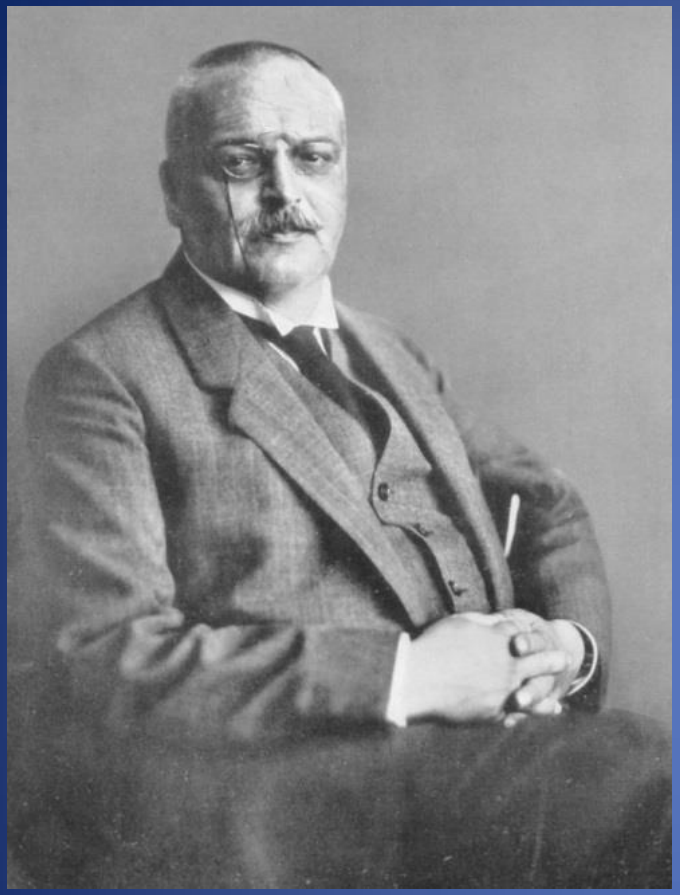
MMSE: Mini-Mental State Exam

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

https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd001525.1



Gastärzte im anatomischen Laboratorium; obere Reihe von links: F. Lotmar, unbek., St. Rosental, Allers(?), unbek., Alzheimer, M. Achucarro, F. H. Levy; untere Reihe von links: Frau Grombach, U. Cerletti, unbek., F. Bonfiglio, G. Perusini

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

The discovery of Alzheimer's disease Dialogues Clin Neurosci. 2003 Mar; 5(1): 101–108

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:

The discovery of Alzheimer's disease Dialogues Clin Neurosci. 2003 Mar; 5(1): 101–108

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)

NATIONAL INSTITUTE ON AGING ALZHEIMER'S DISEASE FACT SHEET
https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet

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!*

.....

EDITORIAL: Revised criteria for diagnosis of Alzheimer's disease: National Institute on Aging -Alzheimer's Association diagnostic guidelines for Alzheimer's disease
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.

DEMENTIA RESOURCES FOR HEALTH PROFESSIONALS - Alzheimer's Disease Diagnostic Guidelines

National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines

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.

.....

DEMENTIA RESOURCES FOR HEALTH PROFESSIONALS - Alzheimer's Disease Diagnostic Guidelines

National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines

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.

DEMENTIA RESOURCES FOR HEALTH PROFESSIONALS - Alzheimer's Disease Diagnostic Guidelines National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines

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.

DEMENTIA RESOURCES FOR HEALTH PROFESSIONALS - Alzheimer's Disease Diagnostic Guidelines

National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines

role of genetic testing in the revised guidelines? - LESS THAN 5% genetic

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.

DEMENTIA RESOURCES FOR HEALTH PROFESSIONALS - Alzheimer's Disease Diagnostic Guidelines
National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines

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

IMAGING TECHNIQUES

Functional MRI scanning (f-MRI) ≡ 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 1990 by Seiji Ogawa
→ first used for **fMRI** activation studies in the human visual cortex at 4T during on-off photic stimulation in 1992, published in the Proceedings of the National Academy of Sciences

Richard B. Buxton The physics of functional magnetic resonance imaging (fMRI)
Rep Prog Phys. 2013 Sep; 76(9): 096601. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4376284/

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

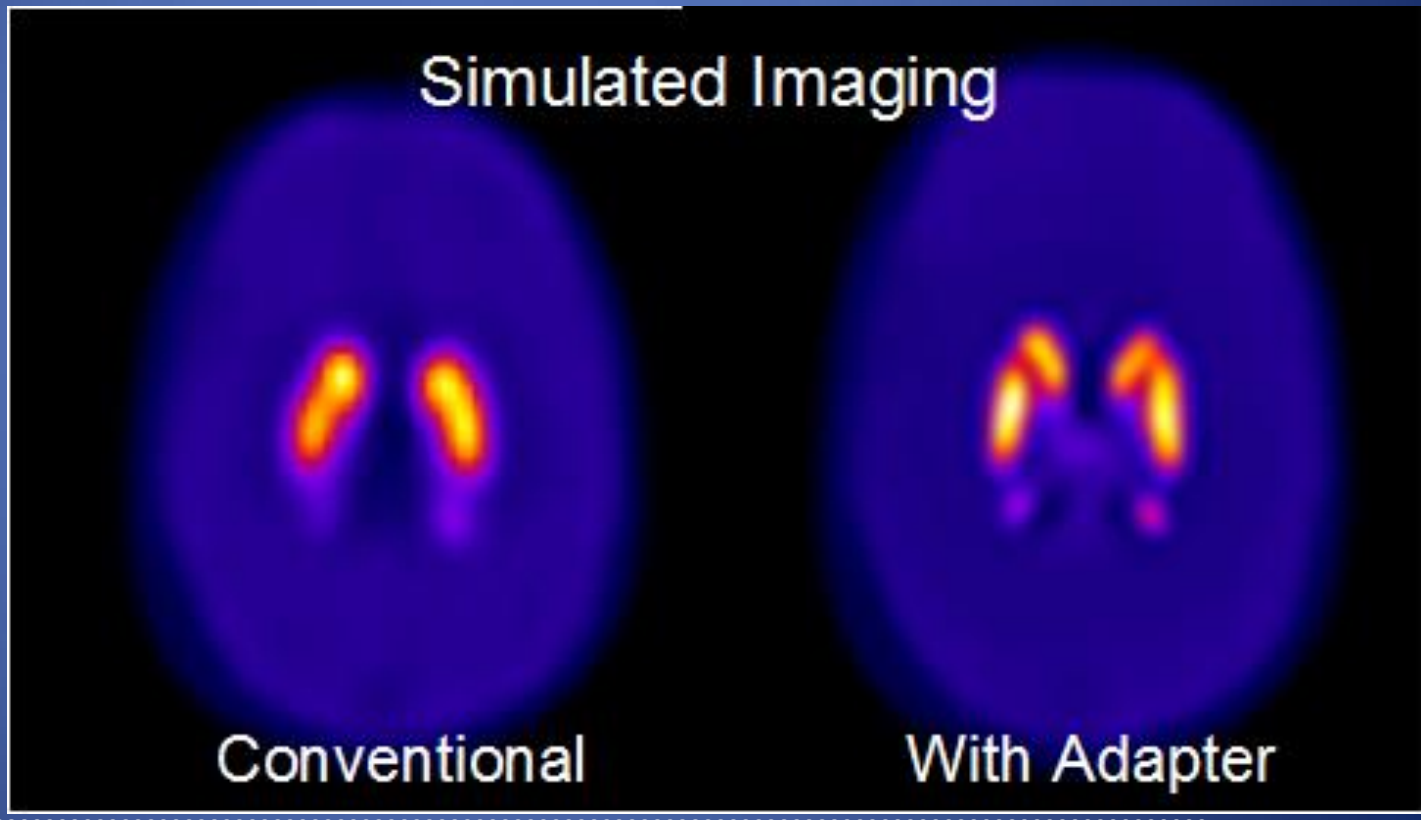
https://www.nibib.nih.gov/science-education/science-topics/nuclear-medicine

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.



Nuclear Medicine - National Institute of Biomedical Imaging and Bioengineering

https://www.nibib.nih.gov/science-education/science-topics/nuclear-medicine

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}C, ^{13}N, ^{15}O, and ^{18}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
Curr Top Med Chem. 2014; 14(7): 875–900.

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

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** (γ) 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
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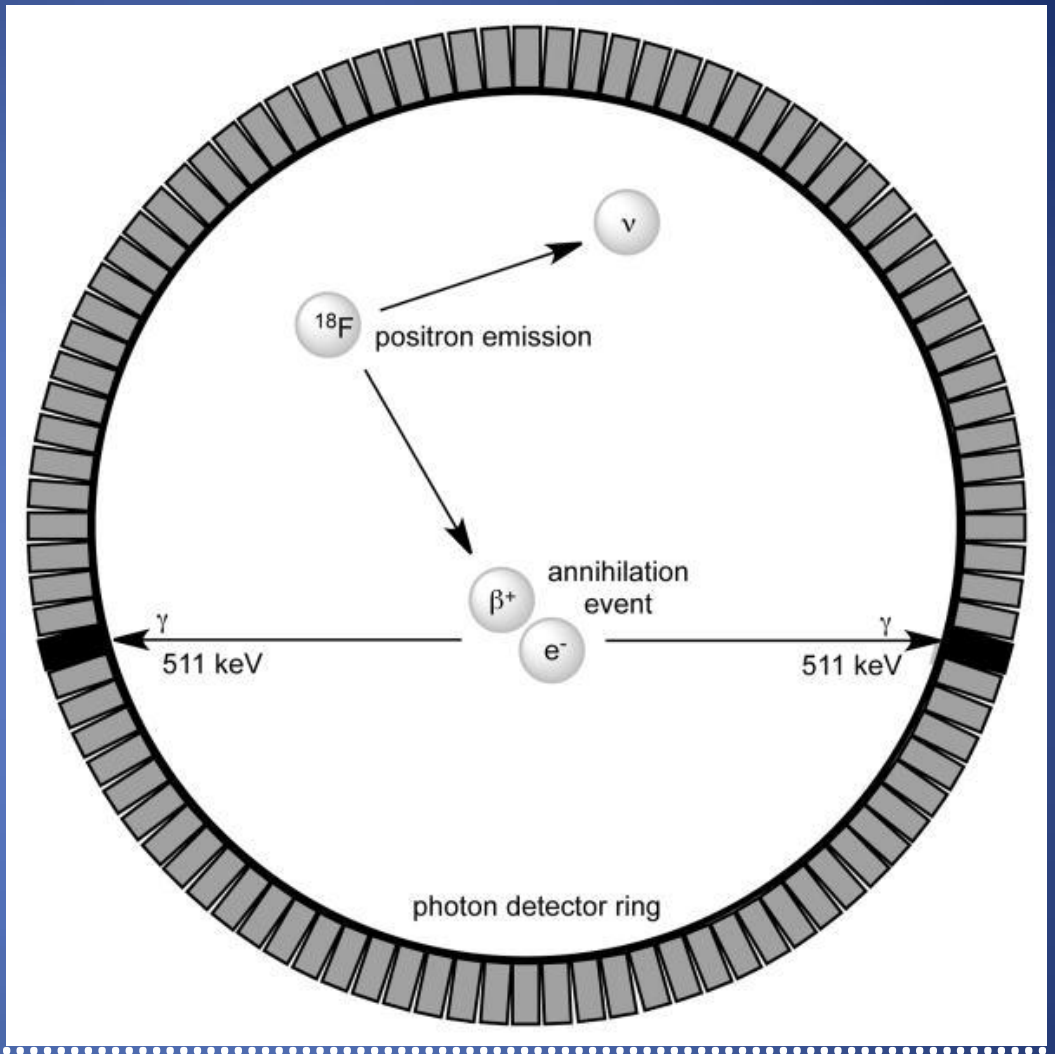
Curr Top Med Chem. 2014; 14(7): 875–900.

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
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Curr Top Med Chem. 2014; 14(7): 875–900.

MAKING TRACERS FOR IMAGING BY POSITRON (β^+) EMISSION TOMOGRAPHY (PET SCAN)

OXYGEN, Z = 8 Standard atomic weight = 15.999

naturally occurring (stable) isotopes:

^{18}O abundance ≈ 0.2 % 10 neutrons with isotope mass = 17.9991610 u
^{17}O abundance ≈ 0.04% 9 neutrons with isotope mass = 17.9991610 u
^{16}O abundance ≈ 99.76% 8 neutrons with isotope mass = 17.9991610 u

FLUORINE produced is in the form of a water solution of [^{18}**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
Curr Top Med Chem. 2014; 14(7): 875–900.

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.
Curr Neuropharmacol. 2016 Jan; 14(1): 101–115.

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

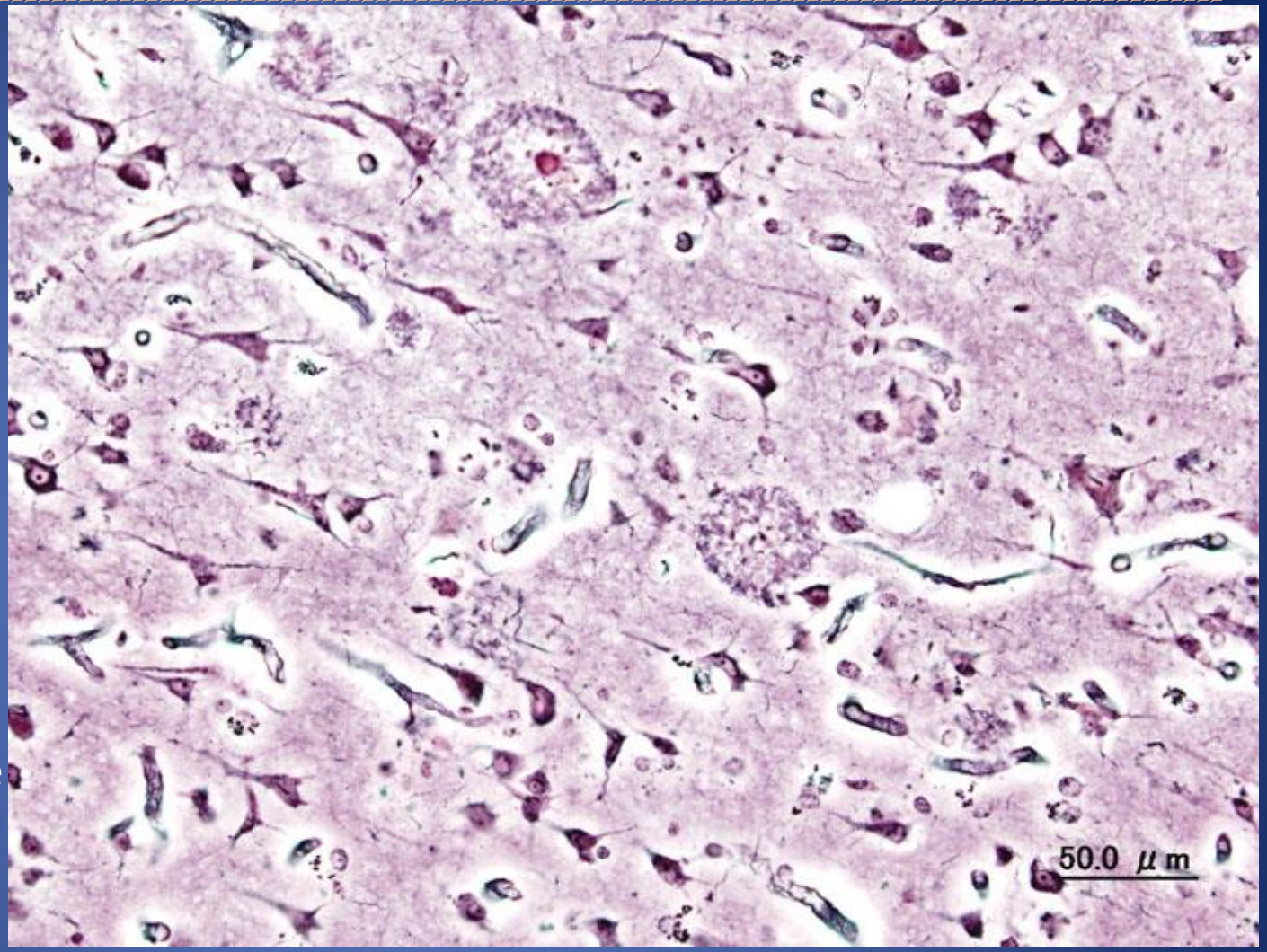
⇒ synaptic dysfunction is a critical element in the pathogenesis of AD

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

Synapse Formation and Function Is Modulated by the Amyloid Precursor Protein

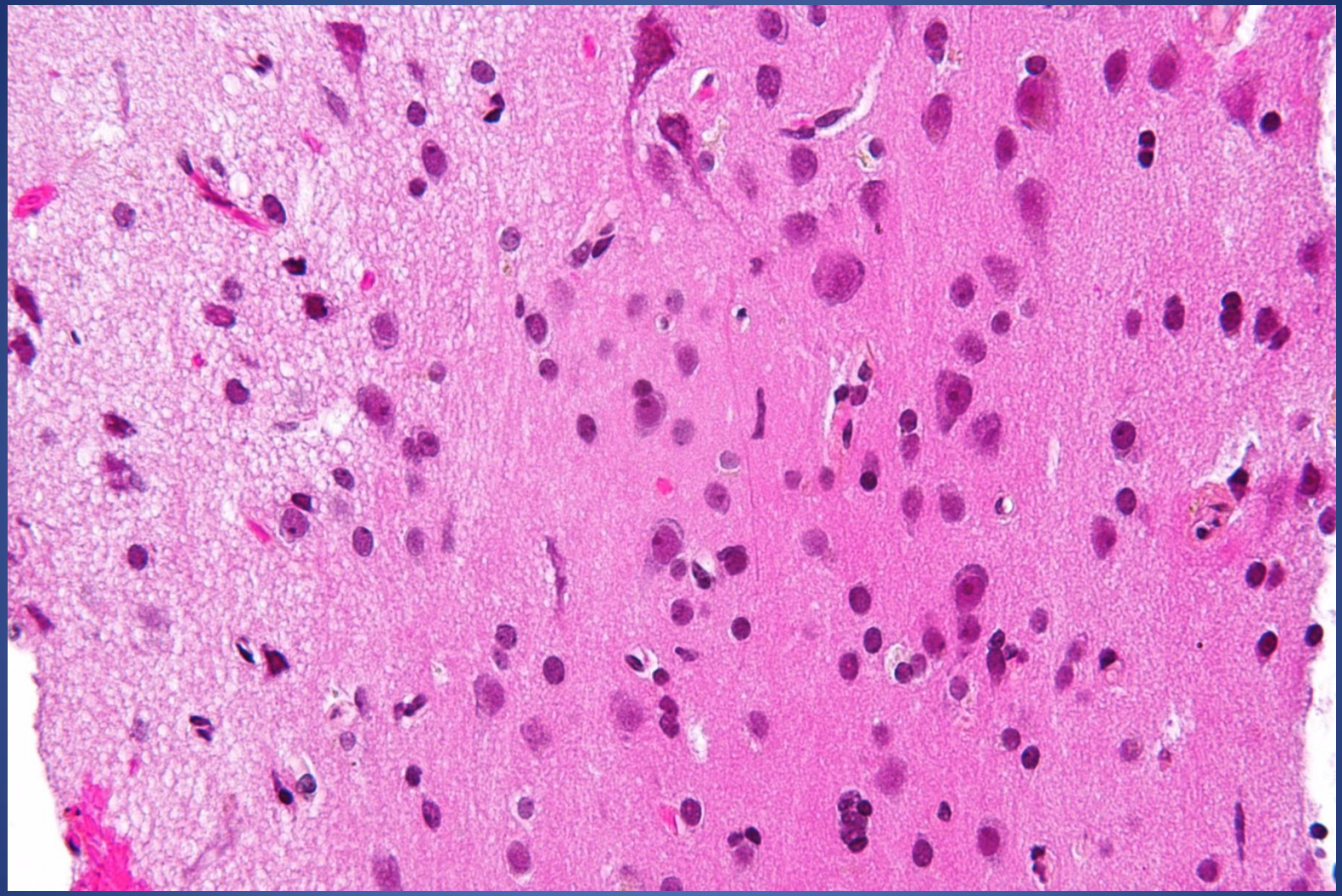
Christina Priller, Thomas Bauer, Gerda Mitteregger, Bjarne Krebs, Hans A. Kretzschmar and Jochen Herms: Journal of Neuroscience 5 July 2006, 26 (27) 7212-7221

https://www.jneurosci.org/content/26/27/7212



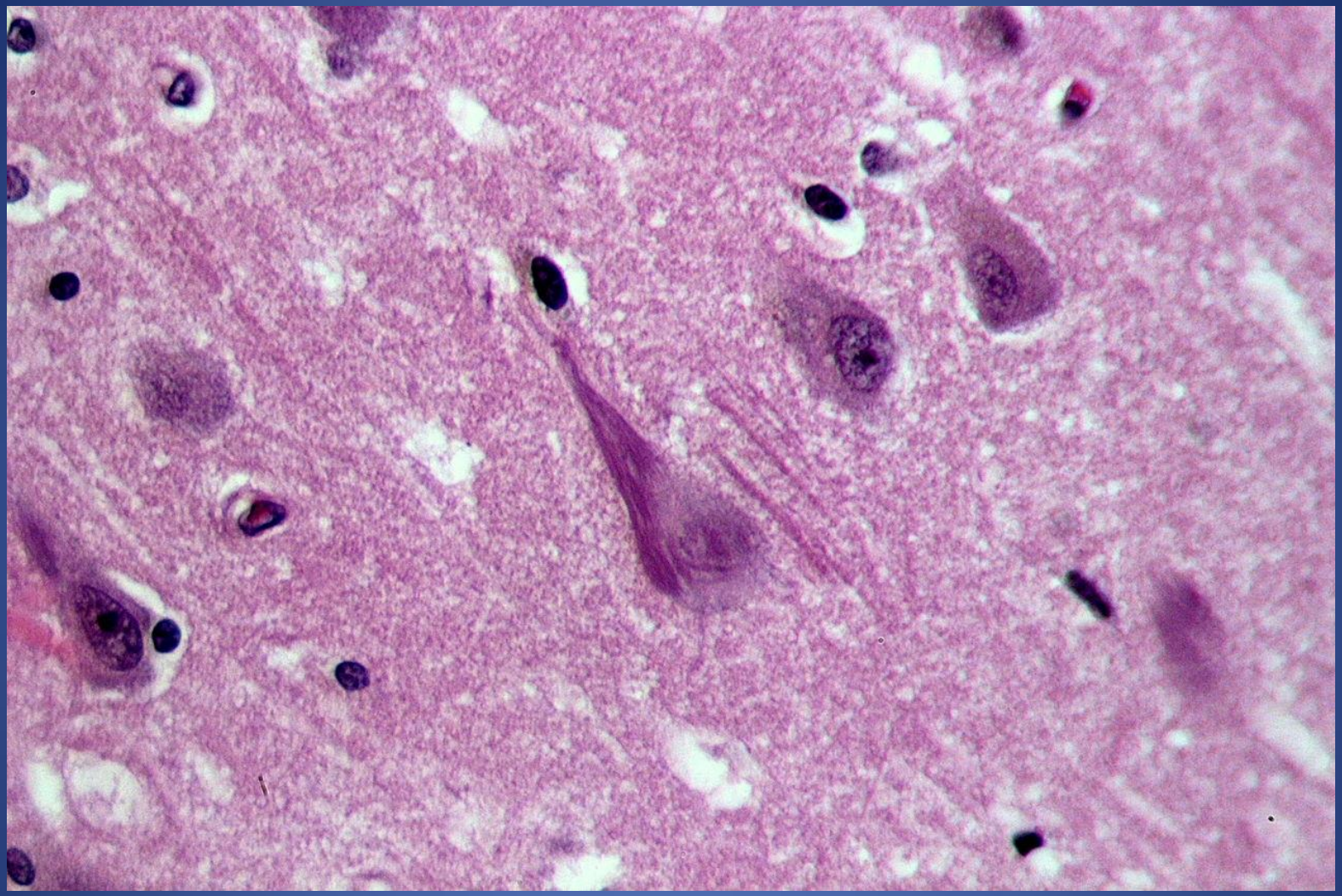
Histopathogic image
SENILE PLAQUES
seen in
cerebral cortex
in a patient with Alzheimer disease of PRE-SENILE ONSET. *Silver impregnation*

Feingeweblicher Schnitt mit Alzheimer-typischen senilen Plaques, Versilberung



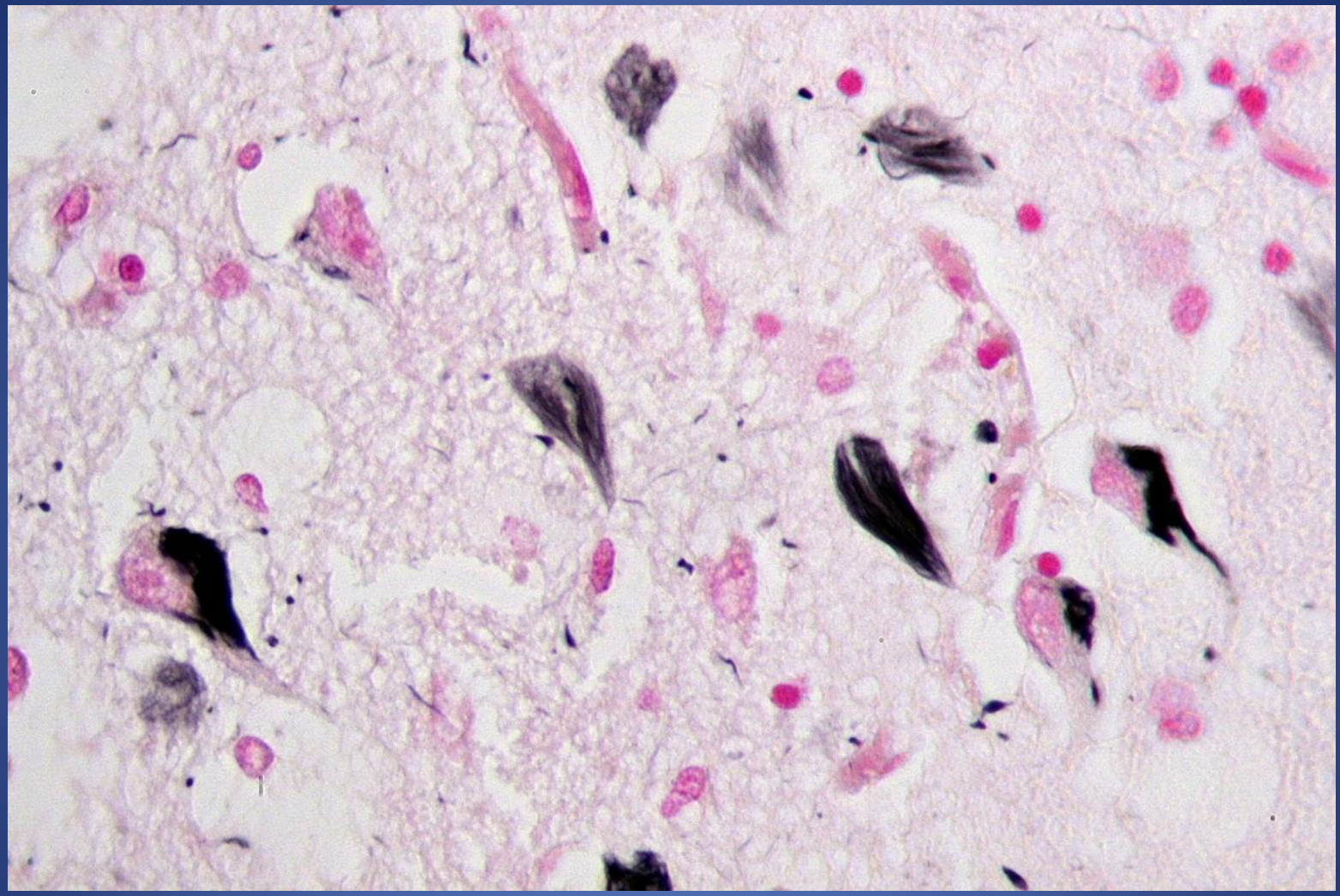
Very high magnification micrograph of brain, showing normal white matter and normal grey matter. HPS stain. Brain biopsy.

File:Grey matter and white matter - very high mag.jpg Nephron
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 Von Patho - Eigenes Werk, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=19844595



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 (espc 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,

- florbetapir florbetaben 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**

.....

New Tracer May Prove Better for Amyloid PET; in reference to: Sundaram GS, Dhavale DD, Prior JL, Yan P, Cirrito J, Rath NP, Laforest R, Cairns NJ, Lee JM, Kotzbauer PT, Sharma V. Fluselenamyl: A Novel Benzoselenazole Derivative for PET Detection of Amyloid Plaques (Aβ) in Alzheimer's Disease. *Sci Rep*. 2016 Nov 2

POSSIBLE CAUSES OF ALZHEIMER'S DISEASE (AD)

"**Tau** represents the subunit protein of one of the major hallmarks of Alzheimer disease (AD), the neurofibrillary 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

.....

Eva-Marie Mandelkow, Eckhard Mandelkow: ***Biochemistry and Cell Biology of Tau Protein in Neurofibrillary Degeneration***: Cold Spring Harb Perspect Med. 2012 Jul; 2(7): a006247.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3385935/

POSSIBLE CAUSES OF ALZHEIMER'S DISEASE (AD)

tau ⊂ MICROTUBULE-ASSOCIATED PROTEINS (MAPs) - *Marc Kirschner 1975*

Tau has 6 isoforms – NFT do not appear to be pure

tau 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 AFFECTED

⇒ MICROTUBULE DYSFUNCTION

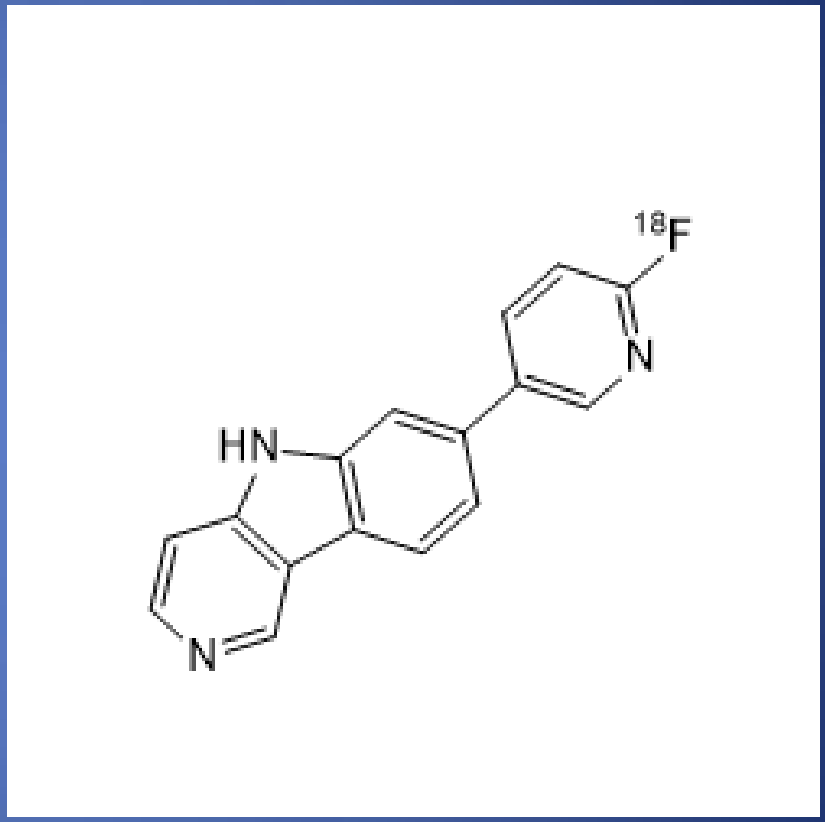
⇒ IMPAIRED DELIVERY SYSTEMS & METABOLISM ⇒ CELL DEATH

Marisol Espinoza, Rohan de Silva, Dennis W. Dickson, Peter Davies: Differential Incorporation of Tau Isoforms in Alzheimer's Disease J Alzheimers Dis. 2008 May; 14(1): 1–16.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882247/

^{18}F-**flortaucipir**

has shown early promise as a marker of tau pathology in AD.



Tau PET Imaging Using 18F-AV-1451

https://www.nia.nih.gov/alzheimers/clinical-trials/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.

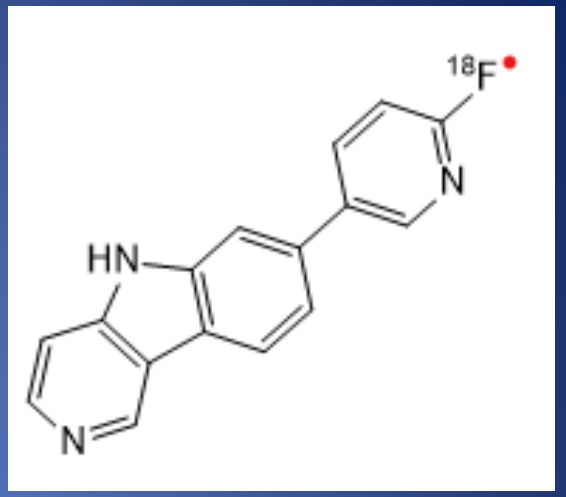
National Institute of Aging announcement
recruiting patients (80 enrolled so far) for study of Tau PET Imaging using
^{18}F-**flortaucipir** (formerly ^{18}F-**AV1451** or ^{18}F-T807)
in identifying tau tangles in positron emission tomography (PET) scans.

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

Tau PET Imaging Using 18F-AV-1451
https://www.nia.nih.gov/alzheimers/clinical-trials/tau-pet-imaging-using-18f-av-1451

Tau PET Imaging using
^{18}F-**flortaucipir** (formerly ^{18}F-**AV1451** or ^{18}F-T807)

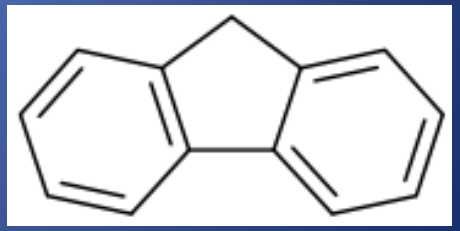
NOTE: pyridine 1 N;
recall ∃ 1,2- or 1,4-diAZINE & Pyrimidine = 1,3 diAZINE



Pyrrole is a heterocyclic aromatic organic compound,
a five-membered ring with the formula C_4H_4NH.

← Indole is an aromatic heterocyclic organic compound with formula C_8H_7N. 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

https://www.nia.nih.gov/alzheimers/clinical-trials/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.[1,2,3] and Jack R. Wands, M.D
Alzheimer's Disease Is Type 3 Diabetes–Evidence Reviewed
J Diabetes Sci Technol. 2008 Nov; 2(6): 1101–1113
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

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

Mol Metab. 2016 Aug; 5(8): 589–601. 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

.....

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

Published byLynette Morris

HISTORY OF INSULIN IN MEDICAL SCIENCE

CELL TYPES OF ISLETS OF LANGERHANS

α-cells (glucagon)
β-cells (insulin)
Δ-cells (somatostatin)

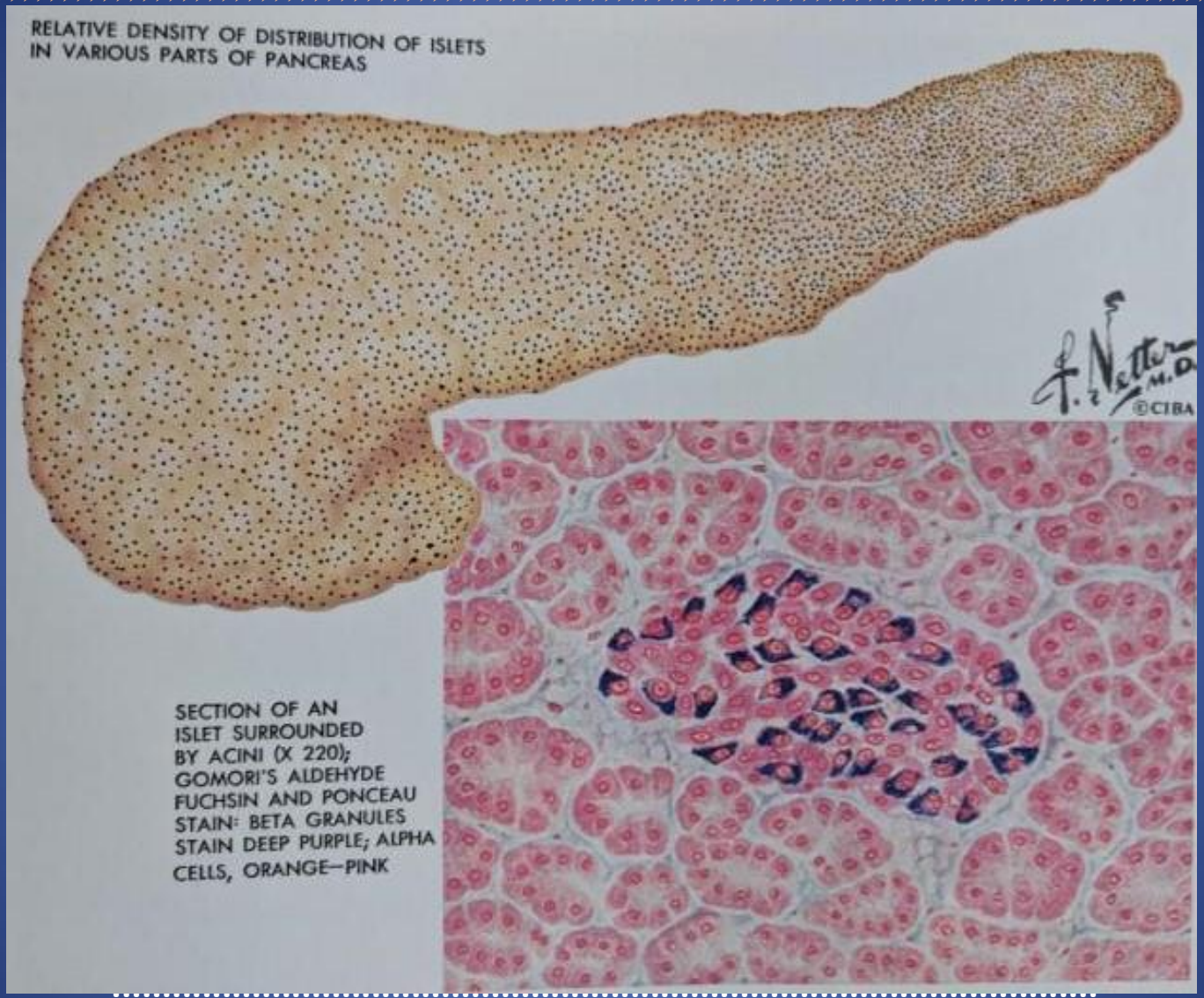
ε-cells (grehlin „hunger hormone“)

PP- (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 $[Ca^{2+}]_i$ 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 Ca^{2+} Signaling in β-Cells;

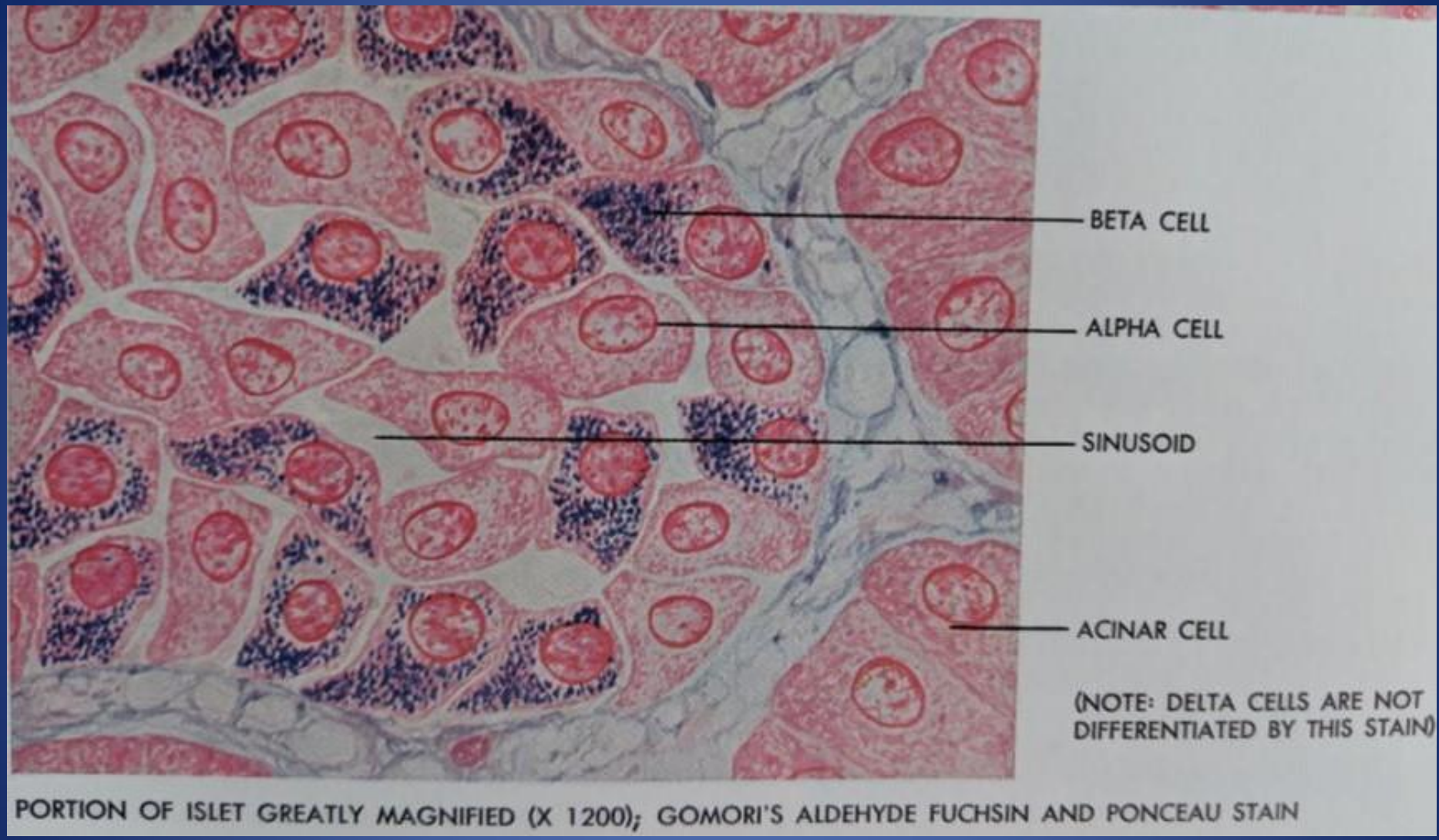
Katsuya Dezaki, Hiroshi Hosoda, Masafumi Kakei, Suzuko Hashiguchi, Masatomo Watanabe, Kenji Kangawa, Toshihiko Yada; Diabetes 2004 Dec; 53(12): 3142-3151.



ENDOCRINE SYSTEM AND SELECTED METABOLIC DISEASES Volume 4

Section V - Plate I, p. 143 Prepared by Frank H. Netter, M.D.

The CIBA Collection of Medical Illustrations 1965



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

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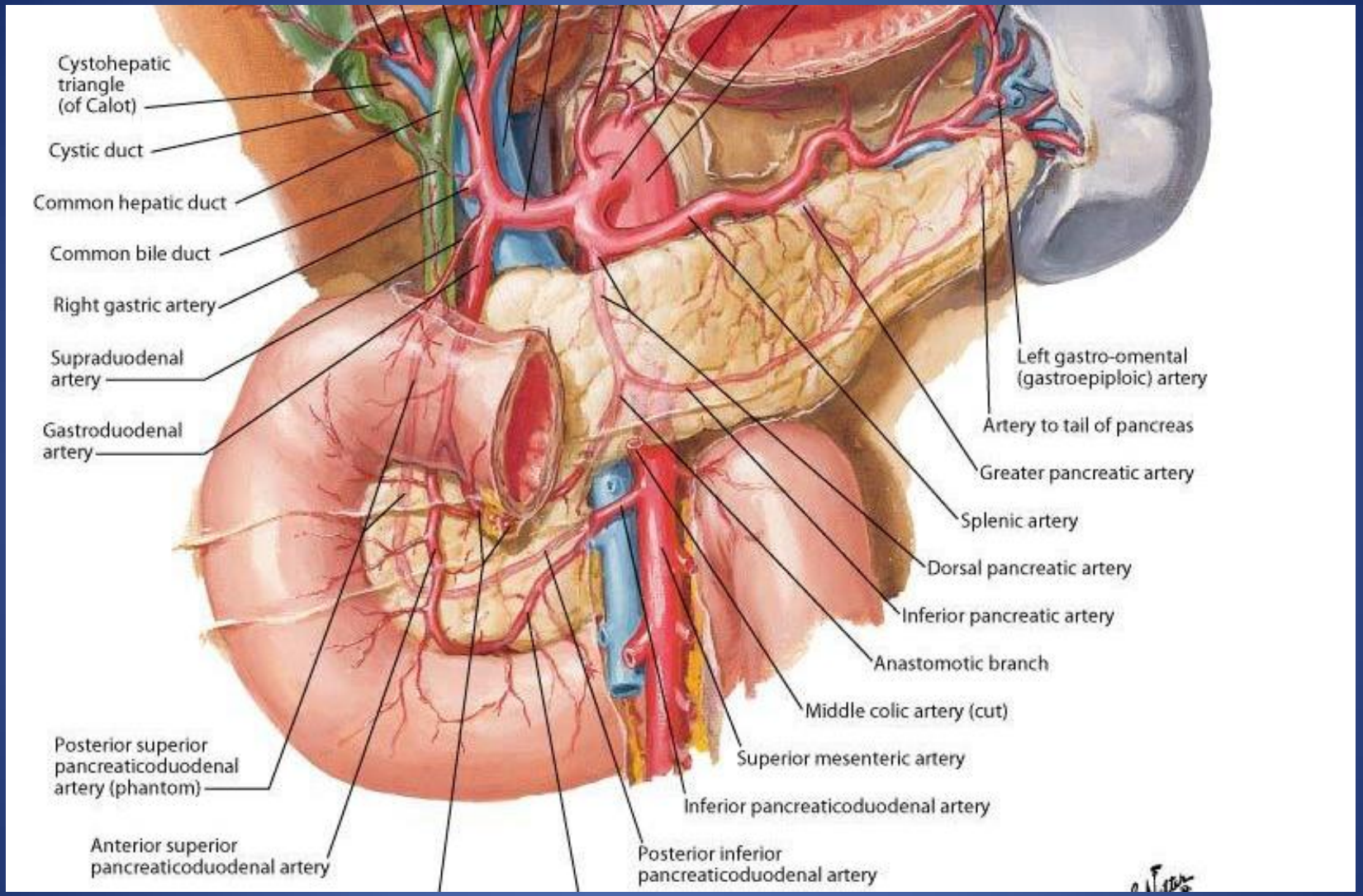

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HISTORY OF INSULIN IN MEDICAL SCIENCE

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.

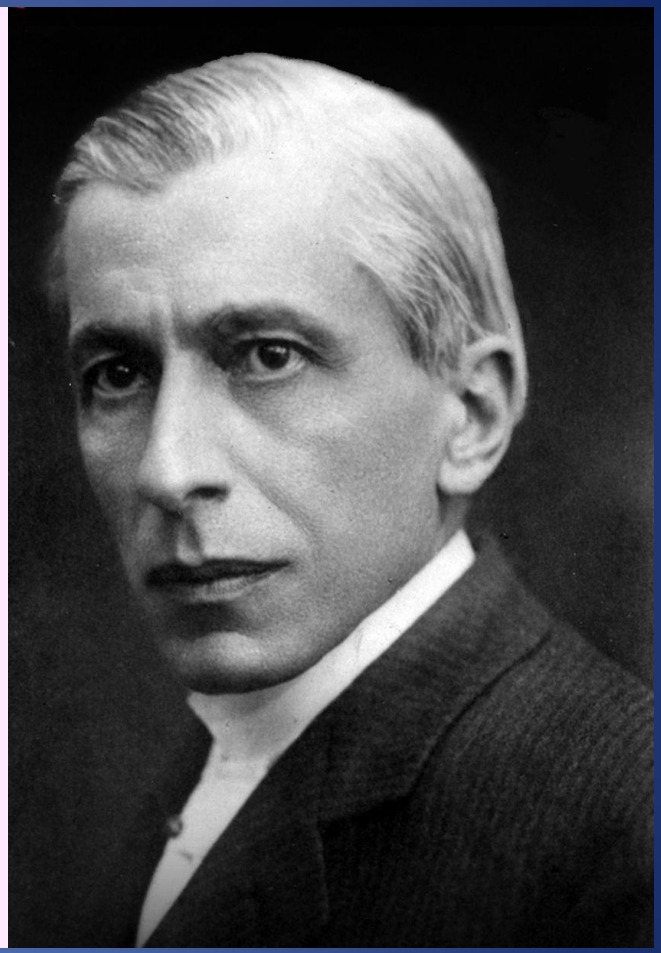
They were awarded the Nobel Prize in Physiology or Medicine in 1923 for the discovery of insulin.

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.

Frederick Banting, Charles Best, James Collip, and John Macleod
These four Toronto researchers discovered and purified insulin, creating a new and effective treatment for diabetes.
Science History Institute - **Headquarters**
315 Chestnut Street
Philadelphia, PA 19106

HISTORY OF INSULIN IN MEDICAL SCIENCE

In 1916, Nicolas Paulescu (1869-1931) succeeded in developing an aqueous pancreatic extract that normalized a diabetic dog. In 1921, he published 4 papers in the Society of Biology in Paris centering on the successful effects of the pancreatic extract in diabetic dogs.
Research on the Role of the Pancreas in Food Assimil-ation **by Paulescu was published in August, 1921 in the Archives Internationales de Physiologie, Liège, Belgium.**



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

Figure 10. License 6254. Pancreine

.....

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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&targetText=Dorothy%20Hodgkin%20was%20one%20of,hormone's%20chemical%20and%20biological%20properties.

HISTORY OF INSULIN IN MEDICAL SCIENCE

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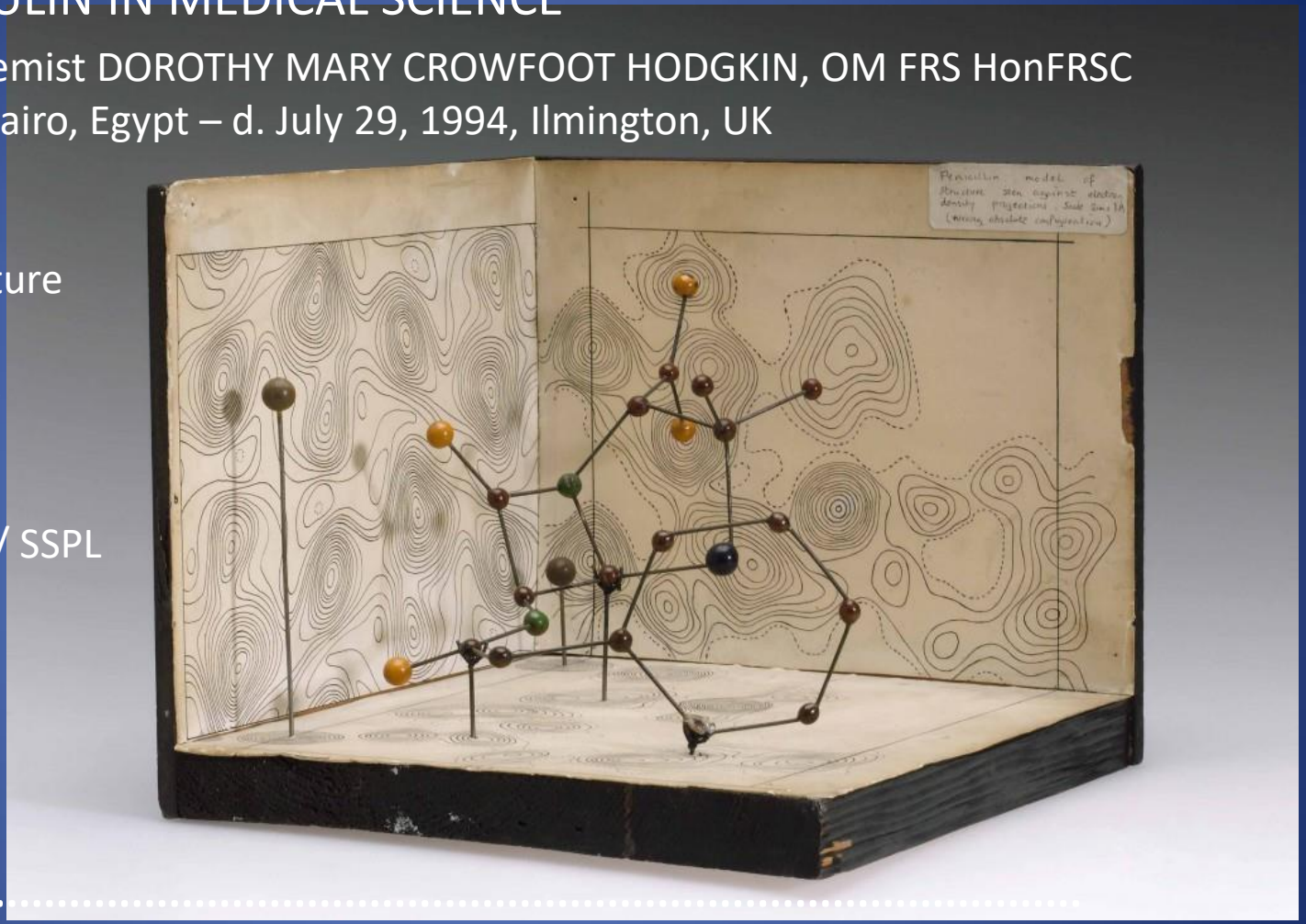
Molecular model of
3-dimensional structure
of penicillin
by Dorothy Hodgkin,
c.1945.
Image credit:
- Science Museum / SSPL



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HISTORY OF INSULIN IN MEDICAL SCIENCE

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**

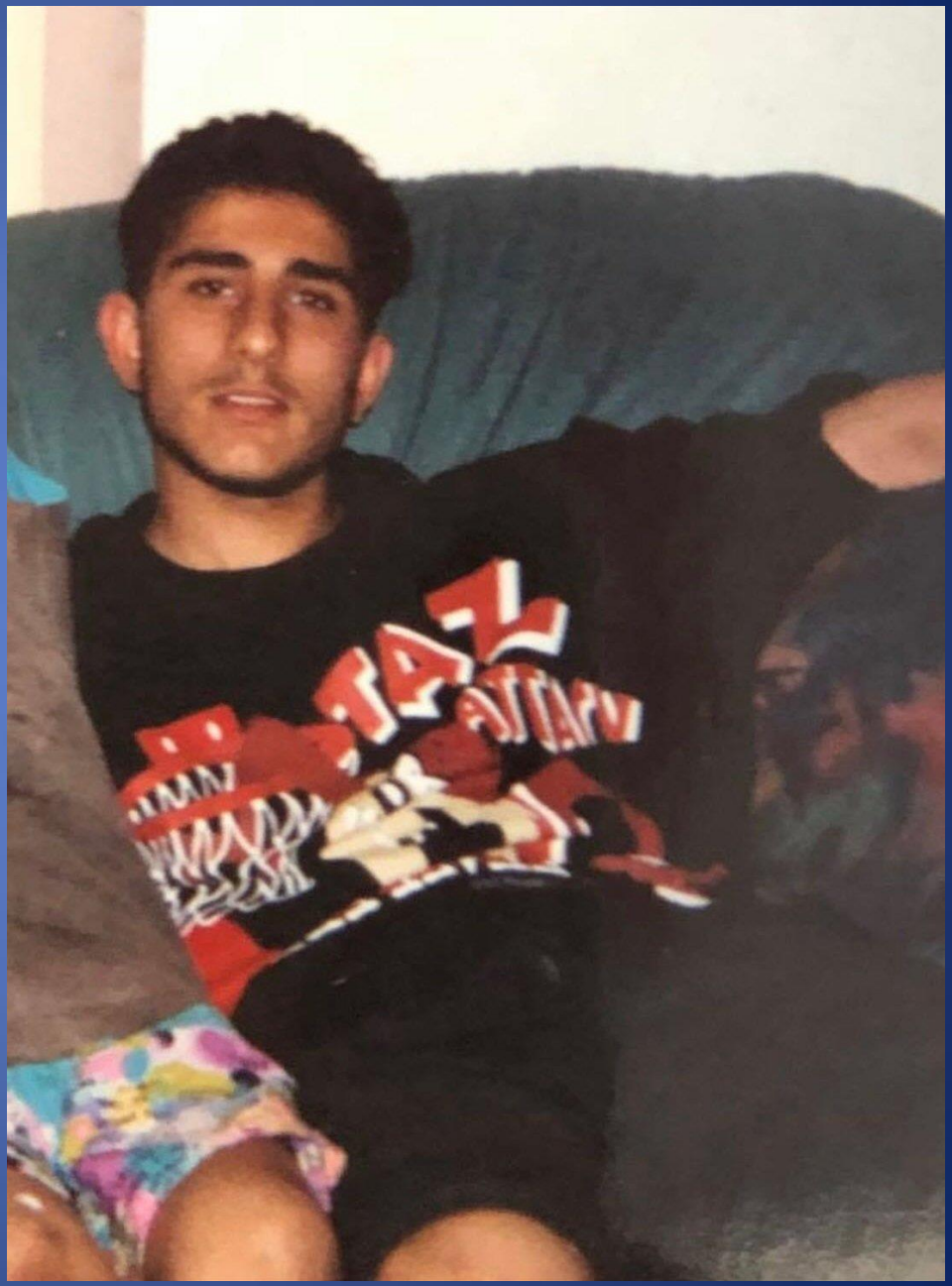
American medical physicist Rosalyn Sussman Yalow (19.July 1921 – 30.May 2011) received the 1977 Nobel Prize in Medicine for the Development of the radioimmunoassay for insulin

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
Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood.
Mol Metab. 2016 Aug; 5(8): 589–601. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021669/

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
Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood.
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Alzheimer's Disease as TYPE III DIABETE MELLITUS
SAMPLE FINDINGS - EXCERPT FROM REFERENCE BELOW

Table 2

Intranasal insulin treatment outcomes.

CNS function	Clinical subjects	Intranasal insulin	Phenotype	Treatment outcomes
Memory	Amnestic MCI or early AD or healthy	single dose (20 IU or 40 IU)	Verbal memory	Facilitated recall on two measures of verbal memory in memory-impaired APOE-ε4- adults. These effects were stronger for memory-impaired APOE-ε4- subjects than for memory-impaired APOE-ε4+ subjects and normal adults.
	Amnestic MCI or early AD	3 weeks (20 IU)	Verbal memory	Enhanced verbal memory, selective attention, and functional status. Raised fasting plasma A beta 40/42 ratio.
	Amnestic MCI or AD or healthy subjects	5 days (10, 20, 40, or 60 IU)	Verbal memory	Facilitated recall on two measures of verbal memory in memory-impaired APOE-ε4- adults. Differentially modulated plasma amyloid-β for memory-impaired subjects and normal controls, with effects that differed by APOE genotype.
	Amnestic MCI or mild to moderate AD	4 months (20 or 40 IU)	Dementia Testing	Improved delayed memory with 20 IU intranasal insulin. Preserved cognition and functional abilities with 20 and 40 IU insulin. Correlation between effects on memory and function with CSF Aβ42 and tau/Aβ42.
	APOE-ε4 carriers with mild-moderate AD	Single dose (40 IU)	Memory	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.

Mol Metab. 2016 Aug; 5(8): 589–601. 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