Tartu 2009 I

Introduction to Neuropathology

& General Aspects

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Special Features of the CNS

- Complex and diverse topography
- Complex and diverse cytology
- Axoplasmic transport
- Myelin
- 3 classes of intermediate filaments –
  neurofilaments, glial fibrillary acidic protein, vimentin
- Neurotransmitters
- Separate population of interstitial cells-glia
- Blood brain barrier
- Cerebrospinal fluid
- Absent lymphatic vessels and lymph nodes
- Special aspects of cranial cavity (intracranial pressure)

Neuropathology – in a broader sense

Neurology of the

Central Nervous System
(Brain and spinal cord, incl. their coverings)

Peripheral Nervous System
(and its coverings)

Skeletal Muscle

Neuropathology in a limited sense

Neuropathomorphology

General Neuropathology =

Neuropathology-related Special Features

Cell Pathology

General „Organ Pathology“

General Principles of neuropathologic disease groups

Neuropathology of

Nerve cells

Glial cells

- Oligodendroglia
- Astroglia and Ependyma
- Microglia

blood brain barrier

peripheral nerves

skeletal muscle

Keyhole Neuropathology

- Brain biopsy
- Nerve biopsy
- extracerebral biopsy in neurodegenerative diseases
  - → in adults
  - → in children

General Principles of Neuropathologic Groups of Diseases

Neurodegenerative Diseases
  Neurometabolic Diseases

Inflammatory Diseases
  Infections
  Autoimmune processes

Toxic Diseases

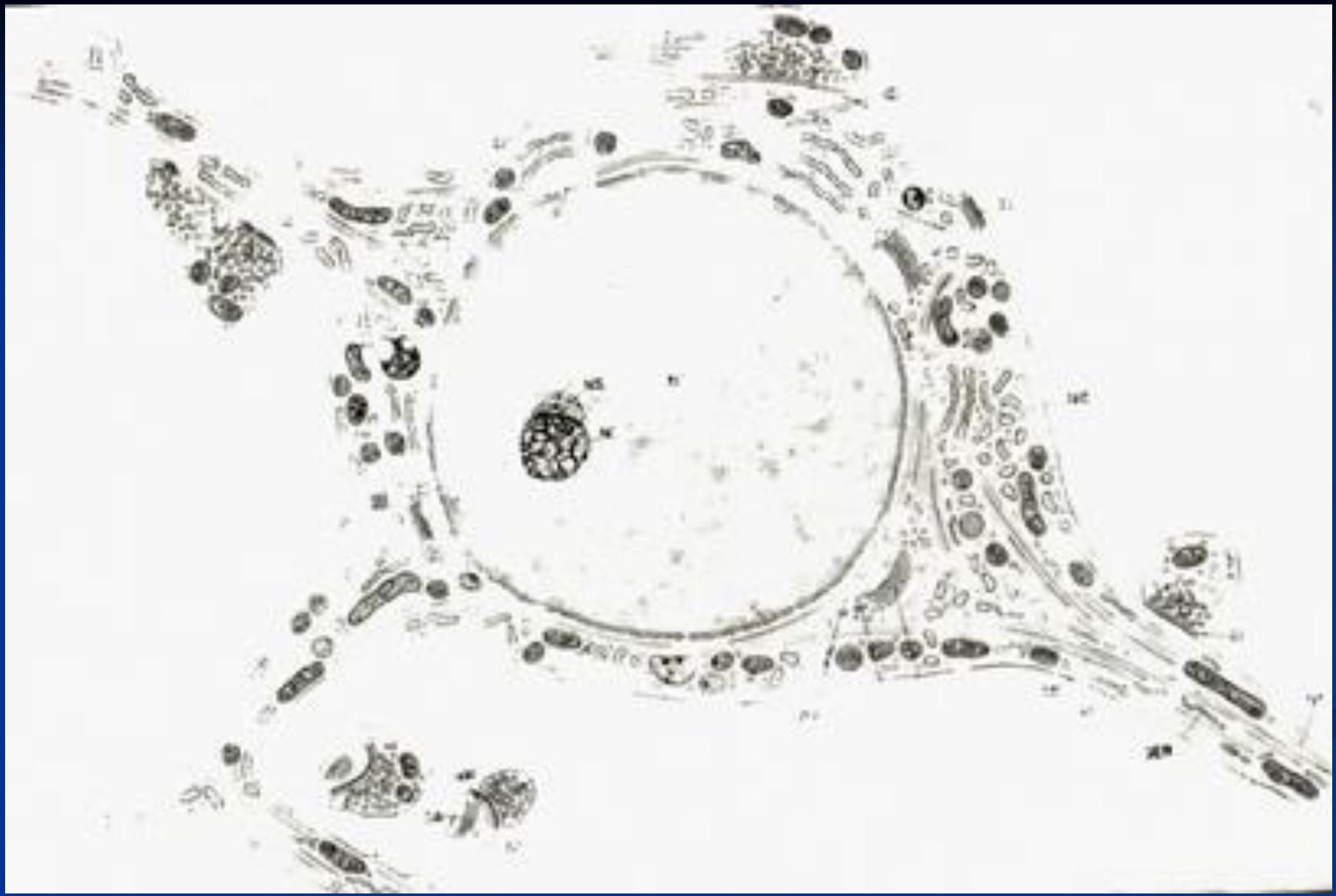
Malformations

Tumors
Circulation Diseases

I. Pathologic Reactions in the CNS

II. Brain Edema

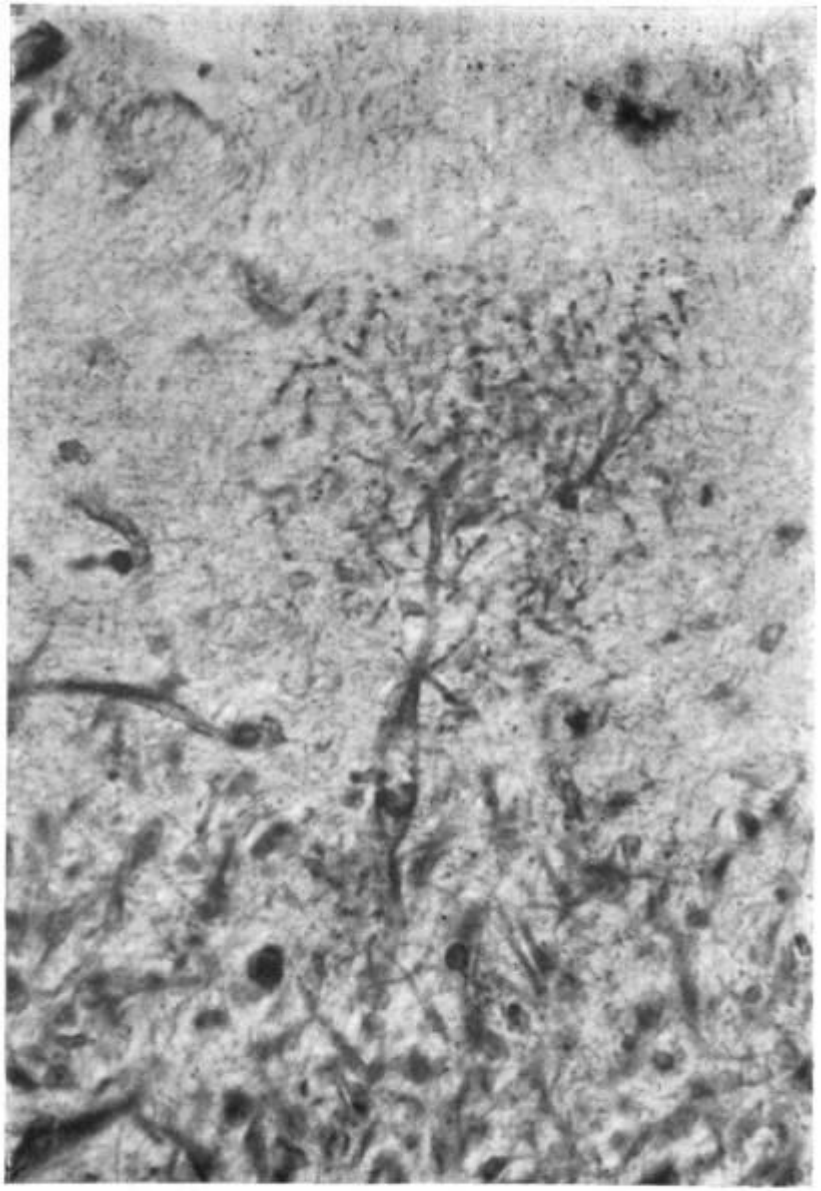
Neuronal Reactions



Pathology of Neuronal Processes

Dendrites

Axons



13-year-old girl with Janský–Bielschowsky type. Purkinje cell with severely stunted dendritic apparatus. $NADH_2$-diaphorase.

Axonal Transport

Anterograde / Orthograde

Fast:

I	100 - 400 mm/day	-	Polypeptides
II	20 - 70 mm/day	-	Polypeptides
III	3 - 20 mm/day	-	Polypeptides

Slow:

IV / V	0,1 - 4 mm/day	-	Components of cytoskeleton and membrane skeleton and associated proteins incl. cytoplasmic enzymes

Retrograde

Pathology of Neuronal Processes

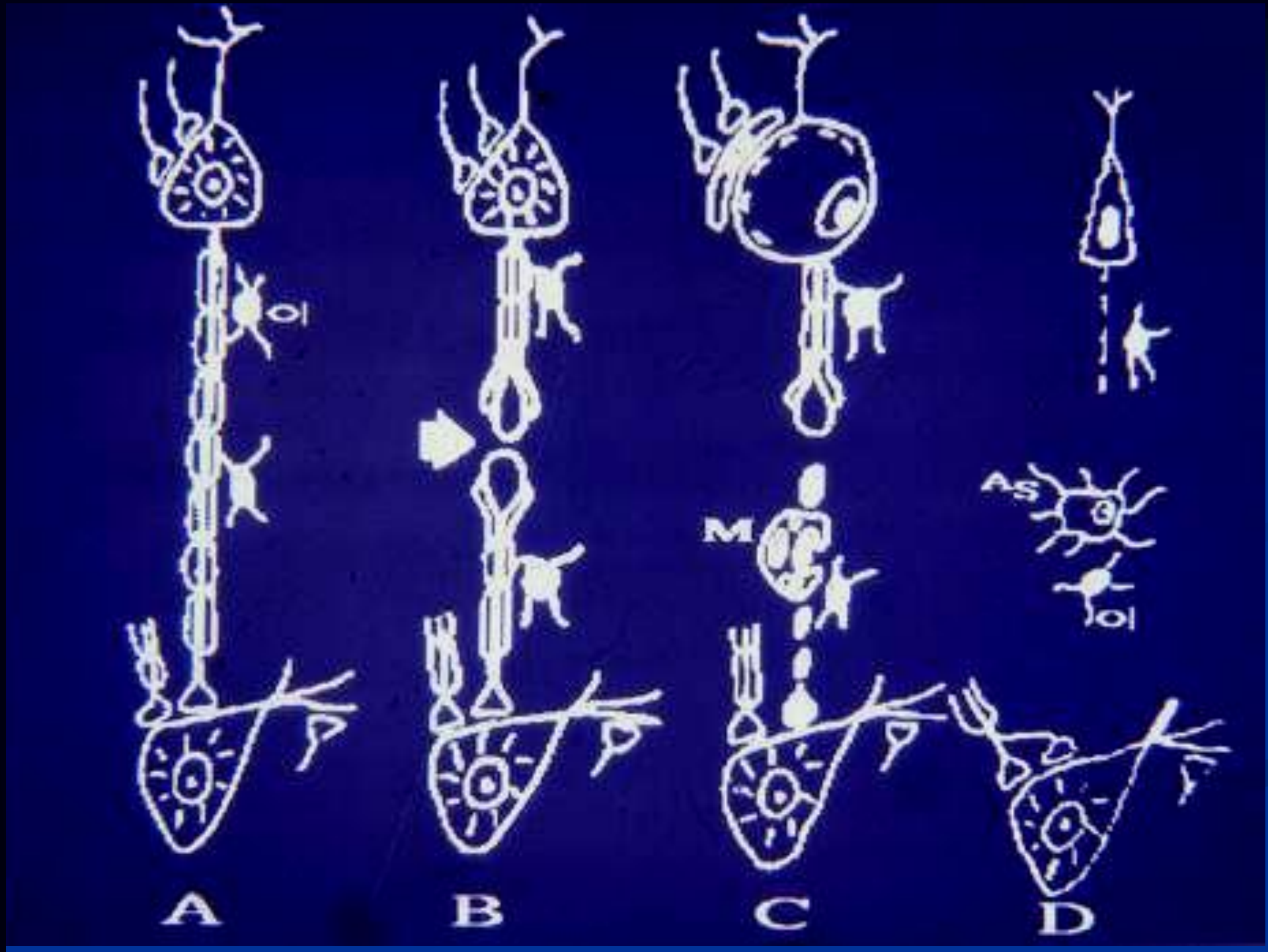
Wallerian degeneration

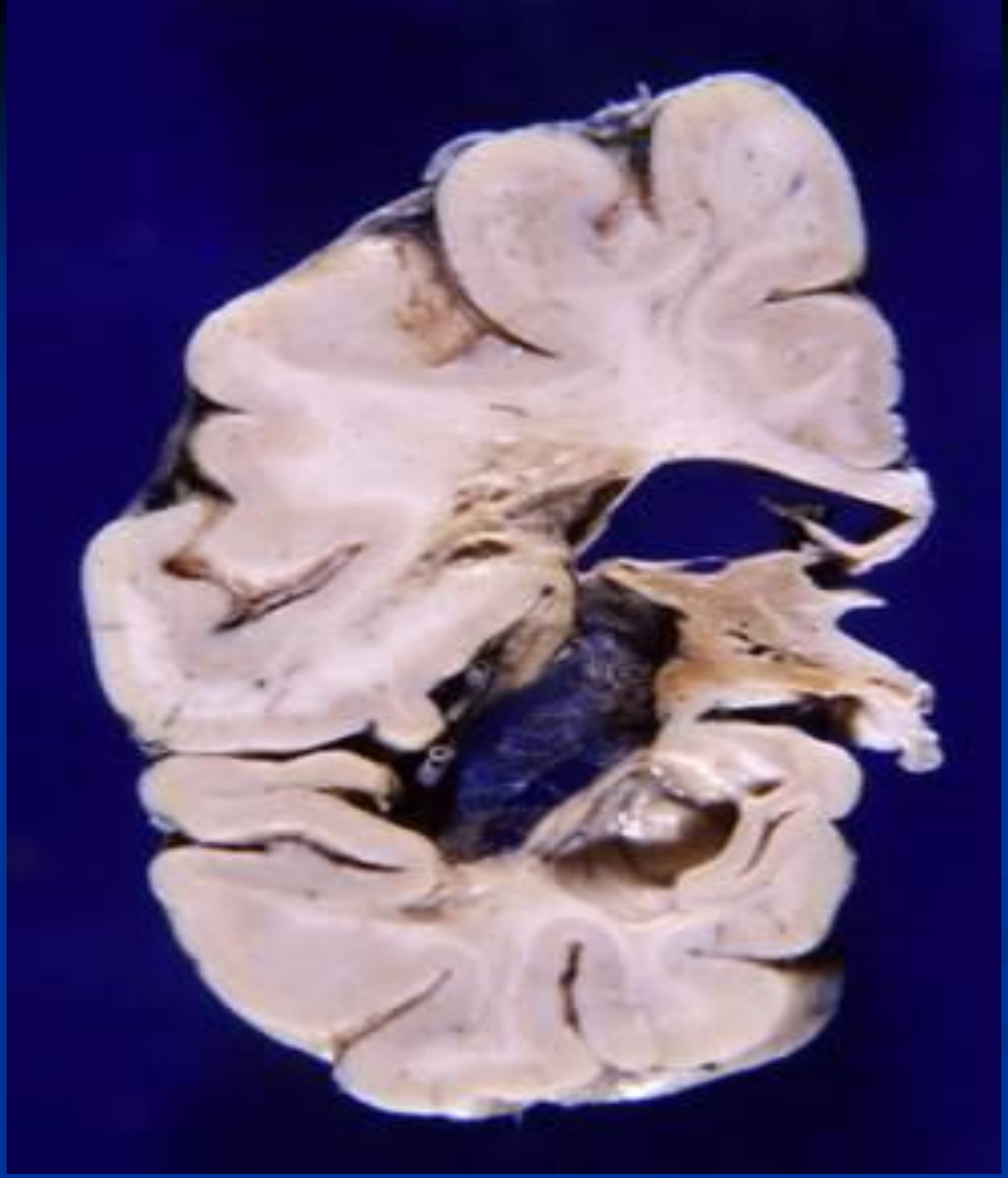
Retrograde reaction

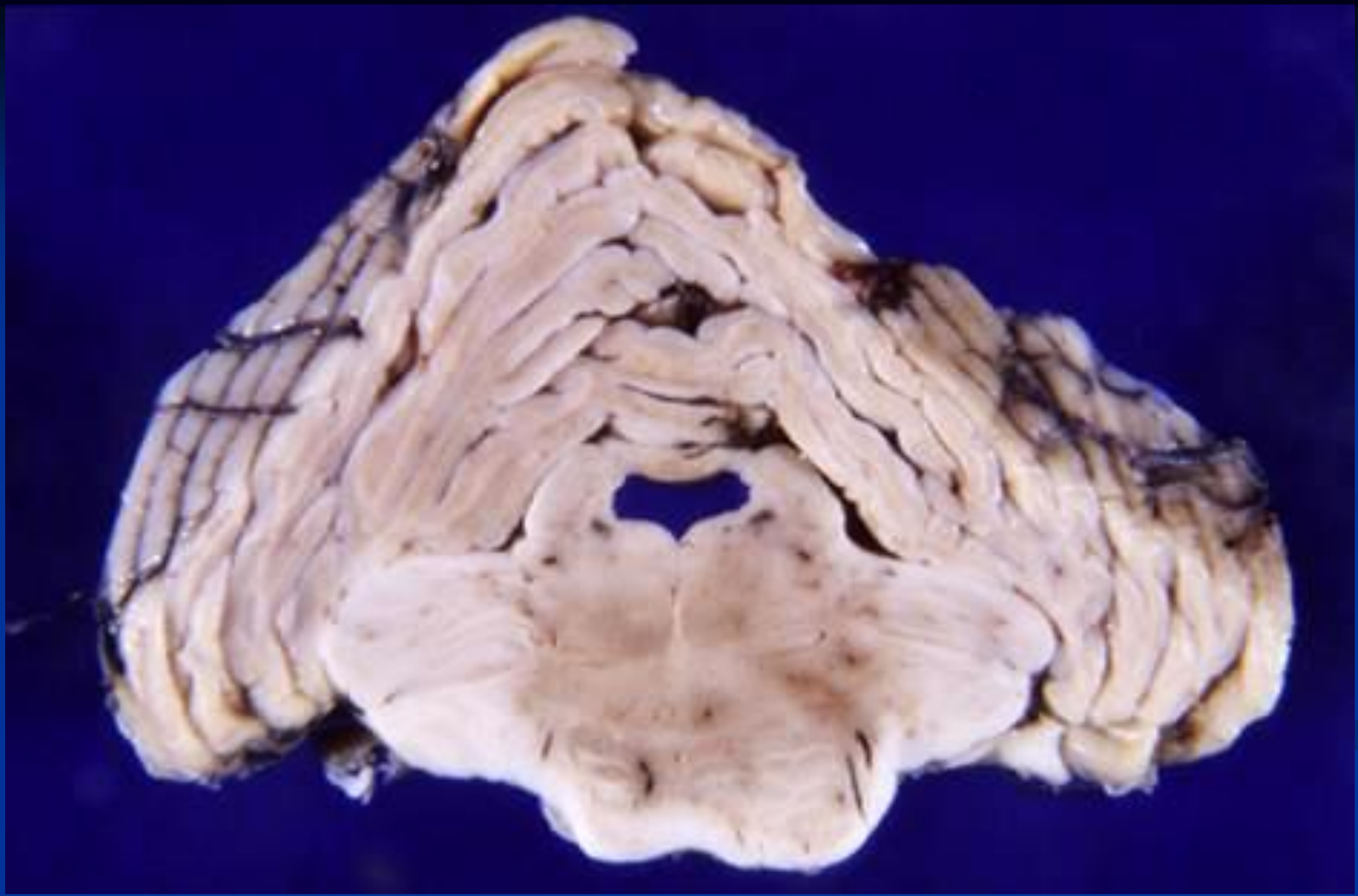
Anterograde transneuronal degeneration

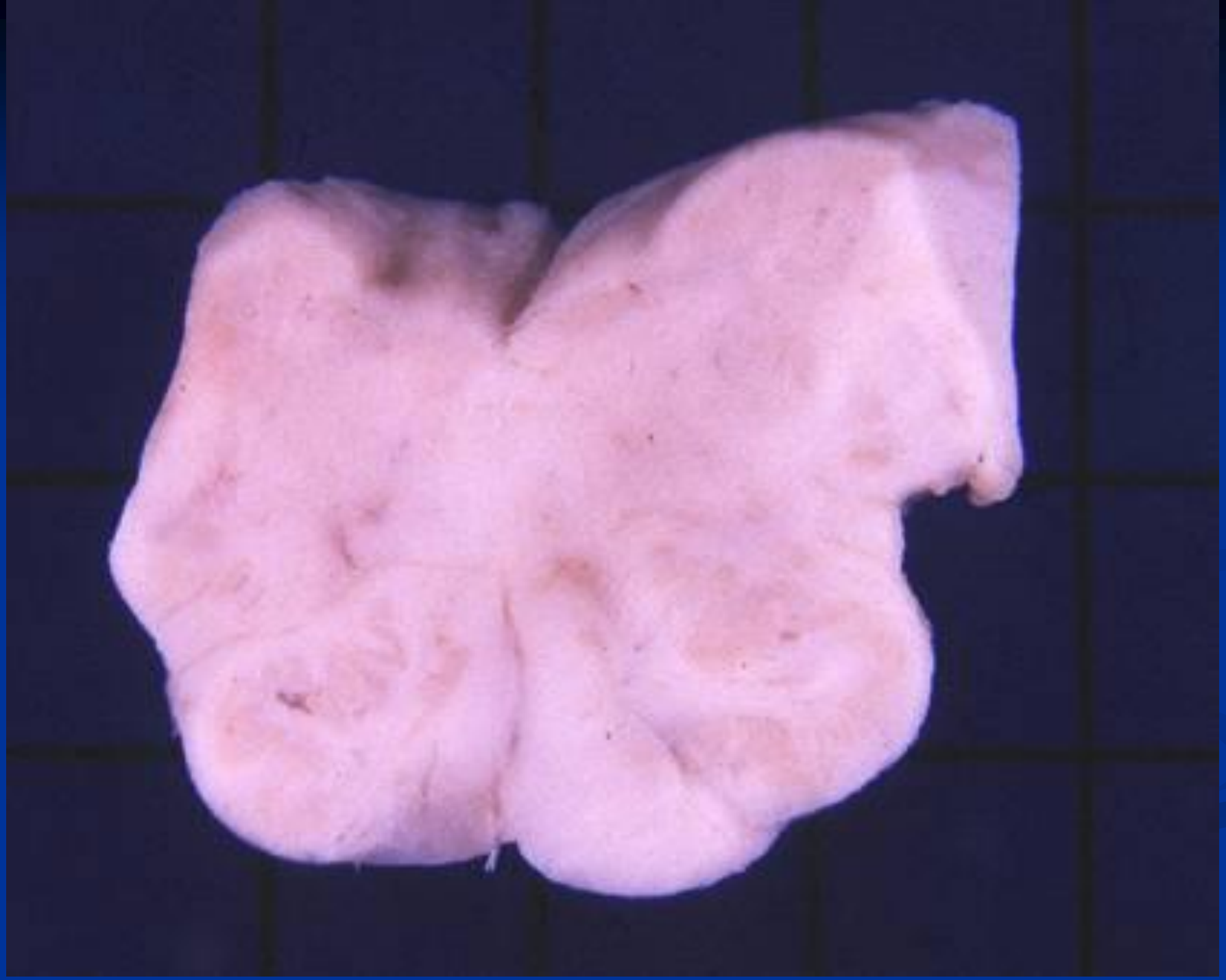
Retrograde transneuronal degeneration

Wallerian Degeneration


OI
M
AS
OI
A
B
C
D







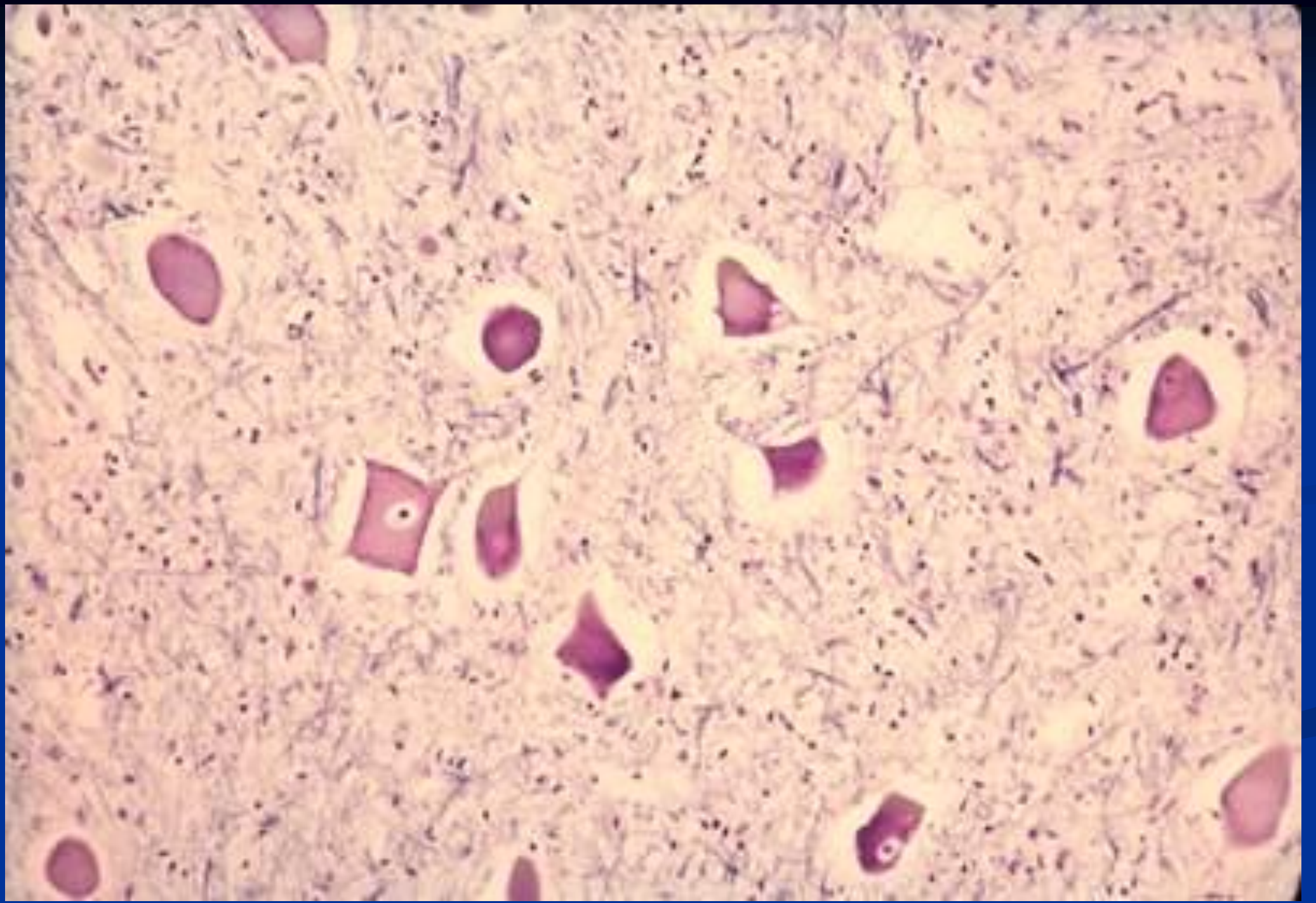
Anterogade transneuronal Degeneration

loss of eye lesion of optic nerve	→	lateral geniculate body
lesions of fornix	→	mamillary bodies
loss of sensory fibers in posterior spinal columns	→	gracilis and cuneate nuclei
loss of cortico-pontine fibers	→	pontine nuclei


M
L

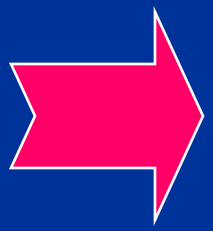
(Central) Chromatolysis – „axonal“ Reaction

- rounding of perikaryon
- loss of central Nissl bodies
- peripheral displacement of nucleus
- retraction of presynaptic terminals



Retrograde Transneuronal Degeneration

Lesions of the optic radiation and calcarine region



degeneration of retinal cells ganglion

Factors which impair Regeneration of CNS Axons

Lack of matrix-proteins,

e.g. laminin and fibronectin

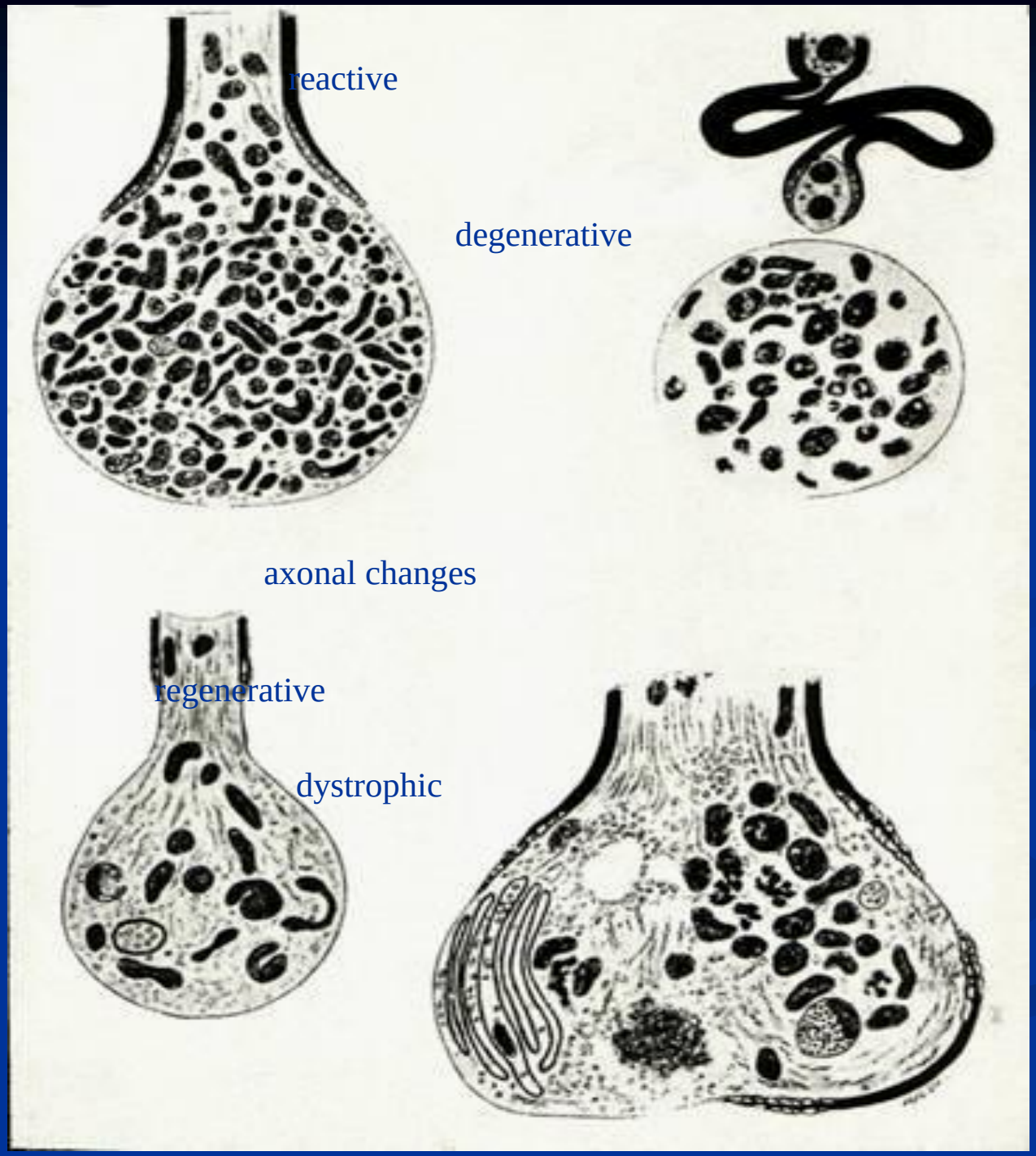
Lack of growth factors,

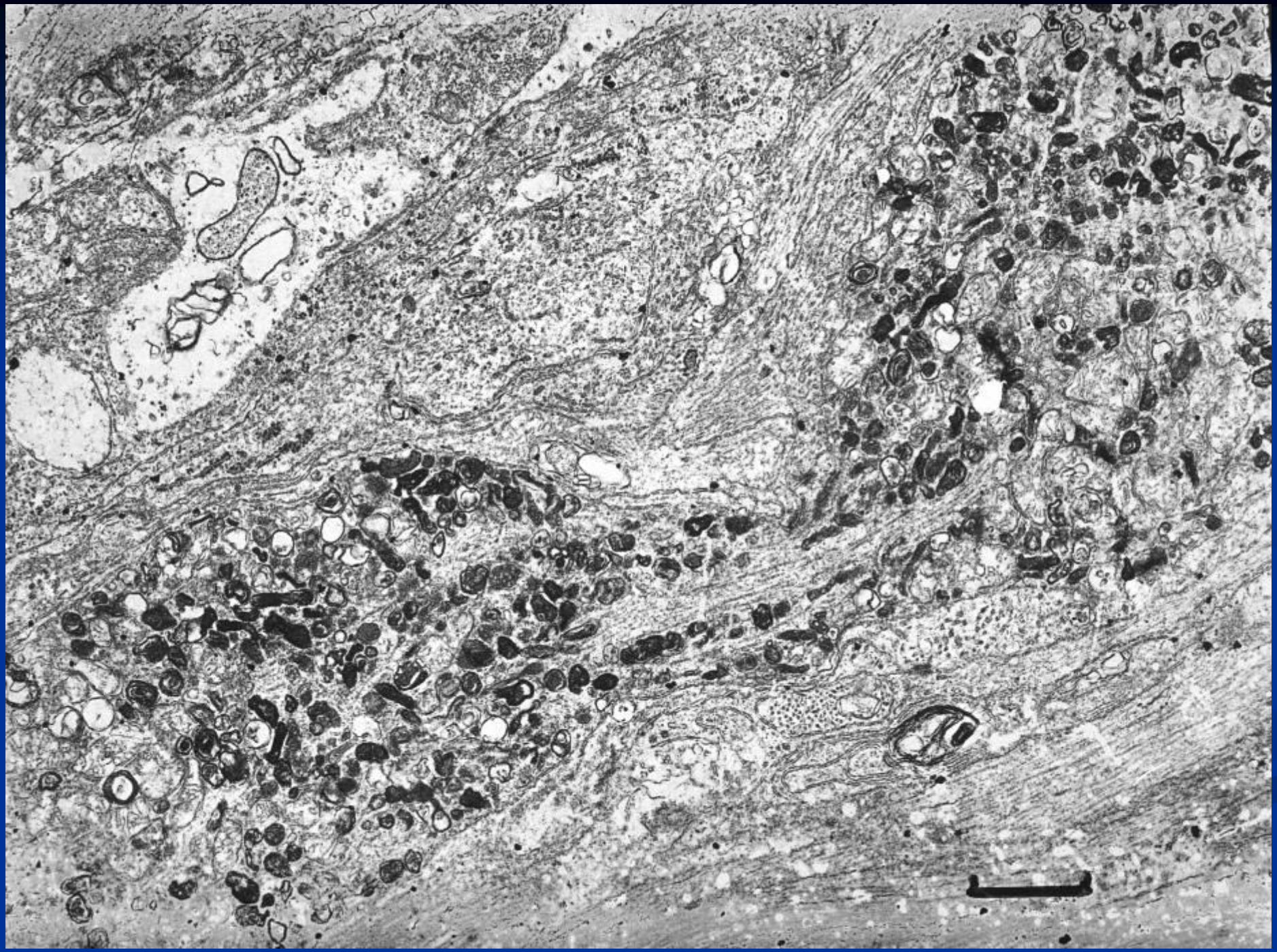
e. g. GAP 43

Formation of inhibitory proteins,

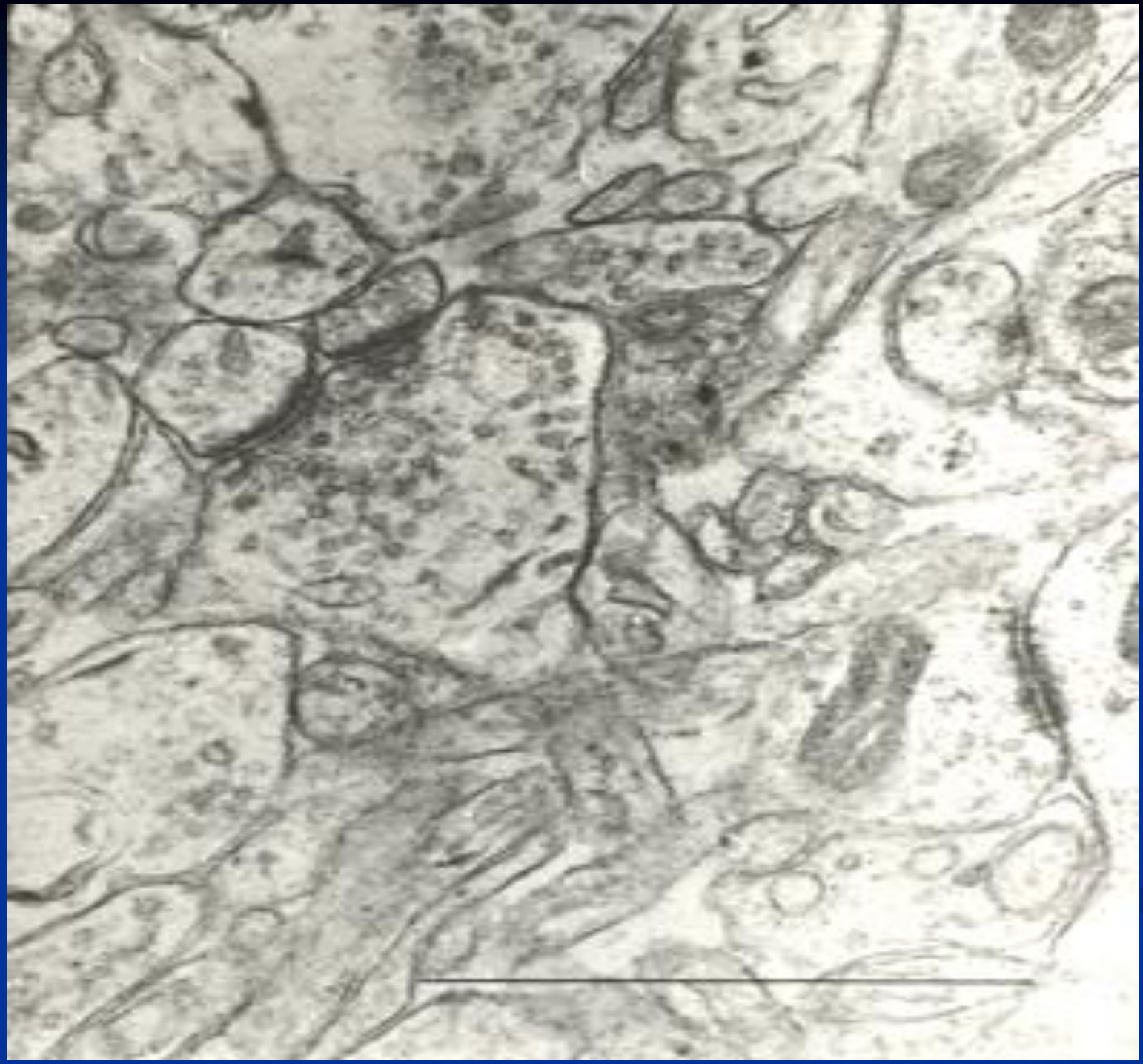
e.g. oligodendroglial glycoproteins

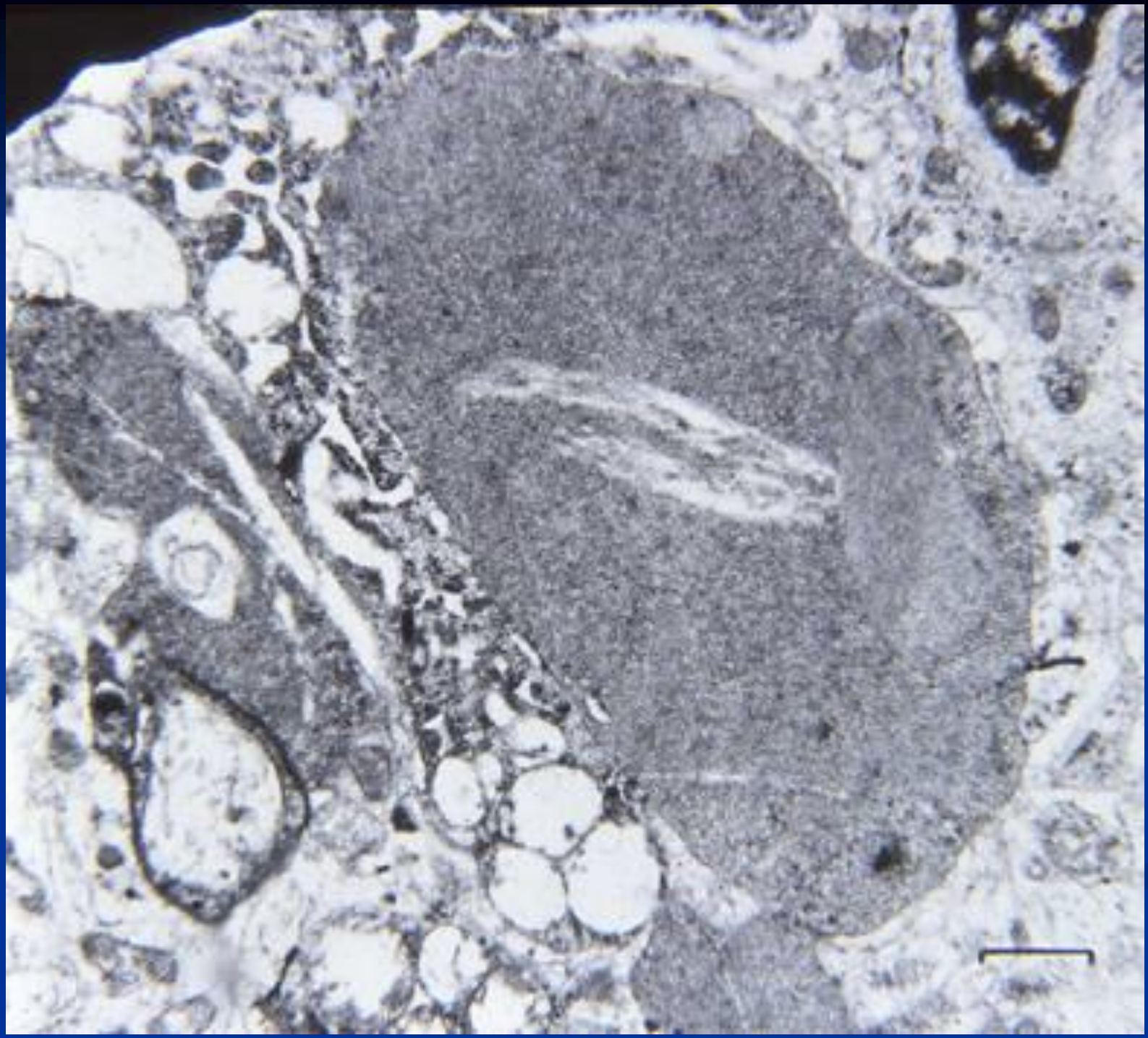
Formation of glial scars


reactive
degenerative
axonal changes
regenerative
dystrophic



Neuroaxonal Dystrophies





Pathology of the Neuronal Perikaryon

retrograde reaction

vacuolisation

cell death

atrophy

aggregation of
- proteins
- lysosomal substrates
- viruses

Cell Death

Types of Cell Death

necrosis

apoptosis

autophagy

„loss“

STAGES OF HYPOXIC NEURONAL DAMAGE

I. MICROVACUOLATION

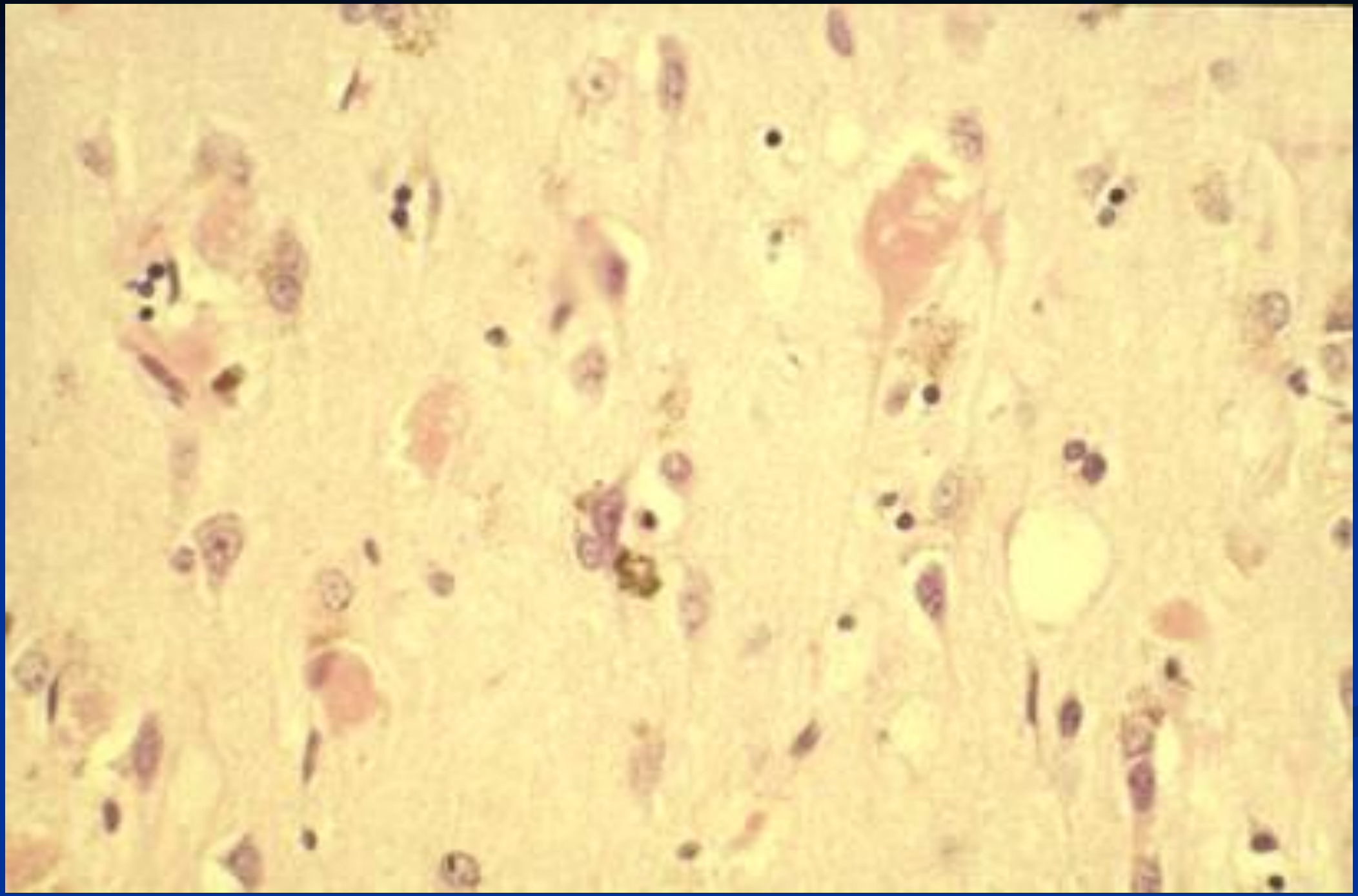
II. ISCHEMIC CELL CHANGE

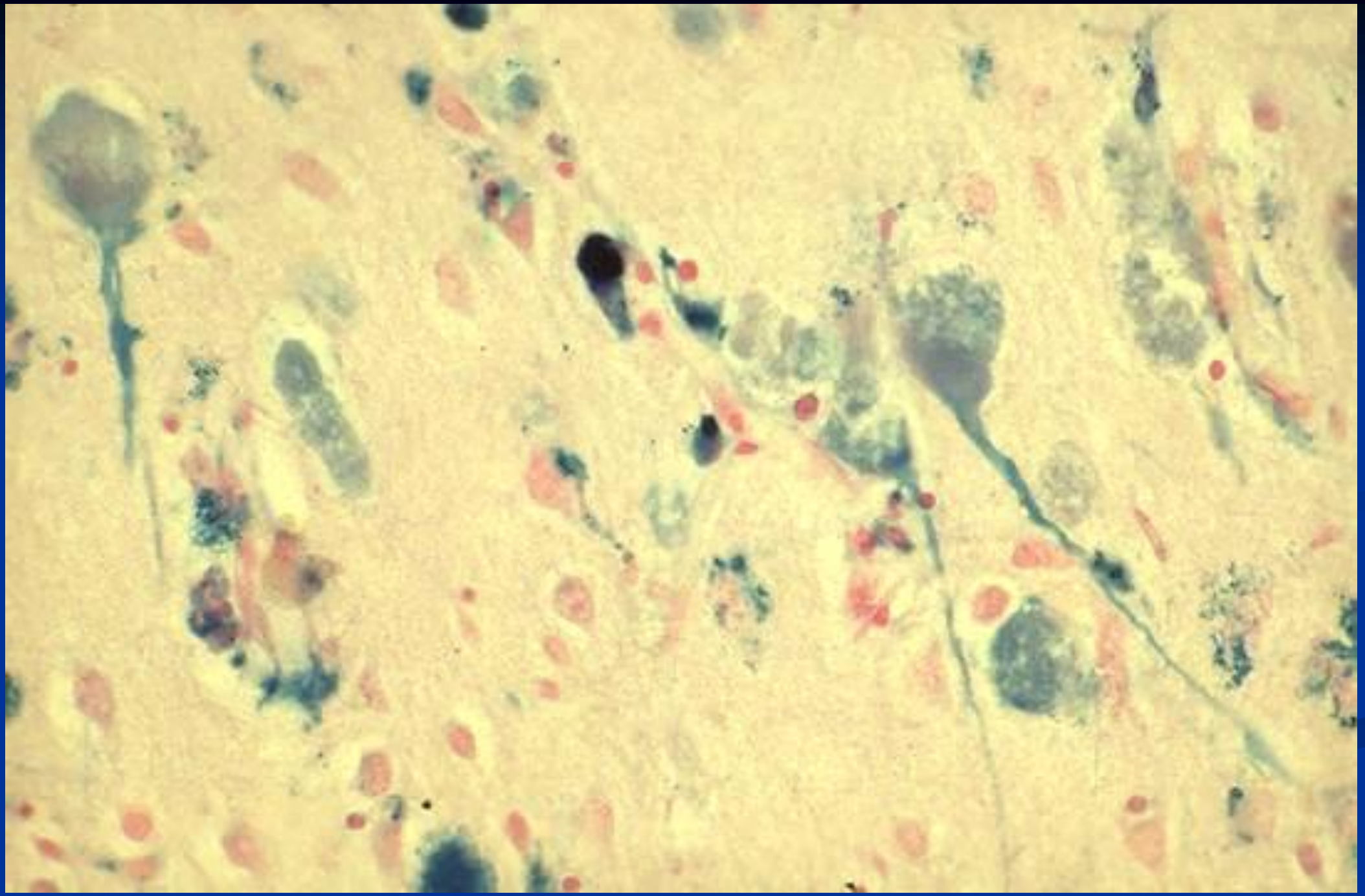
III. INCRUSTATIONS

IV. HOMOGENIZING CELL CHANGE

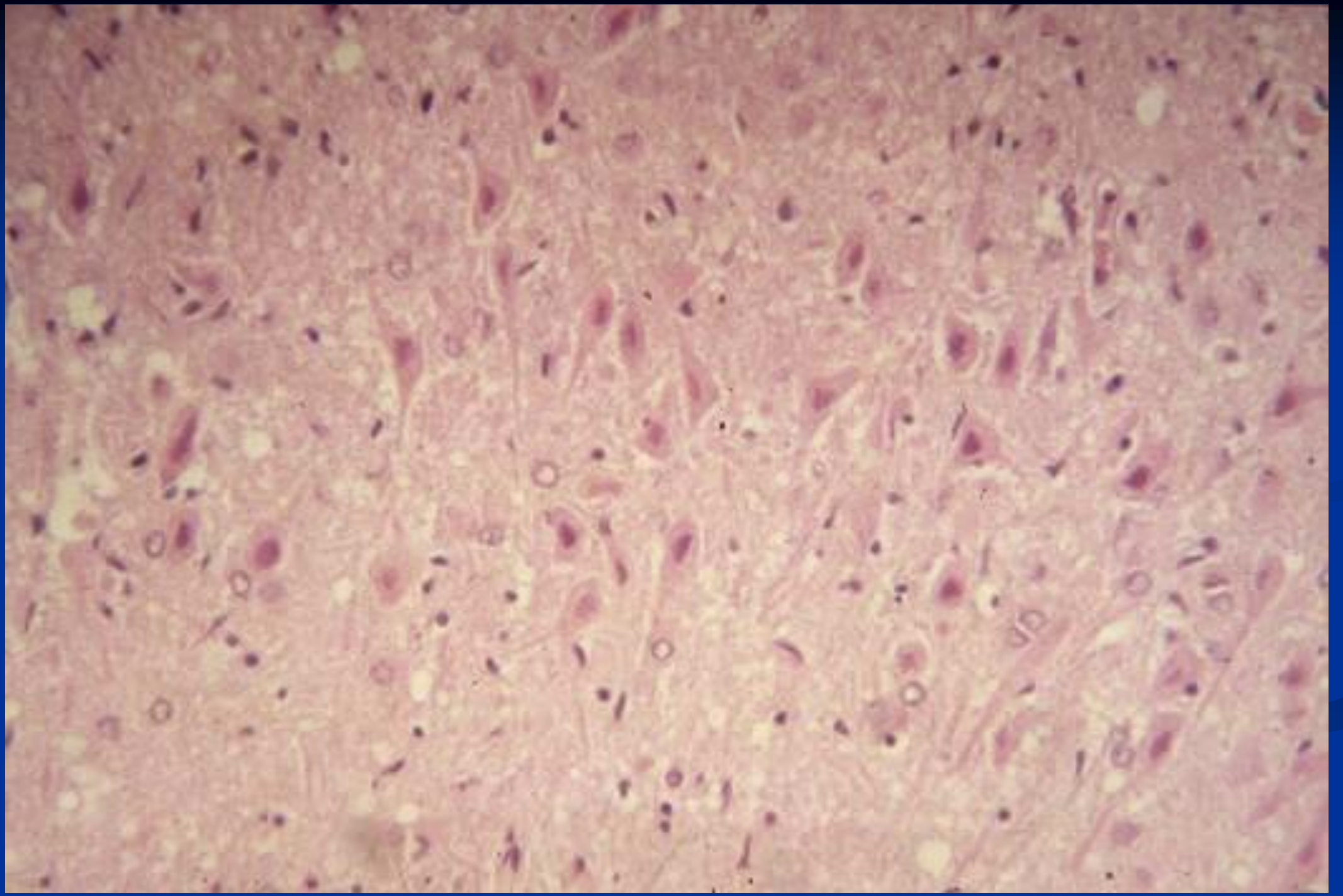
V. BARE PYCNOTIC AND FRAGMENTED NUCLEI

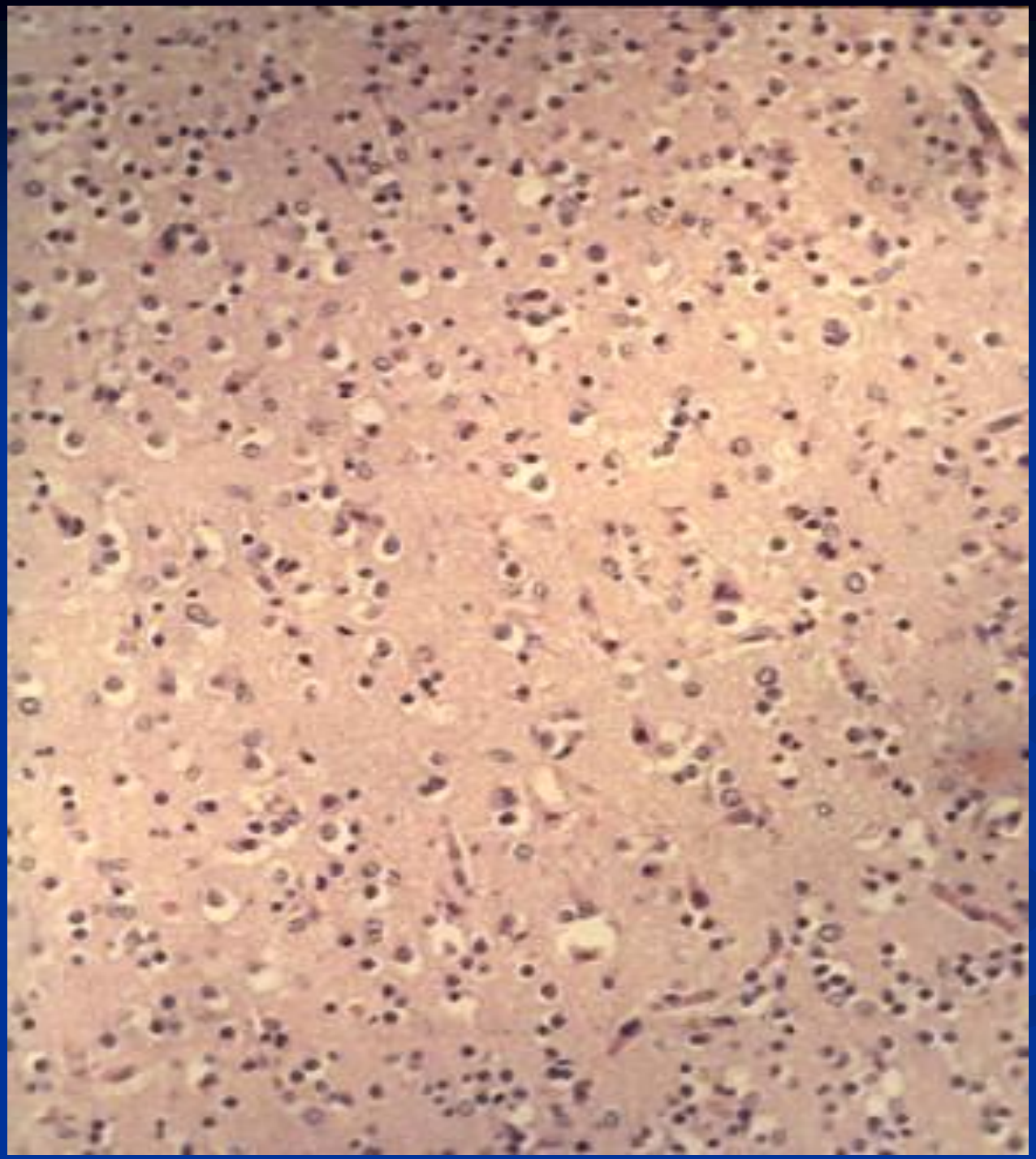
VI. NEURONOPHAGY





Necrophanerosis





Elective Parenchymal Necrosis

=

selective neuronal necrosis

Causes of elective Parenchymal Necrosis

Anoxia / Hypoxia

Cardiac arrest

Anaemia

CO intoxication

Pulmonary disease

Hypoglycaemia

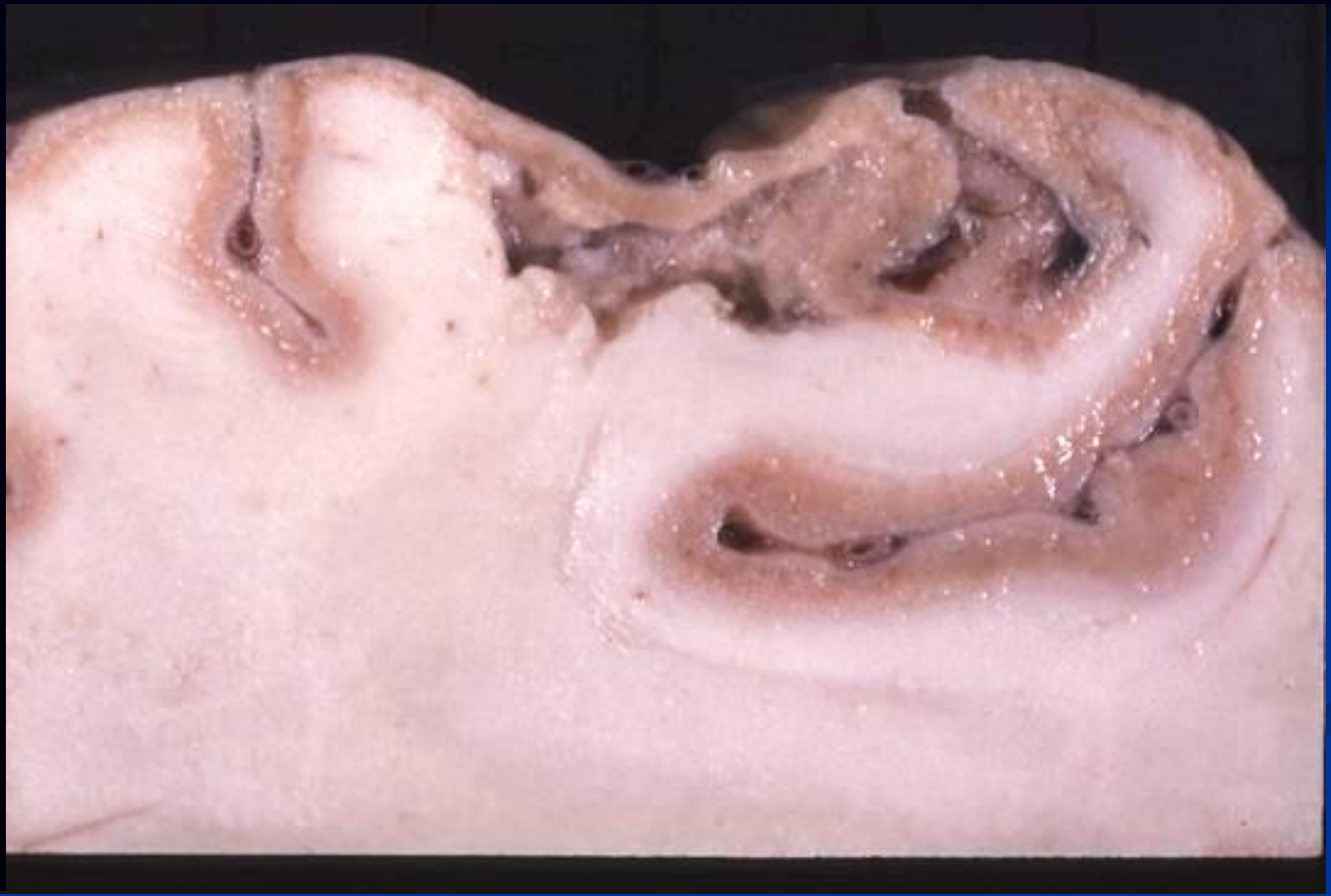
Regions of elective Parenchymal Necrosis

Purkinje cells (cerebellar cortex)

Pyramidal cells of cortex, incl. hippocampus (cerebral cortex)

Striatal neurons

Thalamic neurons



Tissue Death

Types of Tissue Necrosis

Coagulation necrosis

hemorrhagic necrosis

liquefaction necrosis

caseating necrosis (TB)

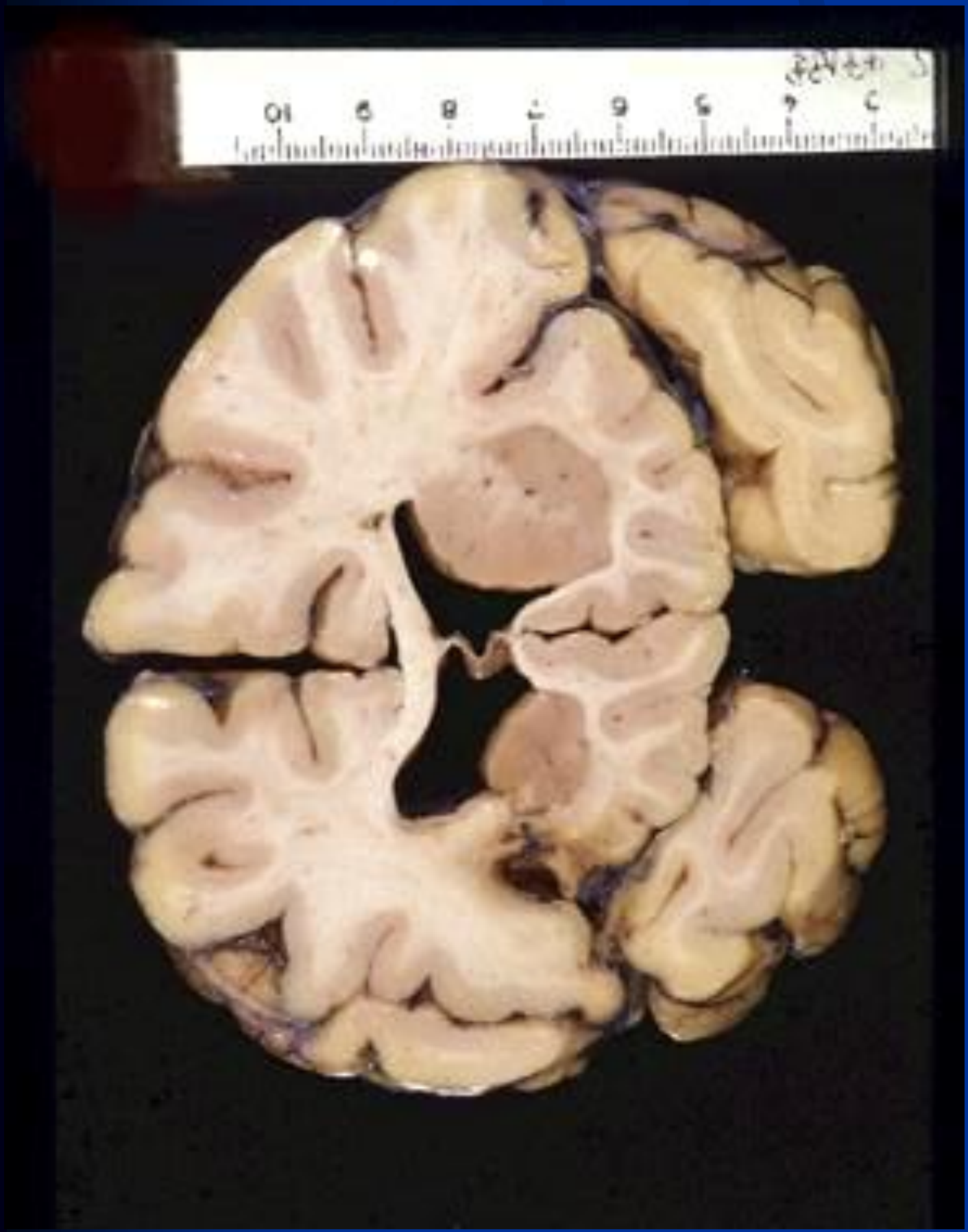
gummous necrosis (Syphilis)

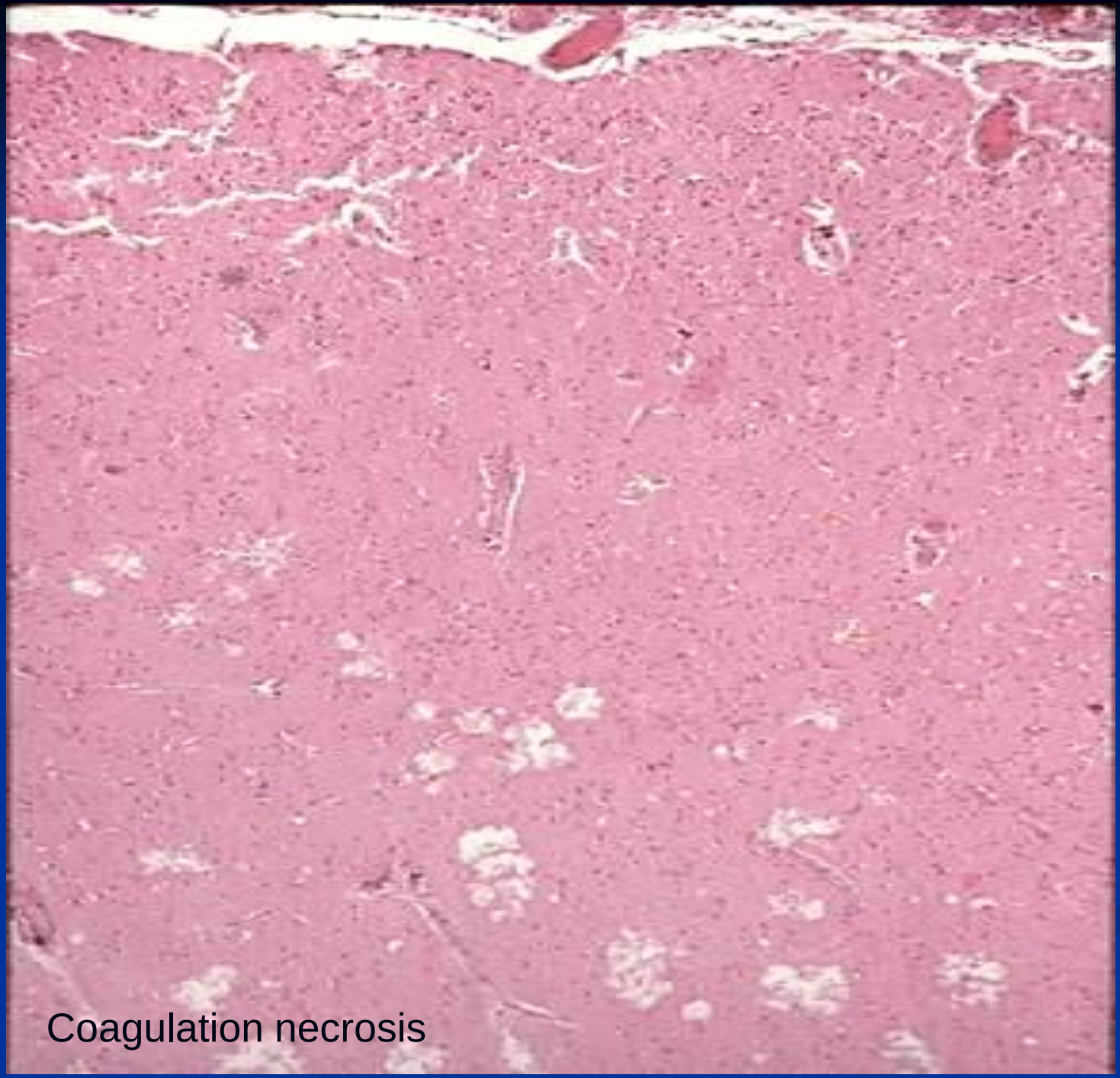
fibrinoid necrosis (arteries)

Infarct

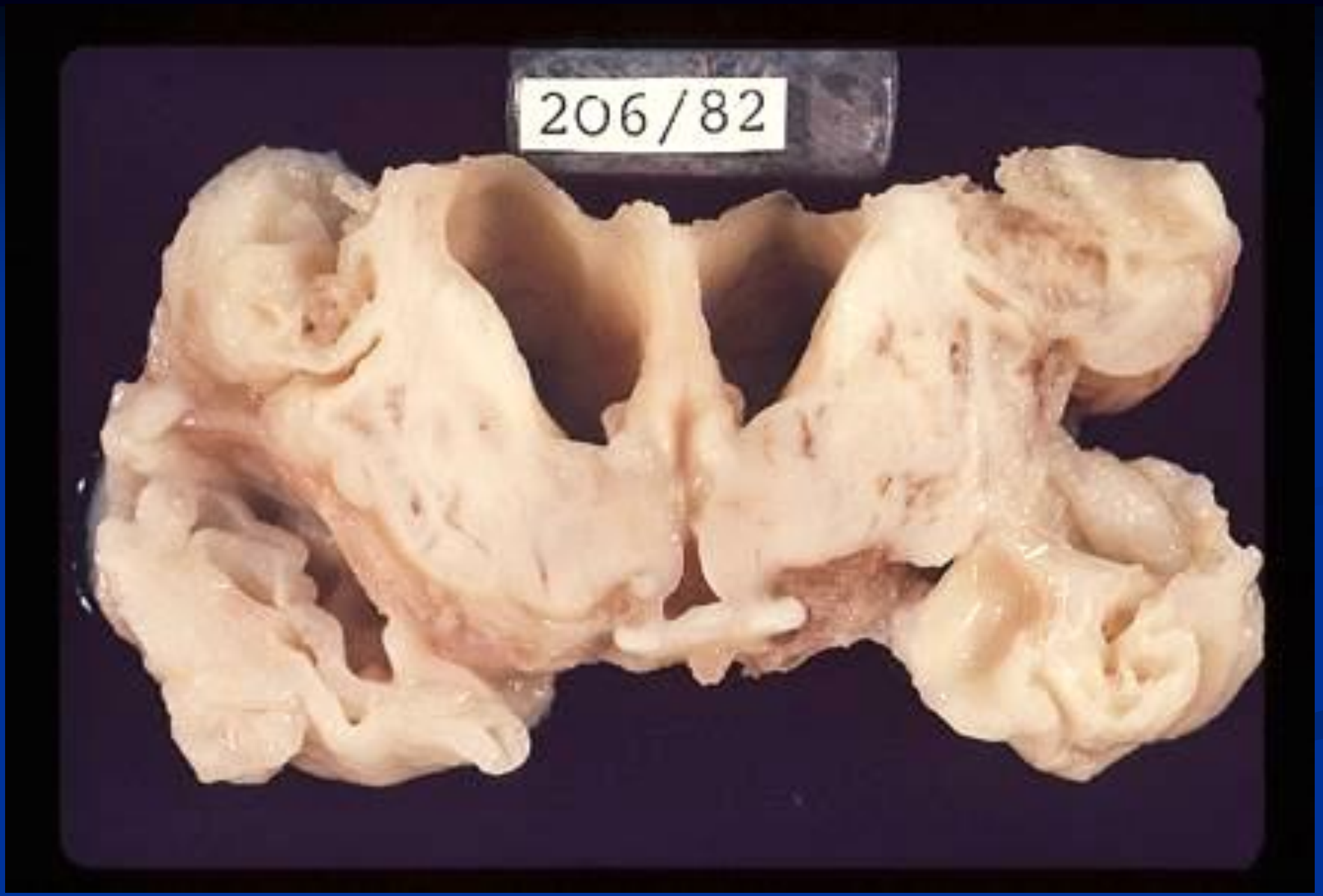
focal tissue necrosis owing to insufficient local blood supply

= Ischemia





Coagulation necrosis


206/82

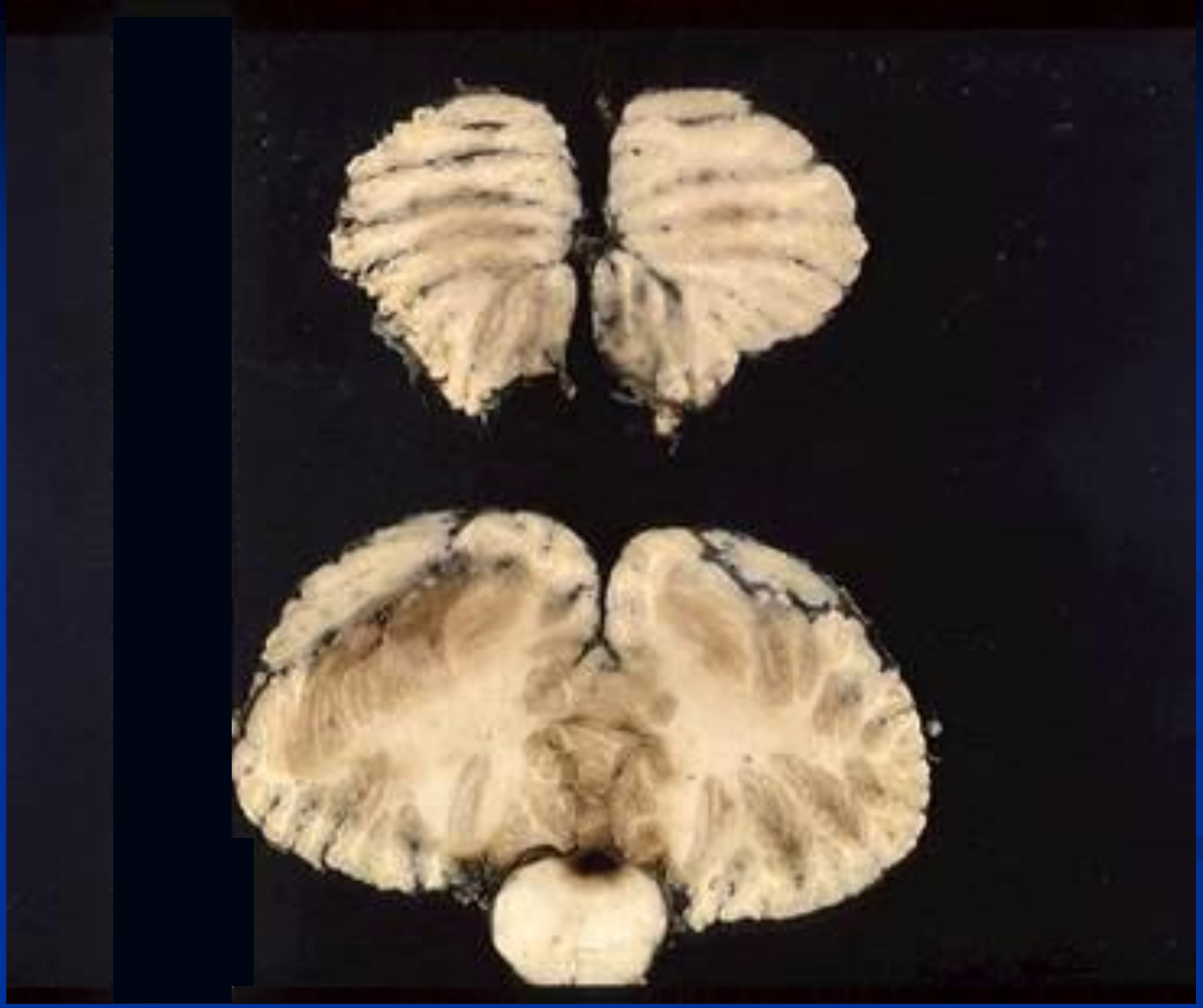
Antemortem brain death

Dissociated (brain)death

Complete infarct of the brain

Antemortem autolysis of the brain

Respirator brain



Morphological Criteria for:

Necrosis

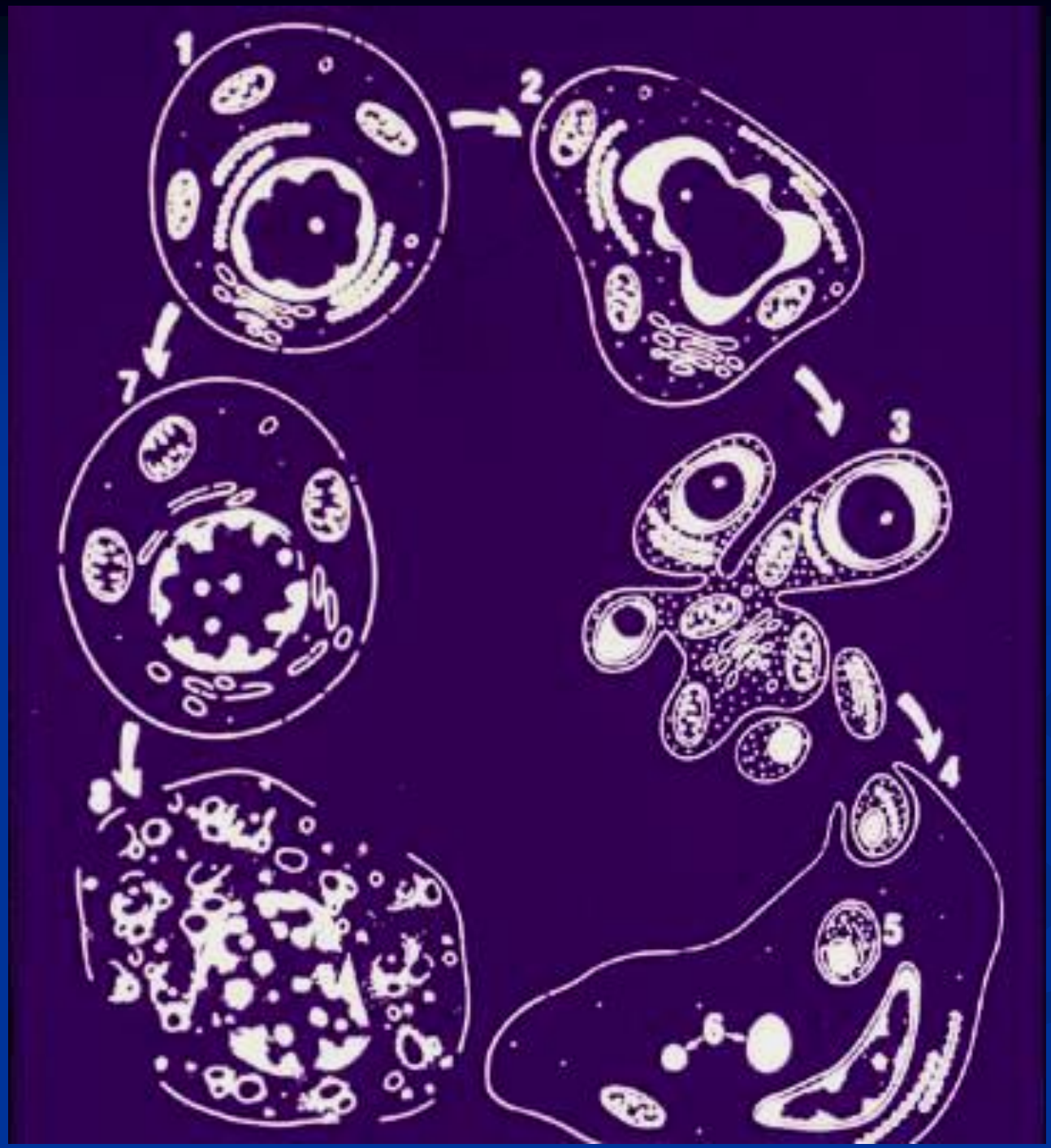
- *Passive* process

Apoptosis

- *Active* process

Morphological differences between necrotic and apoptotic cell death

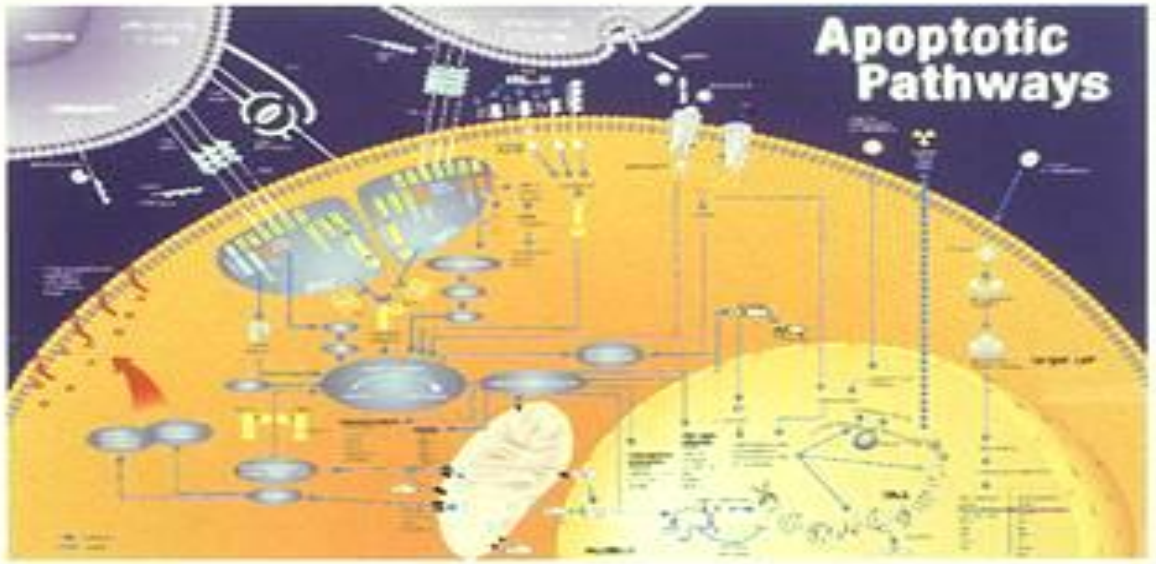
Morphology	Necrosis	Apoptosis
cell	swells	shrinks
nuclear chromatin	disintergrates	condenses, strand breakage
other organelles	swell	normal
cell membrane	ruptures, blebs	remains intact, later: budding
surrounding tissue	inflammation	phagocytosis


1
2
3
4
5
6
7

Phases of Apoptosis:

Initiation phase:	different stimuli
Effector phase:	common to all cells
Degradation phase:	metabolic enzymes activated

Guide to Apoptotic Pathways



Demonstration of APOPTOSIS:

TUNEL technique (terminal deoxynucleotidyl transferase-mediated dUTP biotin end labeling)

ISEL (*in situ* **end labeling**)

pro-Apoptosis

- **bax** (bcl-2-associated X protein)
- **ICE** (interleukin-1β converting enzyme)
- **APO-1/Fas**

anti-Apoptosis

- **bcl-2**
- **bcl-xL**

PROTEINS of the Bcl-2 family involved in Apoptosis:

Inducing:

Bax
Bak

Suppressing:

Bcl-2
Bcl-x_L
Bcl-w
Mcl-1
A1

Virus proteins:

BHRF1 (*Epstein-Barr* virus)
LMW5 HL (*African swine fever* virus)
E-1B 19K (*Adeno*virus)

Location:

Endoplasmic reticulum
Nuclear membrane
Outer mitochondrial membrane

Dimeric partners

Bcl2 — Bax
Bcl-x_L — Bak

Apoptosis in Neuropathology

Axotomy – retrogade

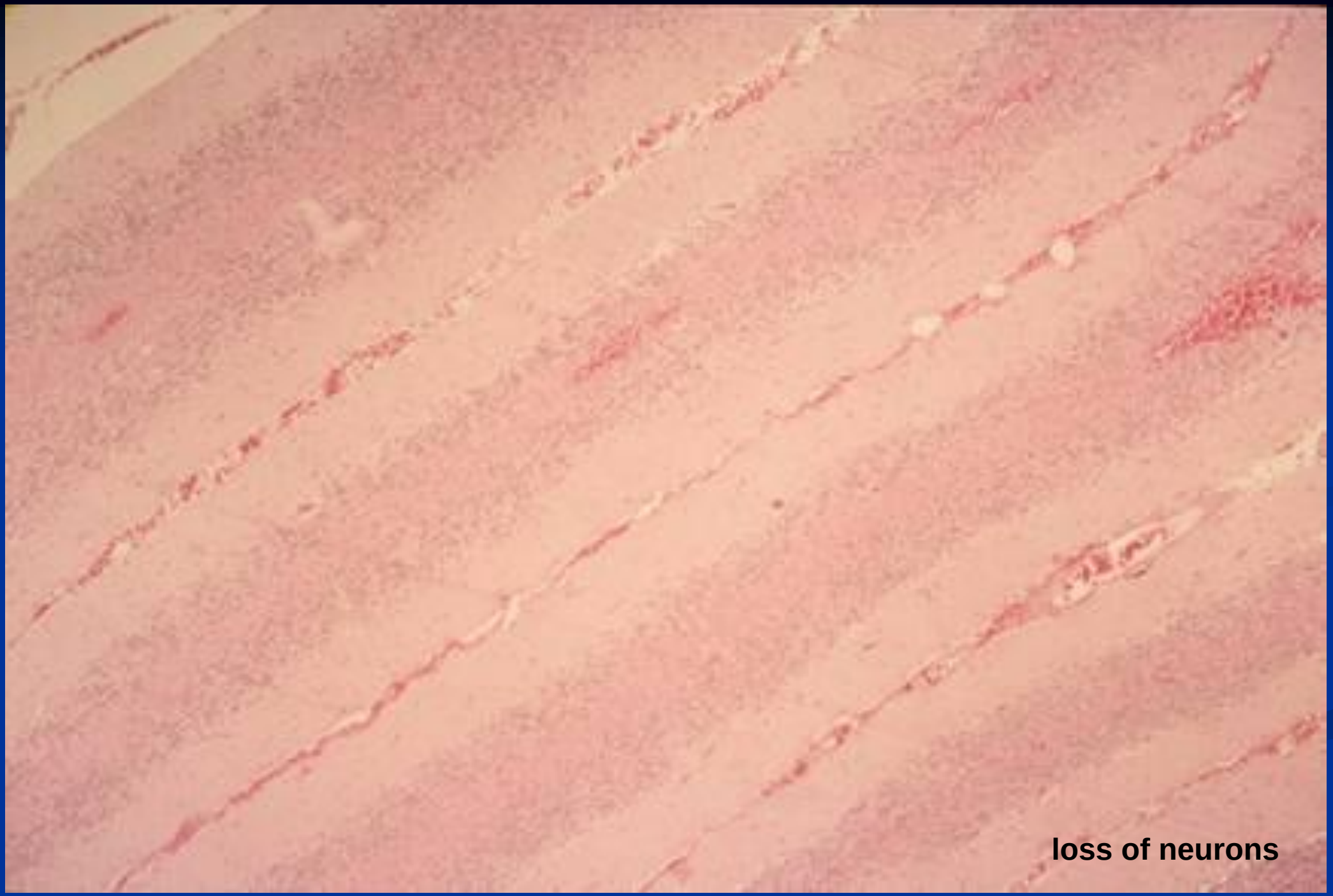
Motor Neuron diseases

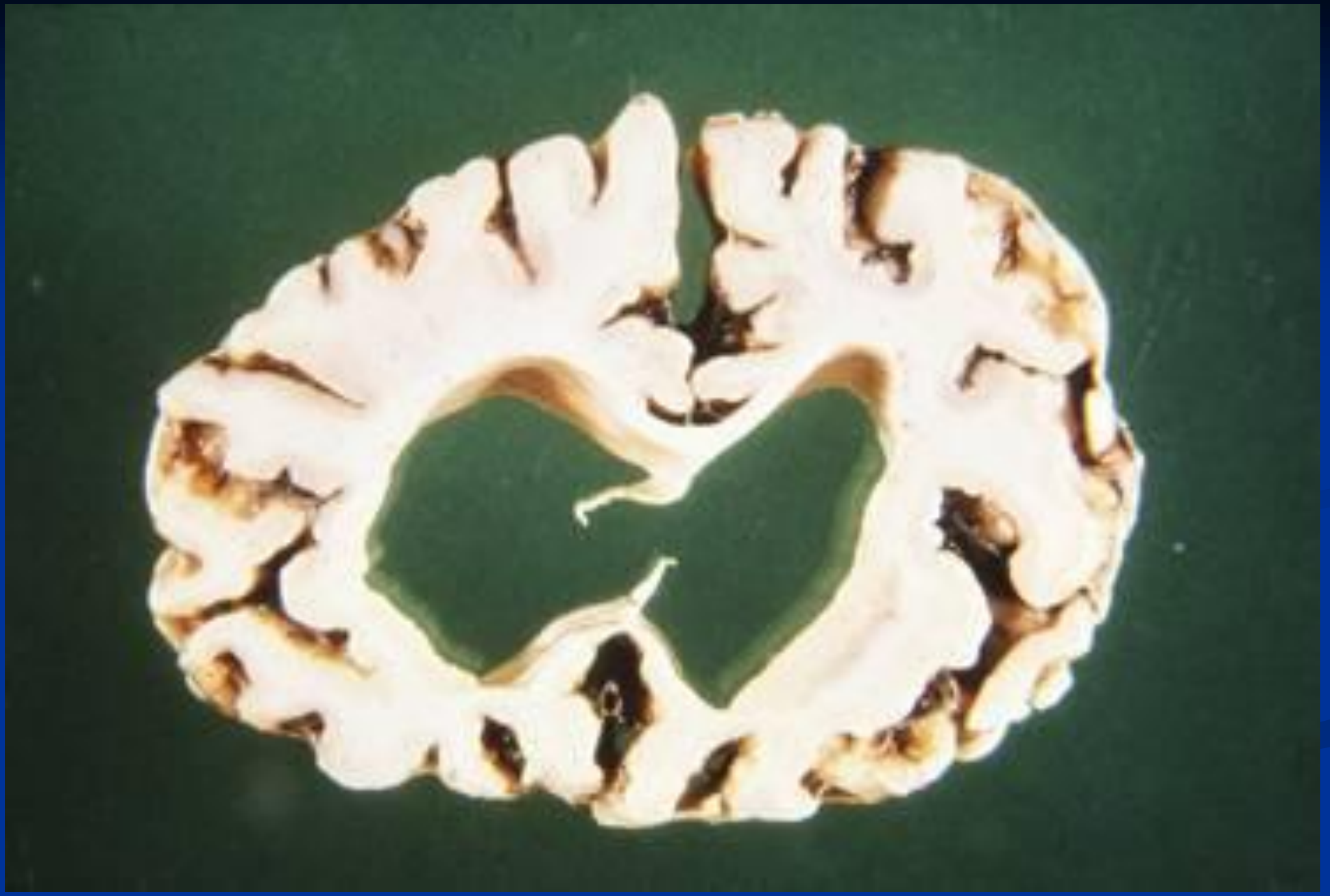
Alzheimer disease

Parkinson disease

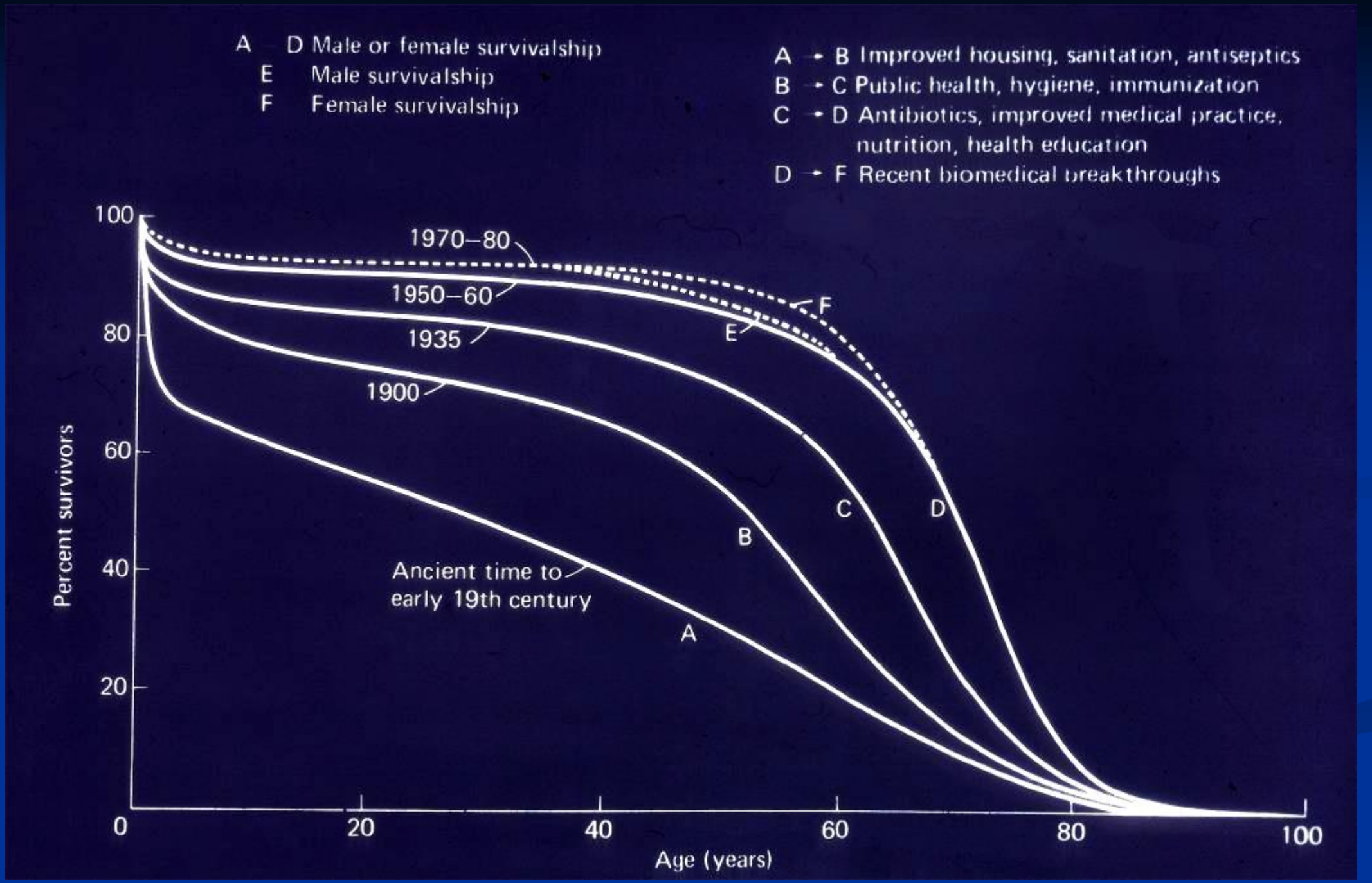
Huntington disease

Ischemia


loss of neurons



Ageing


A D Male or female survivalship
E Male survivalship
F Female survivalship
A → B Improved housing, sanitation, antiseptics
B → C Public health, hygiene, immunization
C → D Antibiotics, improved medical practice, nutrition, health education
D → F Recent biomedical breakthroughs
1970–80
1950–60
1935
1900
Ancient time to early 19th century
A
B
C
D
E
F
Percent survivors
100
80
60
40
20
0
20
40
60
80
100
Age (years)

Cell Biology of Aging

programmed aging

defective DNA-repair

degeneration of extracellular matrix

damage by free radicals

insufficiency of protein degradation

cumulating cell damage

Aging and CNS

Loss of brain weight:
parenchyma, water content

shrinkage of large neurons (loss?)

dendritic proliferation

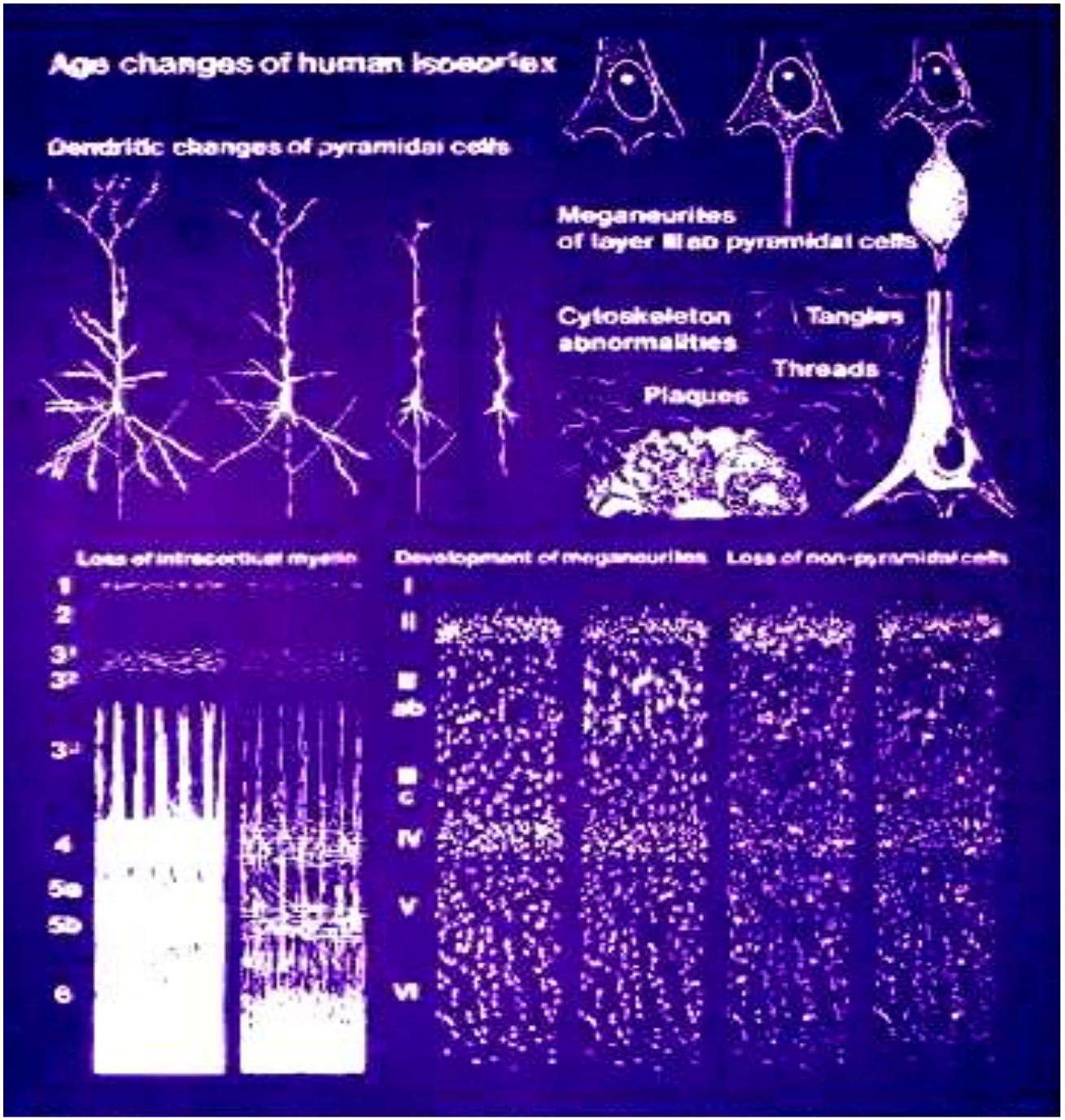
cellular gliosis

NEUROPATHOLOGICAL CHANGES OF AGE IN THE CNS

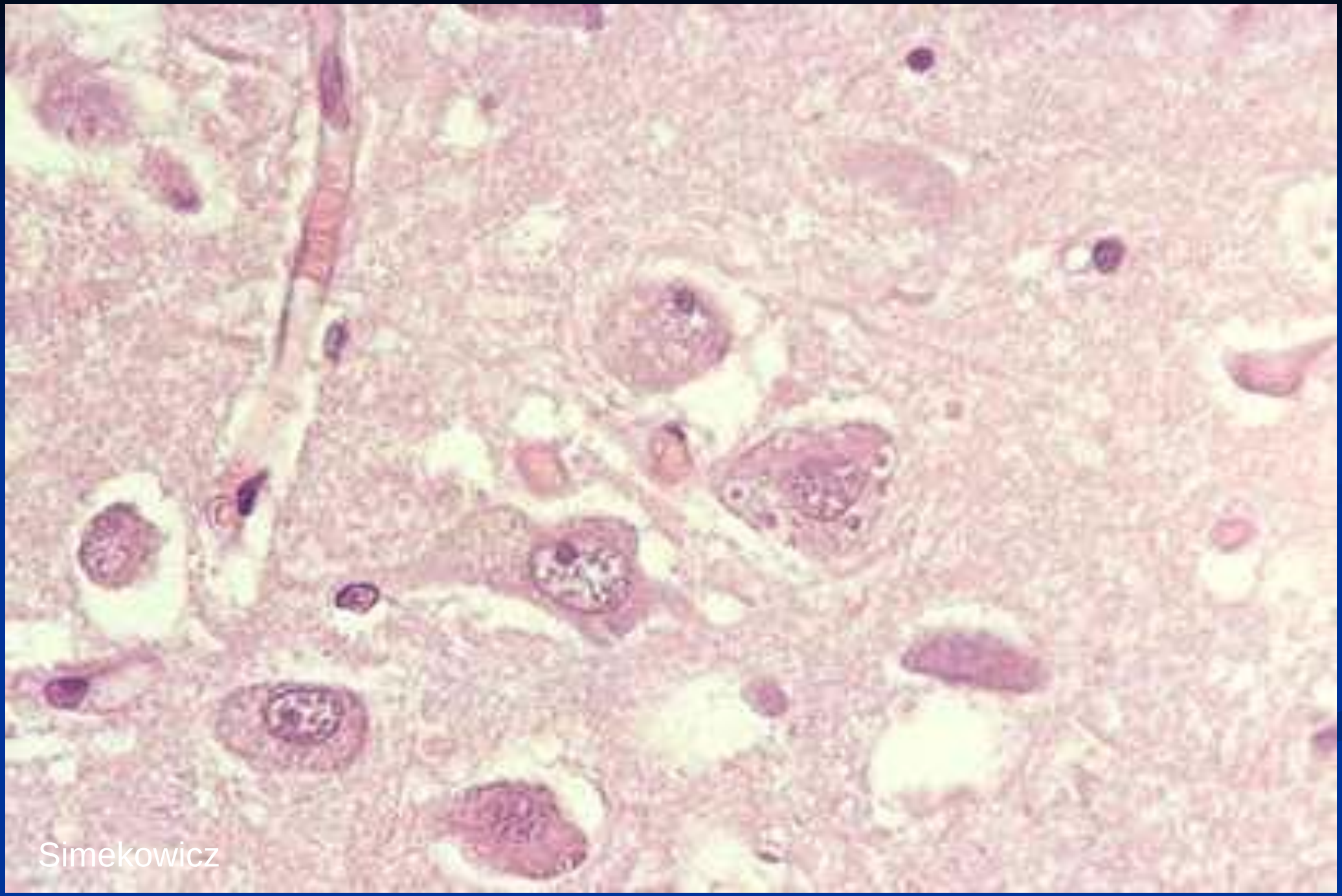
(EXCL. BLOOD FLOW, METABOLIC, NEUROCHEMICAL DATA)

(CREASY AND RAPPAPORT, ANN NEUROL 17:2-10, 1985)

- LOSS OF WEIGHT (7-8%)
  (INCL. INFRATENTORIAL PARTS)
- ATROPHY OF GRAY AND WHITE MATTER
  GRAY-TO-WHITE RATIO: 1.28 (AGE 20 YS)
  1.13 (AGE 50 YS)
  1.55 (AGE 100 YS)
- DILATATION OF VENTRICLES
- SELECTIVE NEURONAL LOSS
  (GOLGI TYPE II NEURONS OF LAYERS II AND IV)
  SUPERIOR FRONTAL
  SUPERIOR TEMPORAL
  PRECENTRAL
  STRIATUM
  HIPPOCAMPUS
  PURKINJE CELLS
  LOCUS CAERULEUS
  AMYGDALA
  THALAMUS
  SUBSTANTIA NIGRA
- REDUCTION IN NEURONAL SIZE
- LOSS OF SPECIFIC GROWTH FACTORS
- LOSS OF NUCLEOLAR VOLUME, RNA CONTENT
- ACCUMULATION OF LIPOFUSCIN, AMYLOID
- SENILE PLAQUES
- NEUROFIBRILLARY TANGLES
- GRANULOVACUOLAR DEGENERATION


Age changes of human isocortex
Dendritic changes of pyramidal cells
Meganeurites
of layer IIIab pyramidal cells
Cytoskeleton
abnormalities
Tangles
Threads
Plaques
Loss of intracortical myelin
Development of meganeurites
Loss of non-pyramidal cells
I
II
IIIab
IIIc
IV
V
VI

Granulovacuolar Degeneration Simchowicz


Simekowicz

Intraneuronal (intraglial) Aggegation

Proteins

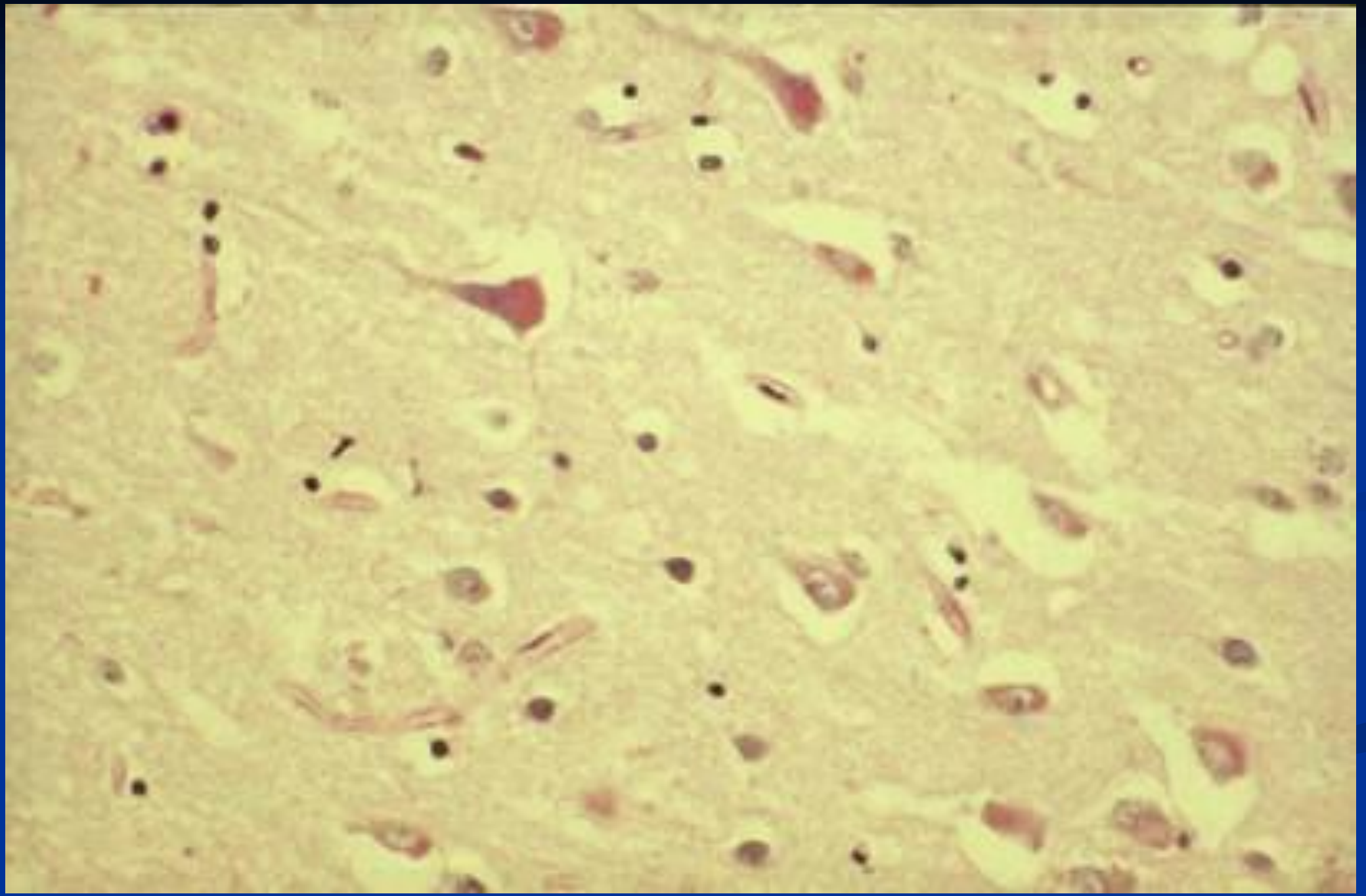
Viruses

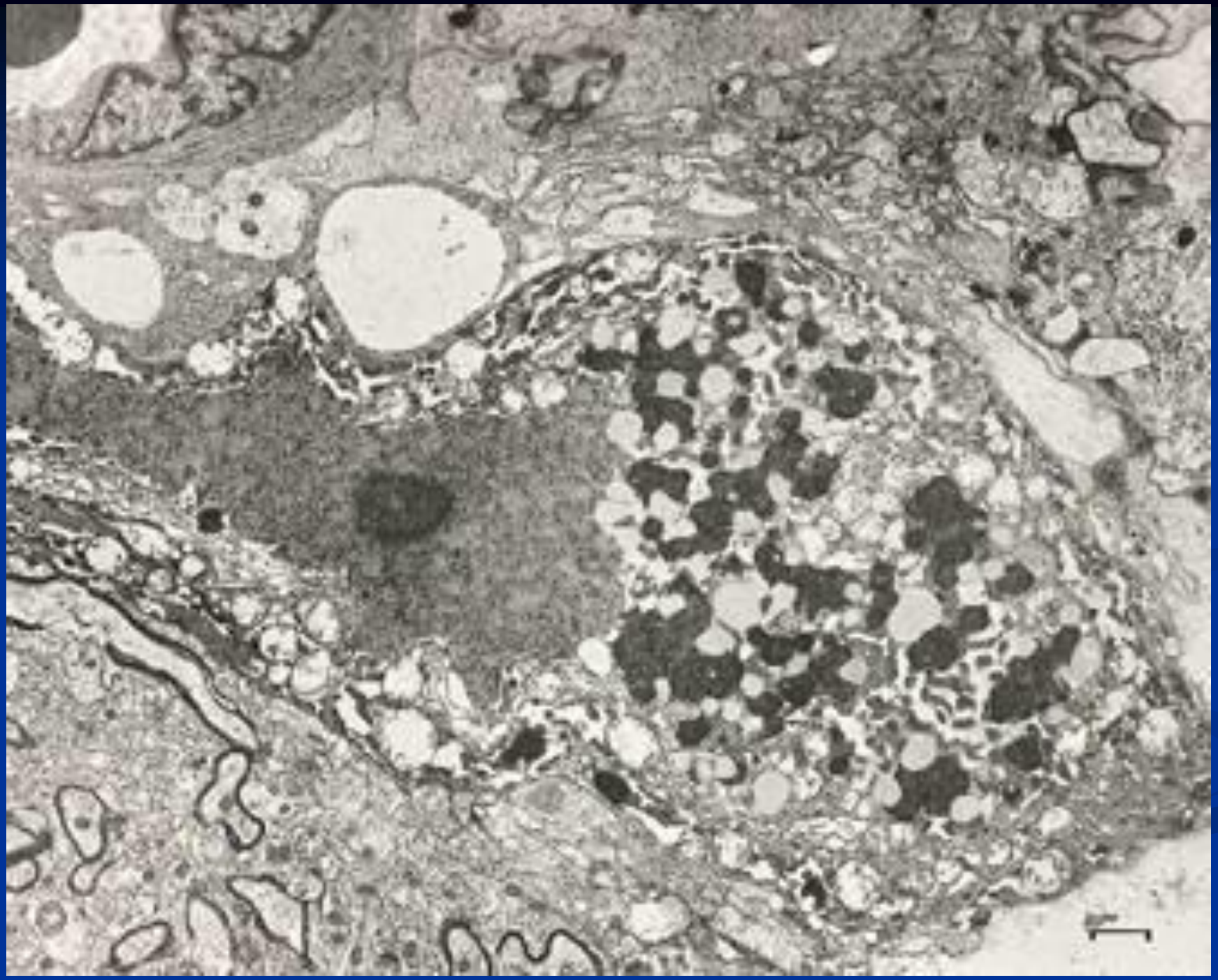
Lysosomal substrates

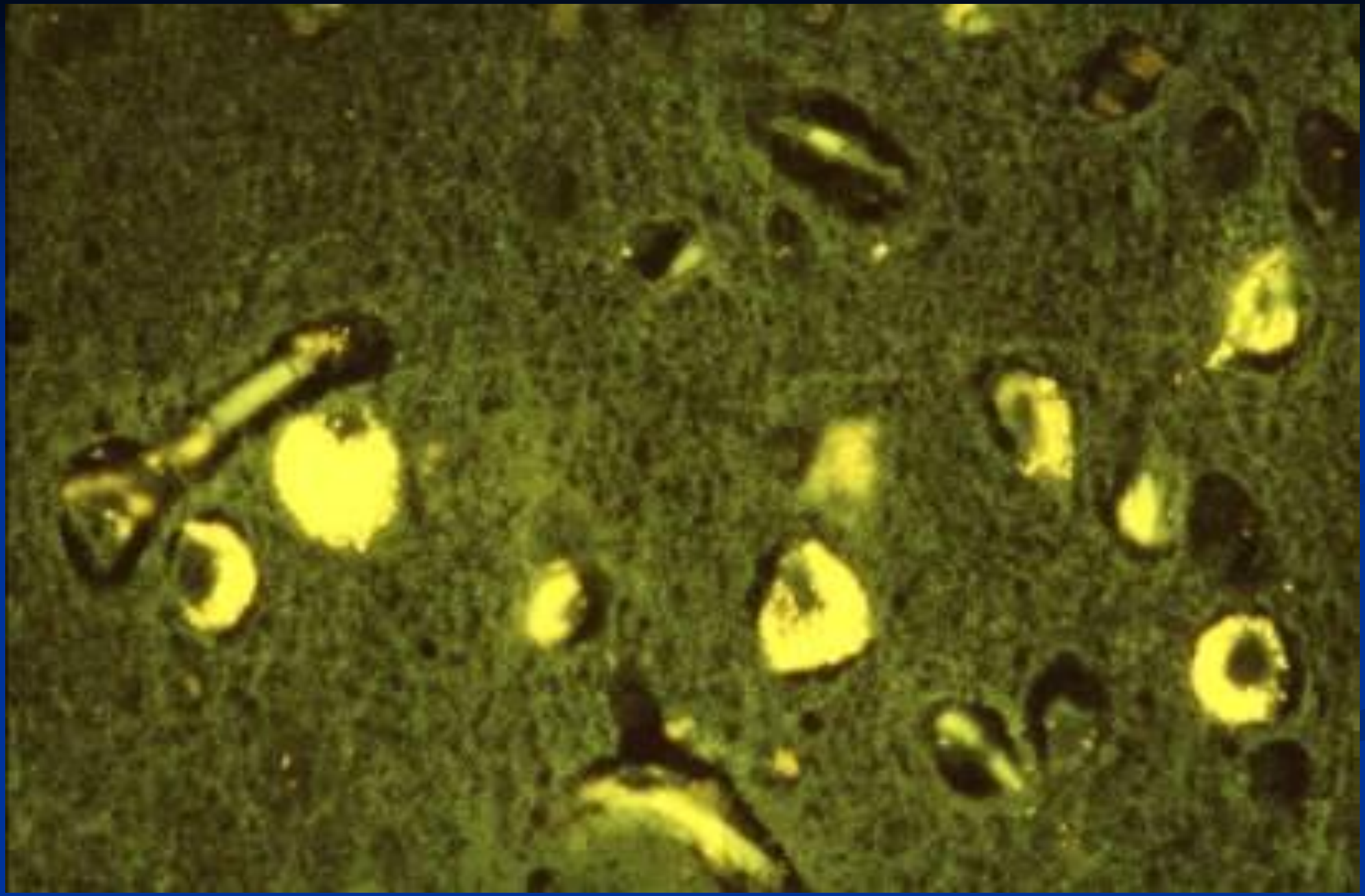
Lipofuscin (Lipopigment)

Age pigment

Wear and tear pigment

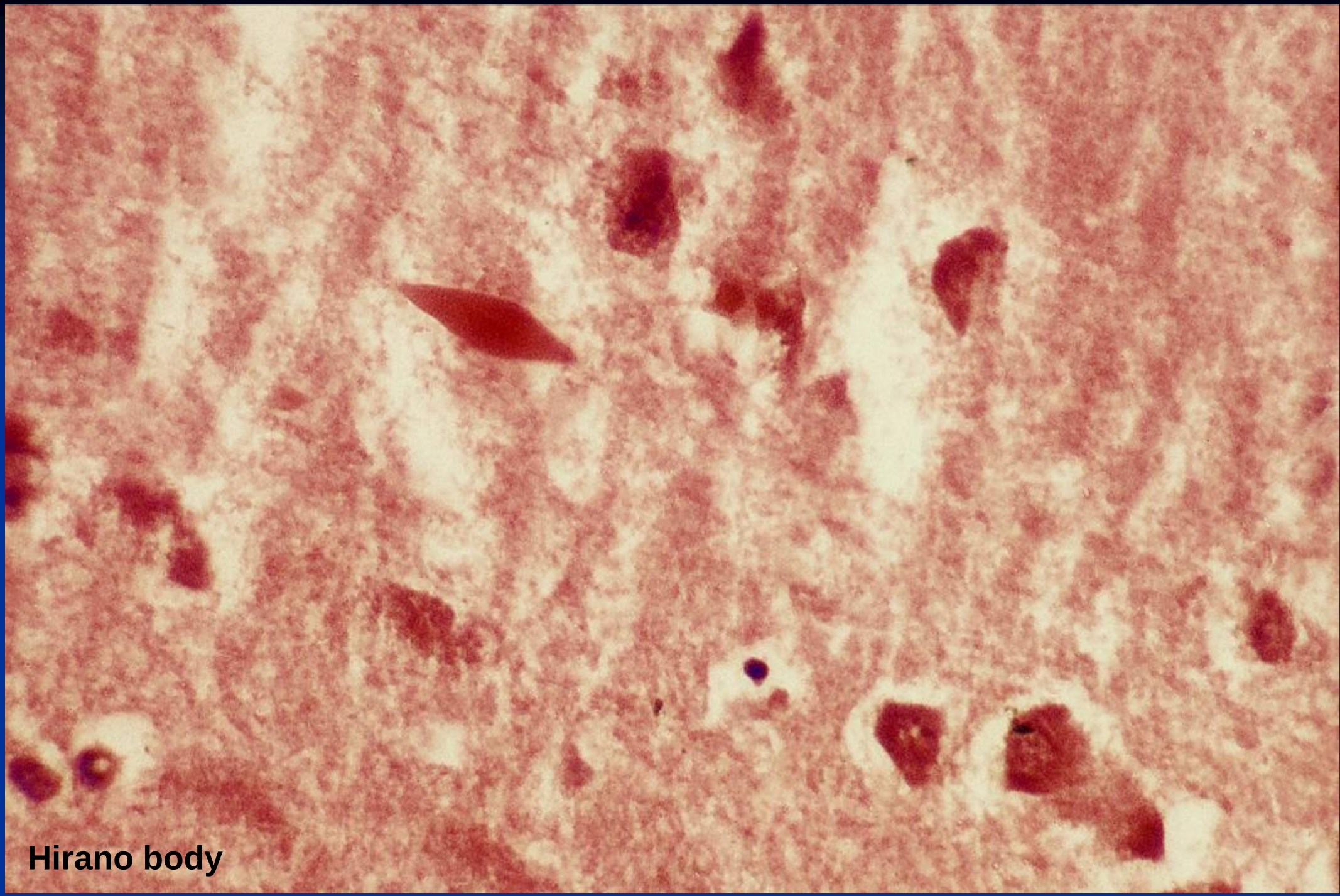


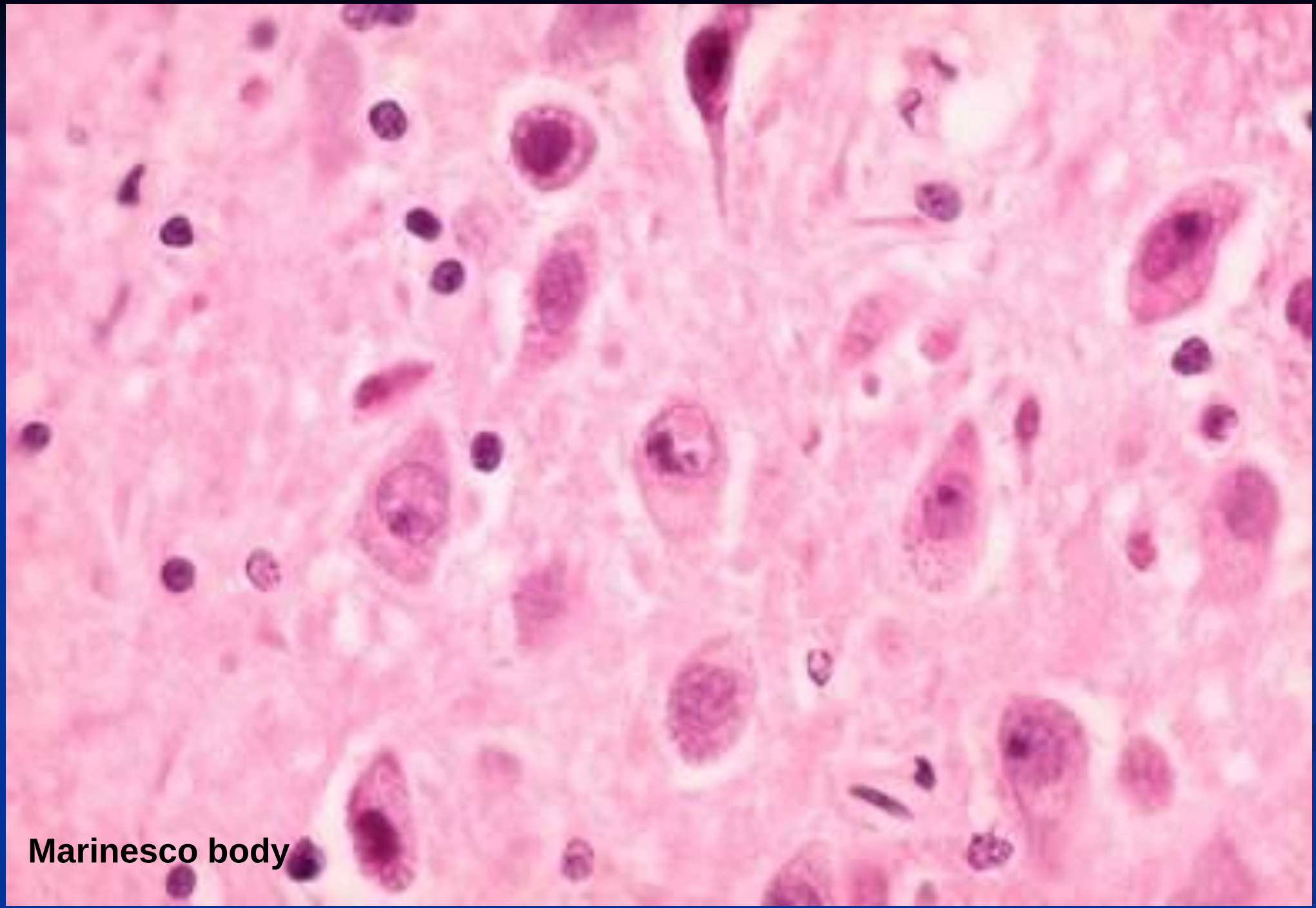




Lipopigments

physiological	
neuronal:	lateral geniculate body inferior olive dentate nucleus
aging:	large neurons (pyramidal neurons)
pathological:	neuronal ceroid-lipofuscinoses Vitamin E deficiency
experimental:	Feeding unsaturated fatty acids

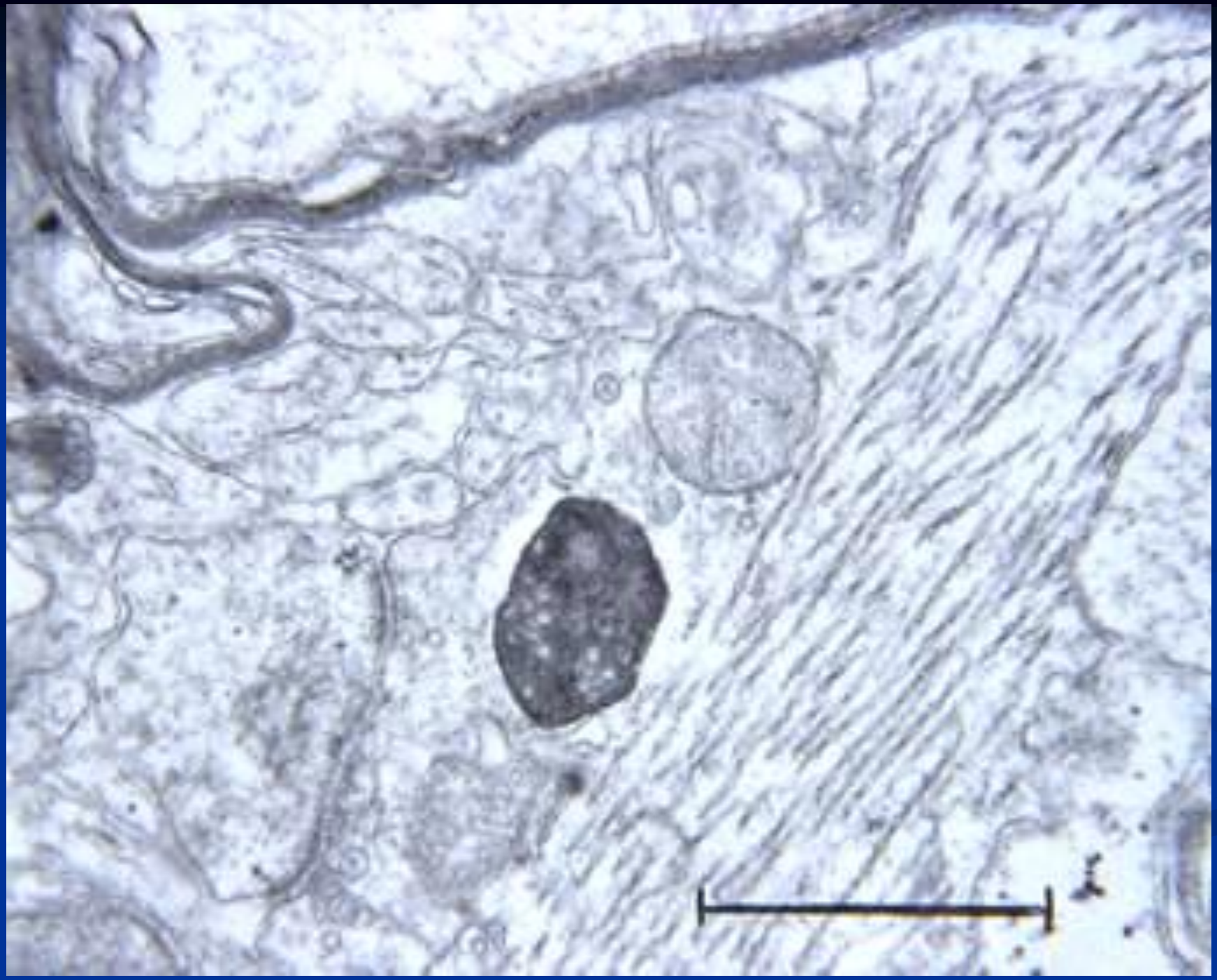

Hirano body

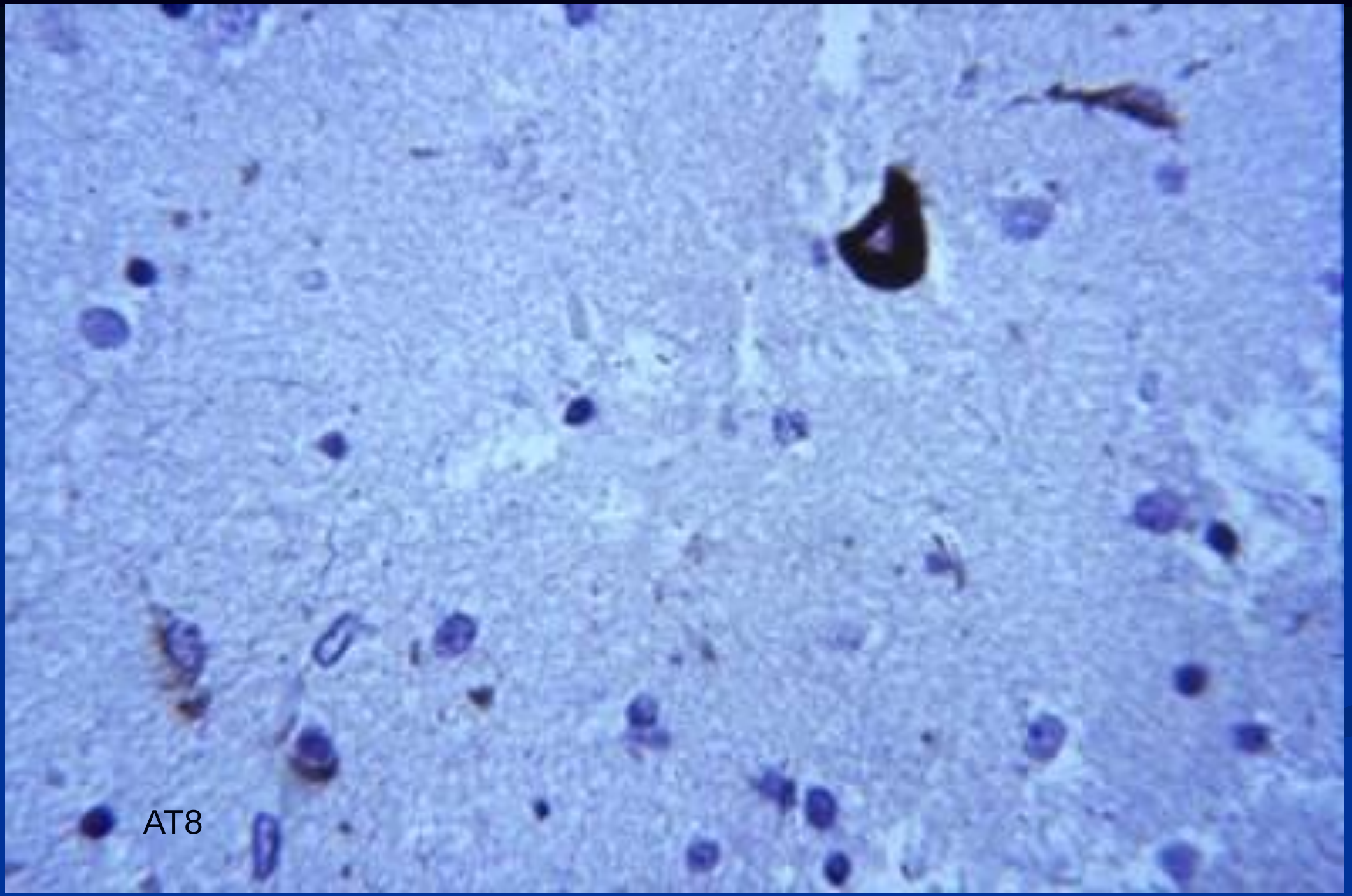

Marinesco body

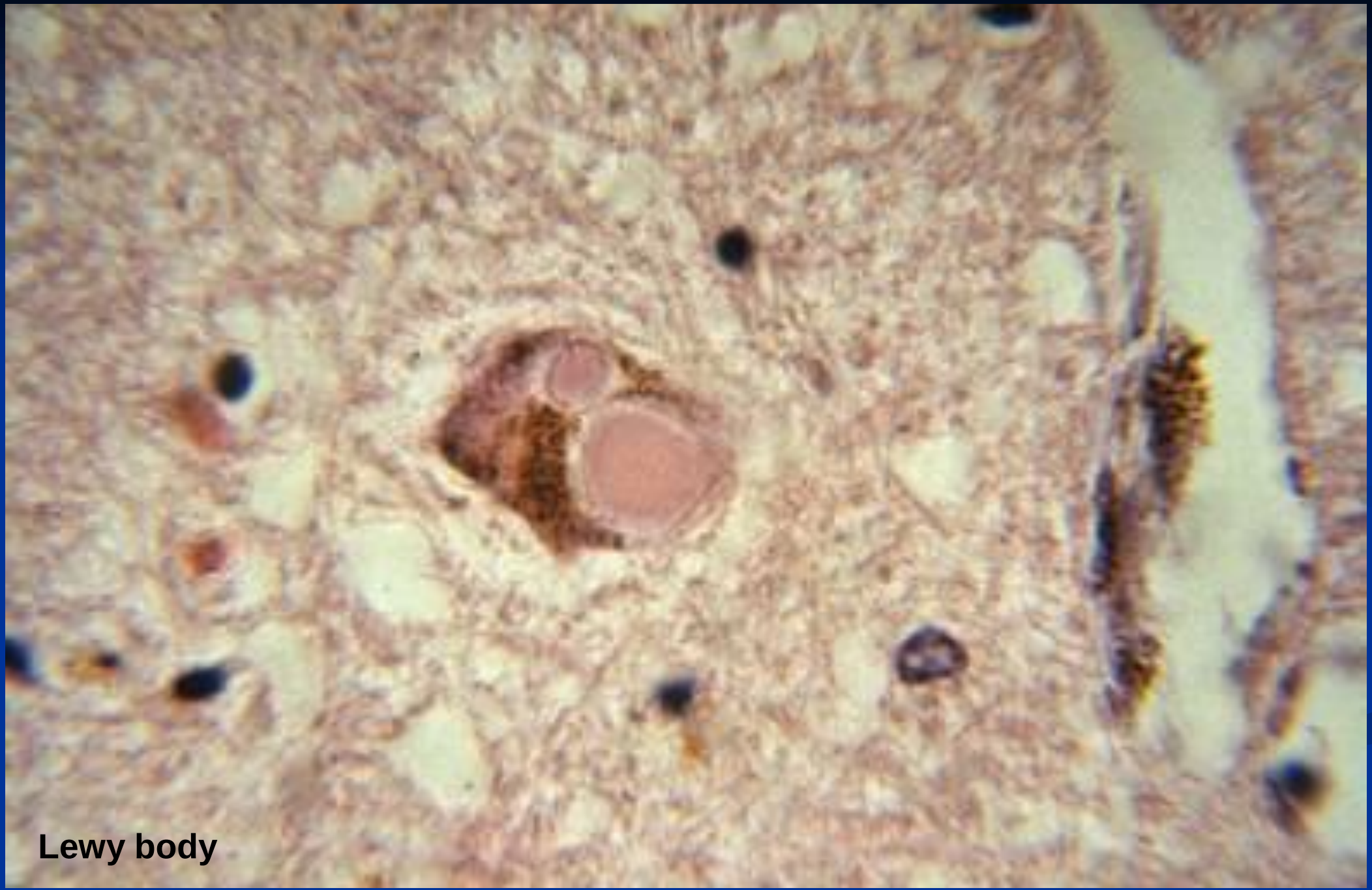
Alzheimer Disease

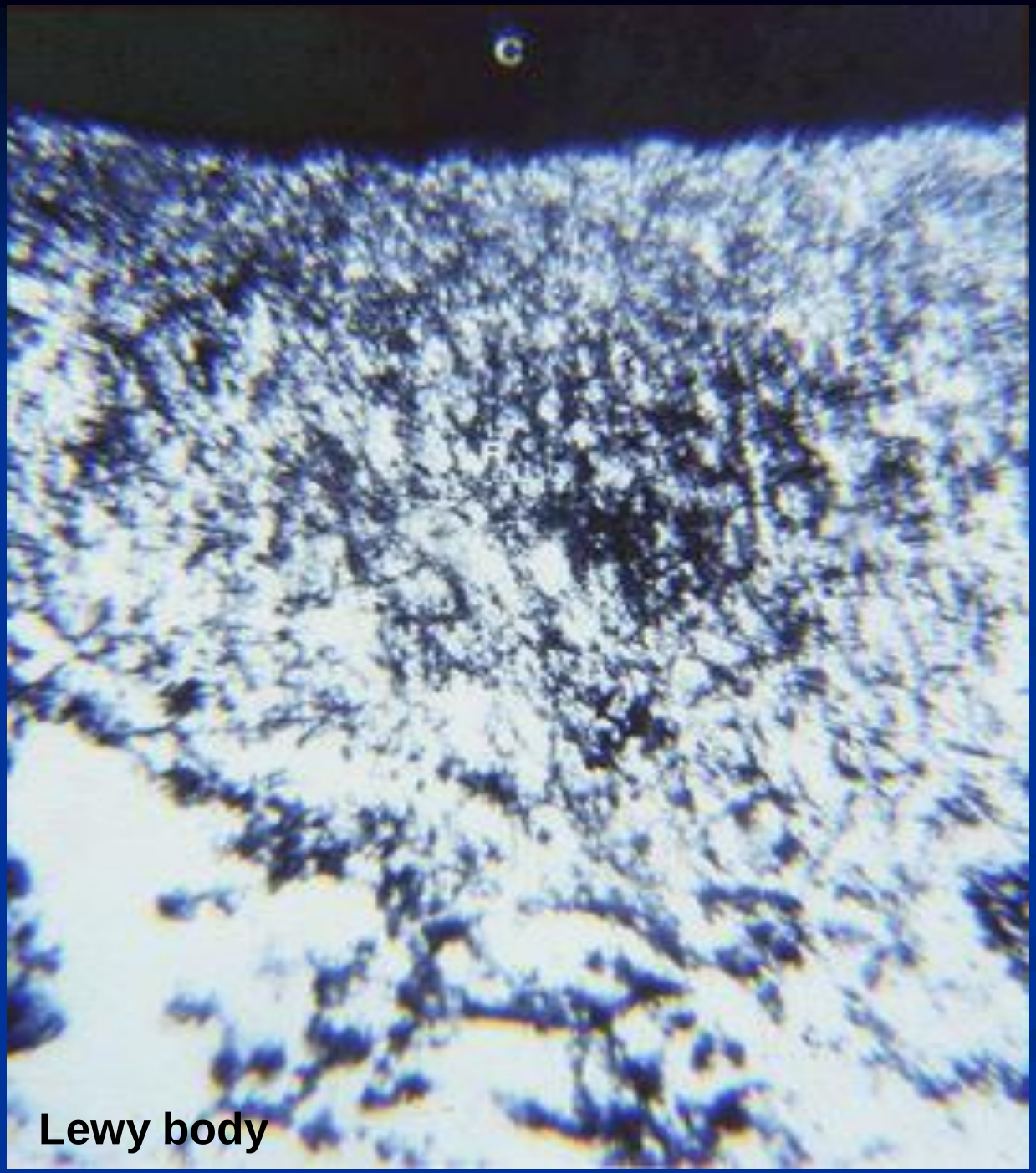
NFT neurofibrillary tangles

PHF paired helical filaments

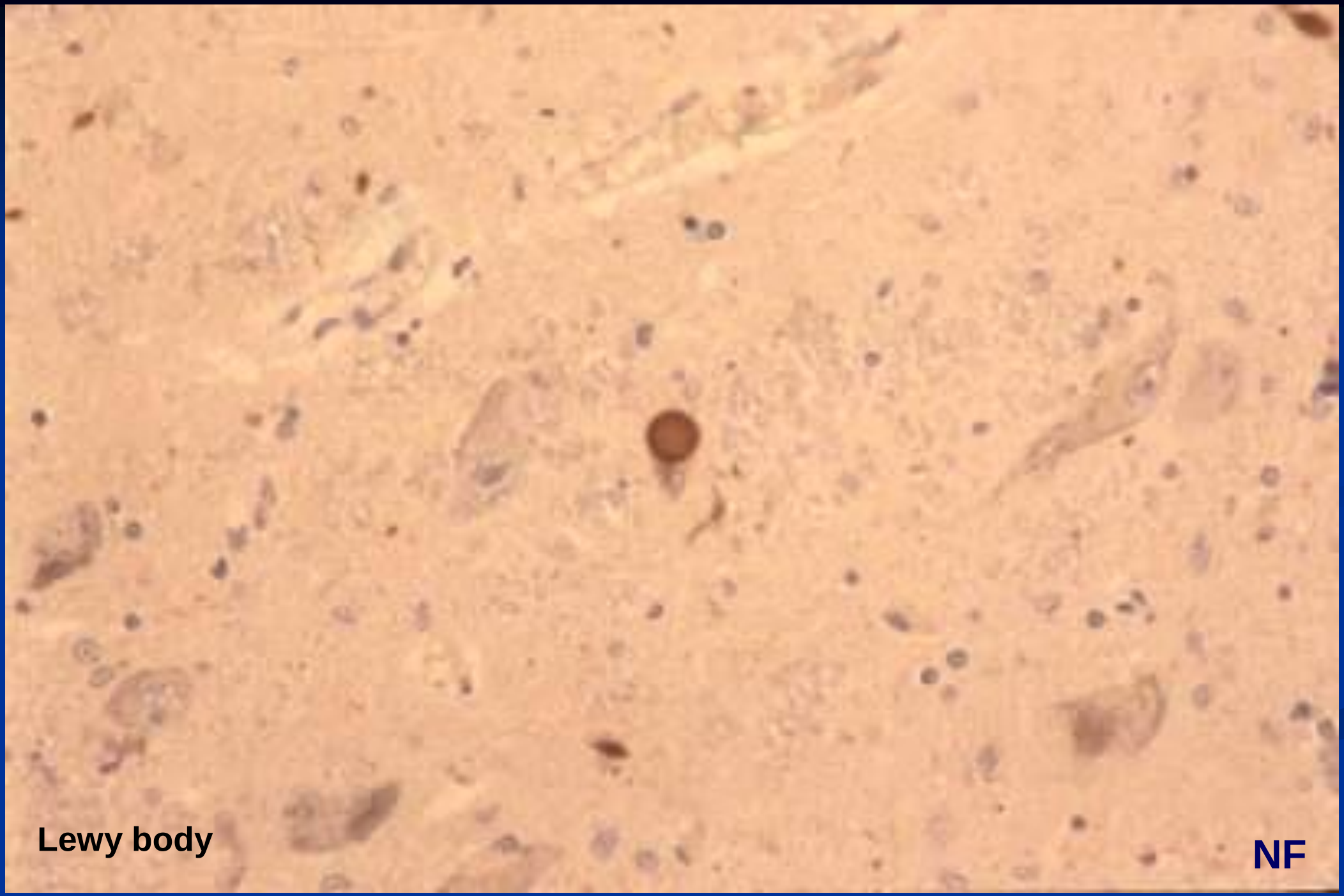



AT8

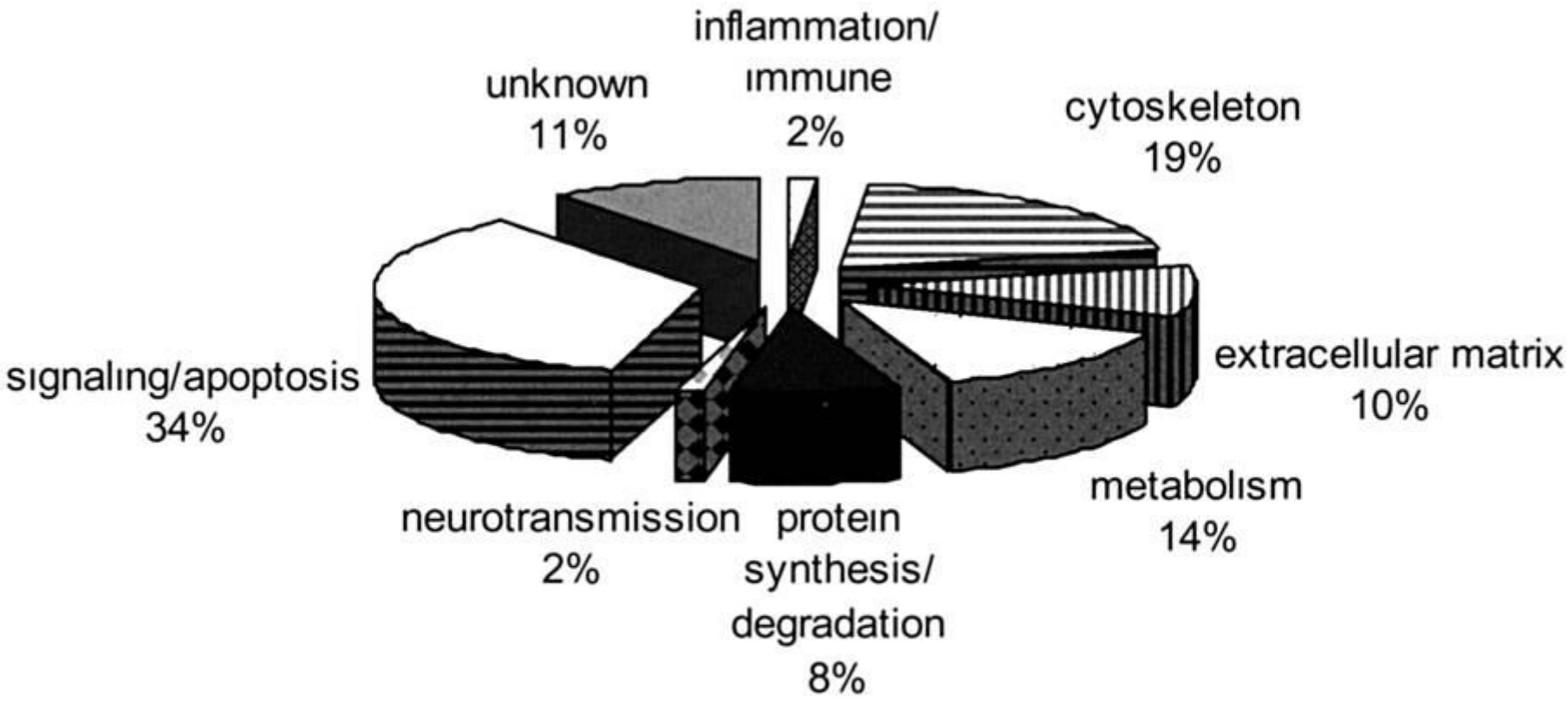

Lewy body



Lewy body


Lewy body
NF

Protein Distribution



Classification of proteins identified in cortical Lewy bodies. Pie chart depicting the 296 proteins characterized by LC-MS/MS. Functional classification of a given protein was based on the one that is best known, although typically, multiple functions may have been associated with that particular protein. Notably, a significant portion of the proteome is novel without known functions.

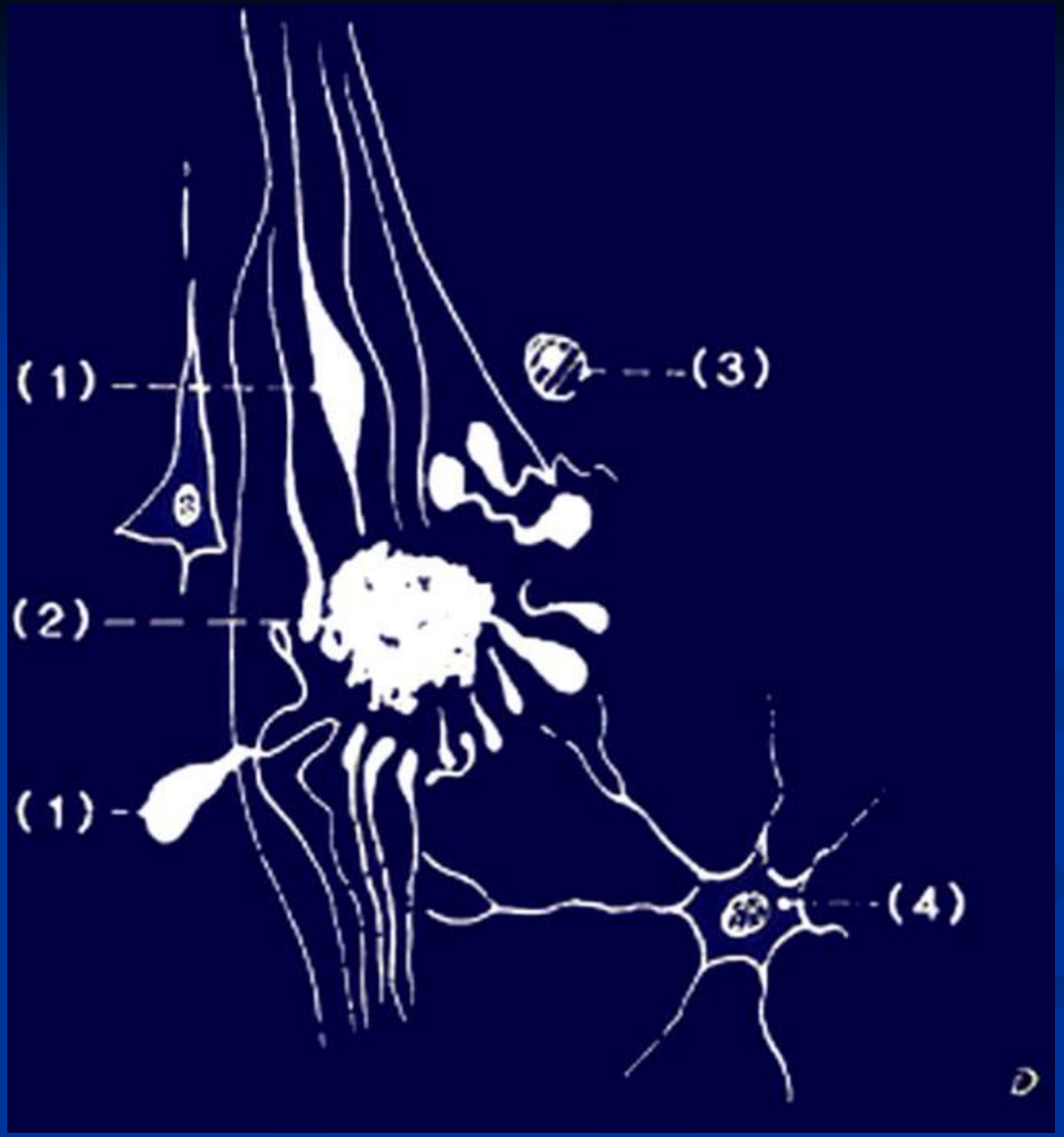
James B. Leverenz et al. Journal Compilation Brain Pathology Volume 17, Number 2 , 2007; 139-145

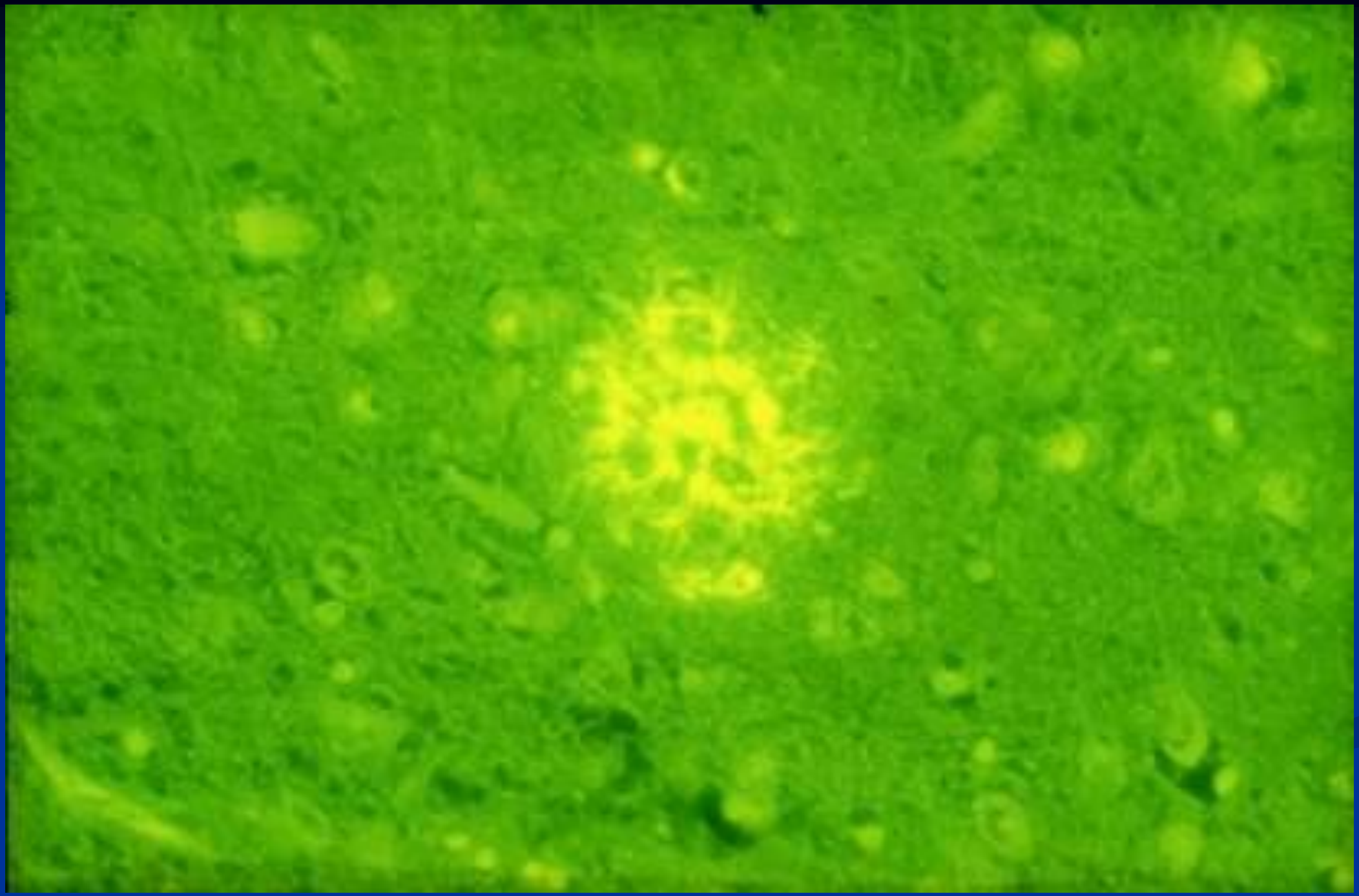
Neurodegenerative diseases with filamentous proteins

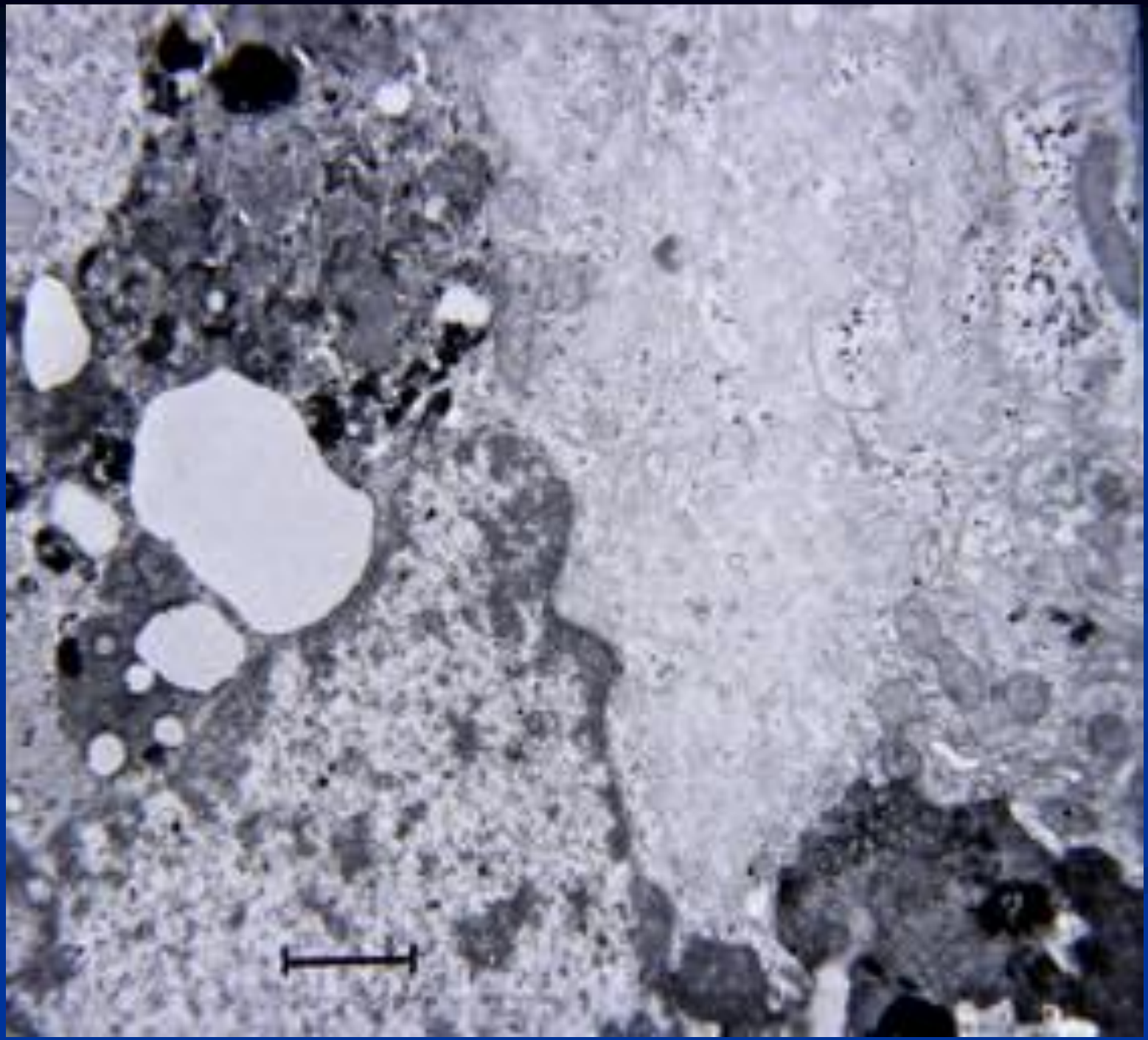
Disease	Proteins	Location
Alzheimer diseases	NFTs/PHFtau	Intracytoplasmic
Amyotrophic lateral sclerosis	Spheroids/NF subunits	Intracytoplasmic
DLB Disease	LBs/NF subunits, α-synuclein	Intracytoplasmic
LBVAD (AD+DLBD)	NFTs/PHFtau	Intracytoplasmic
LBVAD (AD+DLBD)	LBs/NF subunits, α-synuclein	Intracytoplasmic
MSA	GCIs/α-synuclein	Intracytoplasmic
PD	LBs/NF subunits α-synuclein	Intracytoplasmic
Tauopathies	NFTs/AD-like PHFtau	Intracytoplasmic

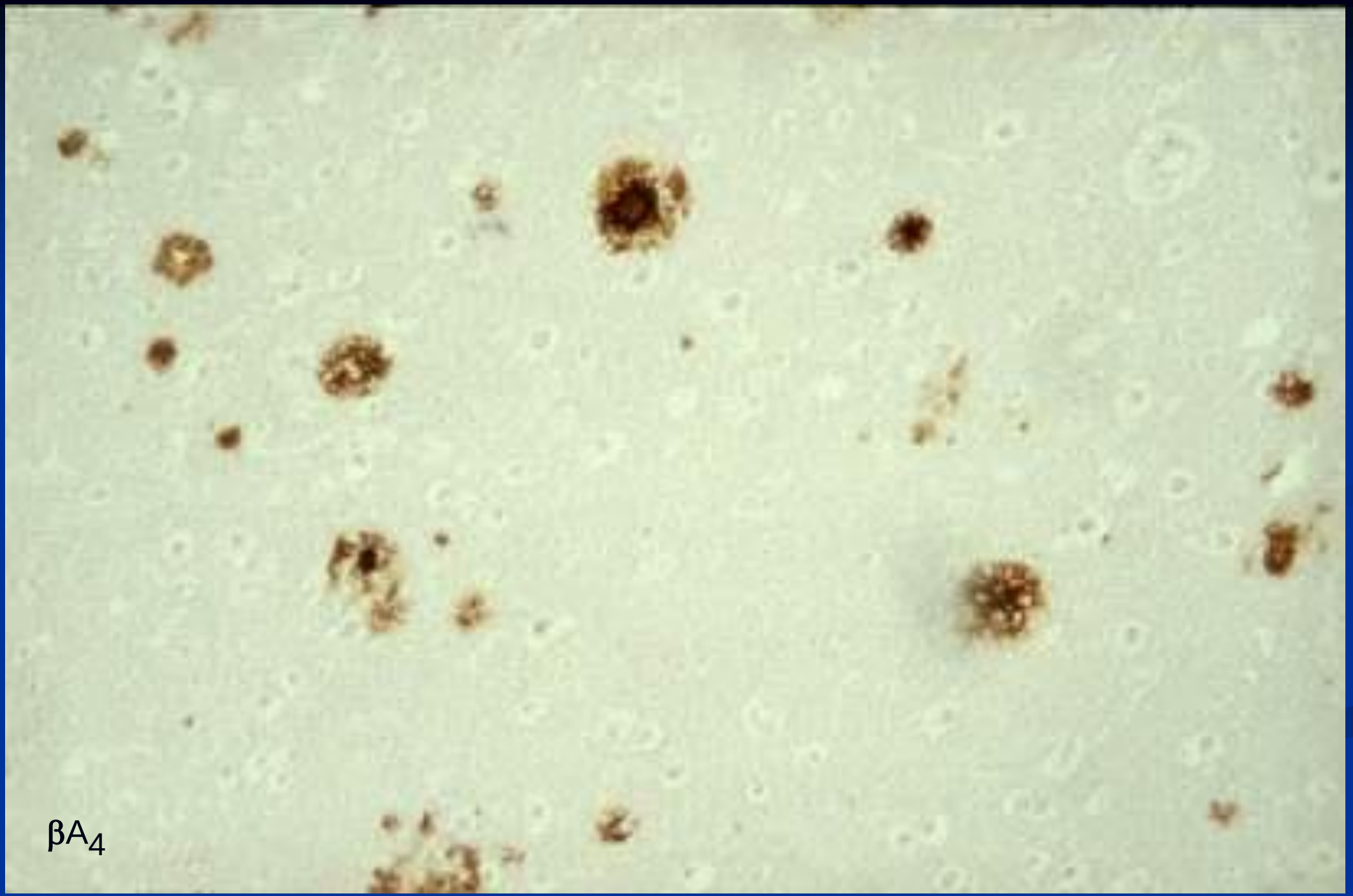
Neurodegenerative diseases with filamentous proteins

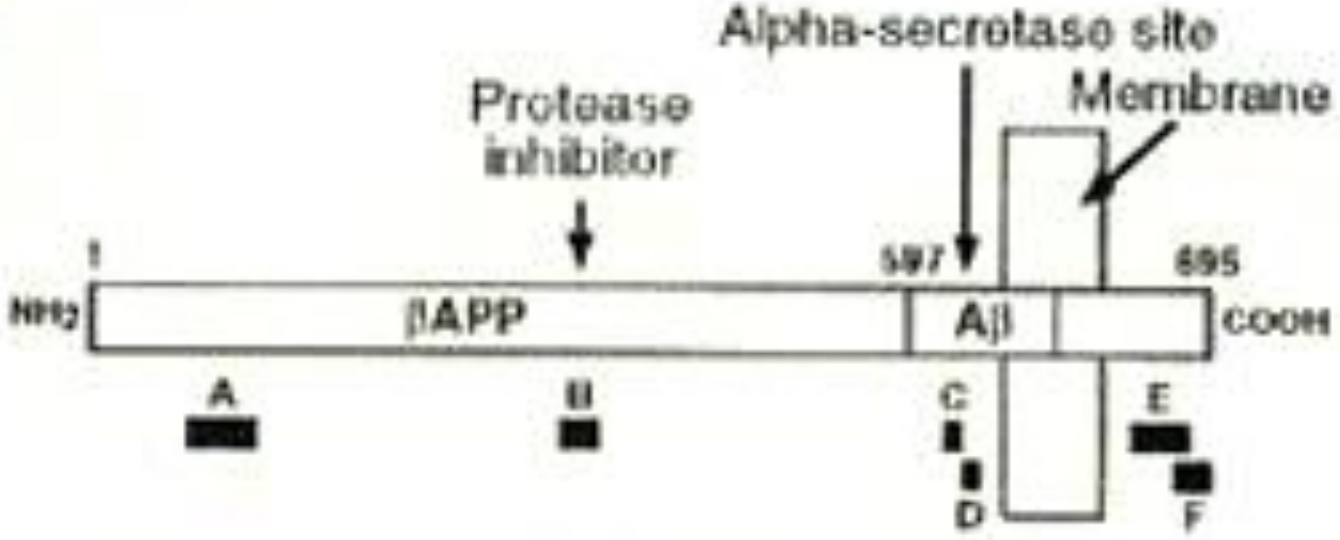
Disease	Proteins	Location
Neuronal intranuclear inclusion disease	Inclusions/expanded polyglutamine tracts	Intranuclear
Tri-nucleotide repeat diseases	Inclusions/expanded polyglutamine tracts	Intranuclear
AD	SPs/Aβ, NonAβ-components	Extracellular
LBVAD (AD+DLBD)	SPs/Aβ, NonAβ-components	Extracellular
Prion diseases	Amyloid plaques/prions	Extracellular


(1)
(3)
(2)
(1)
(4)






βA_4



Anti-βAPP antibodies		Anti-Aβ antibodies	
A:	Residues 60 - 100	C:	Residues 8 - 17
B:	293 - 315	D:	17 - 24
E:	649 - 683		
F:	676 - 695		

Fig. 1. Schematic diagram of βAPP showing the transmembrane region, the boundaries of Aβ, the α secretase site, the position of the Kunitz protease inhibitor insert, and the regions probed by antibodies.

JAN L. DE BLECKER, *et al* 1996

Amyloid (osis)

Organ specific	-	generalised
Hereditary	-	acquired
Primary/Systemic	-	secondary

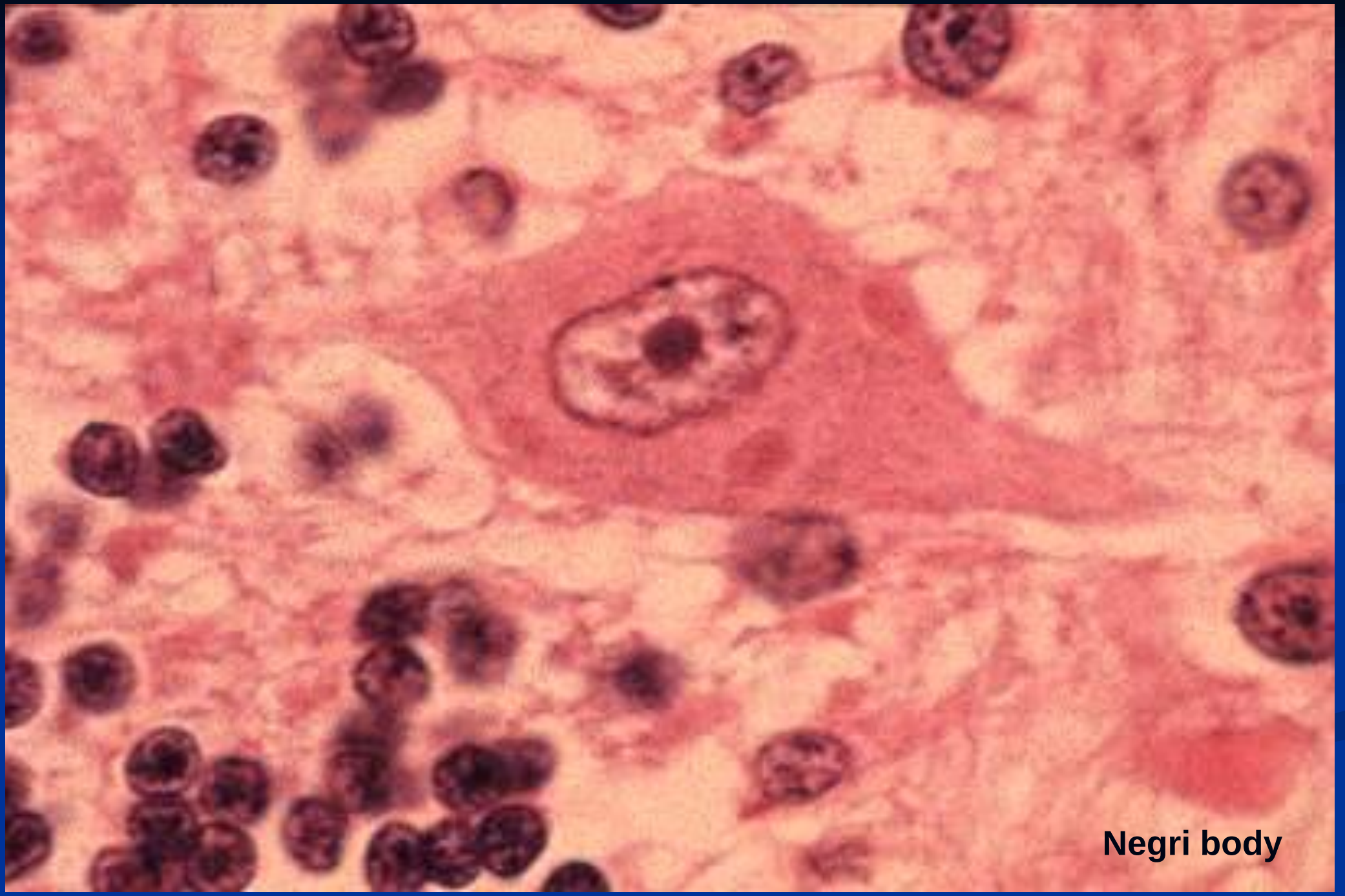
Viral inclusions in nerve cells

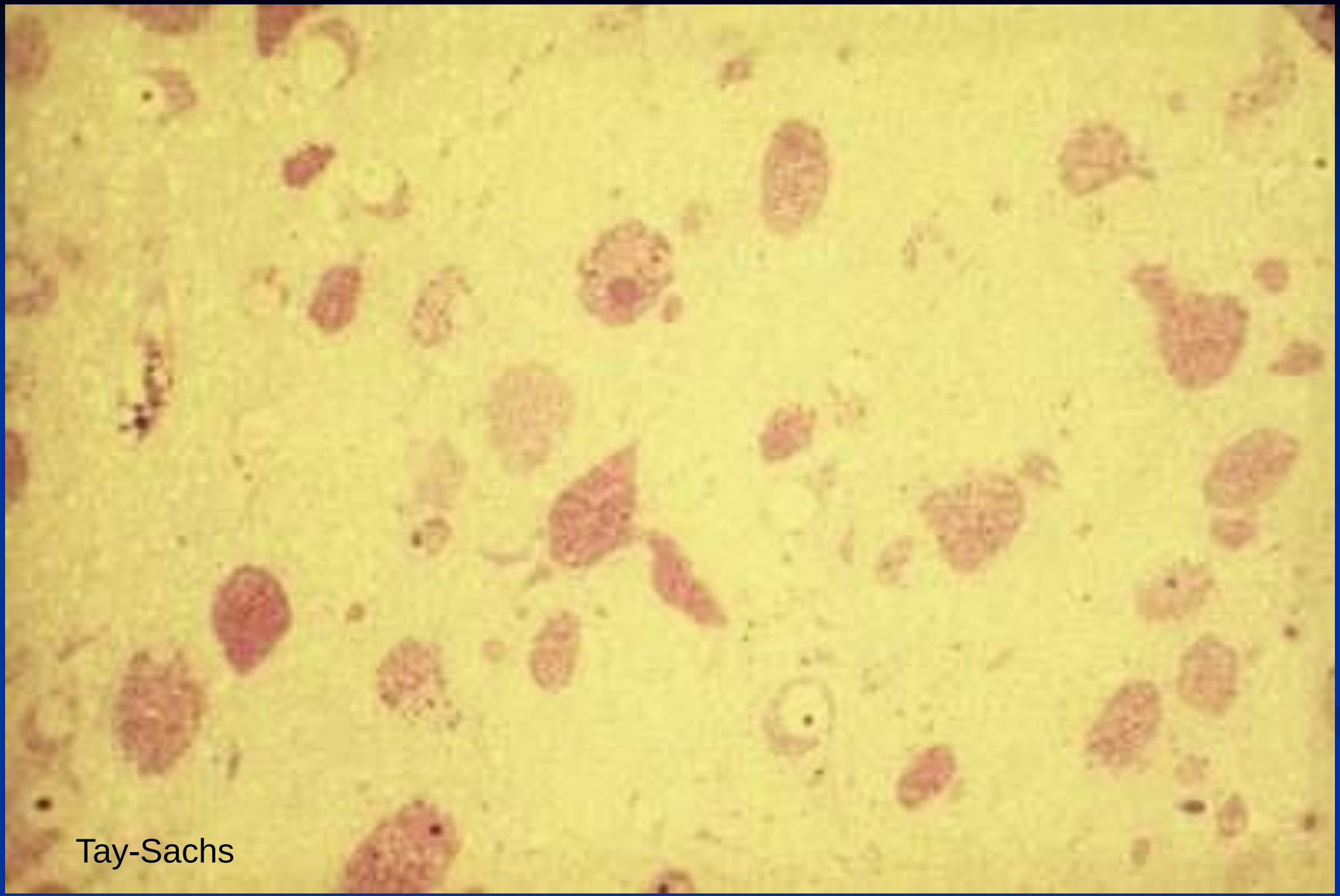
Nucleus (Cowdry type A)

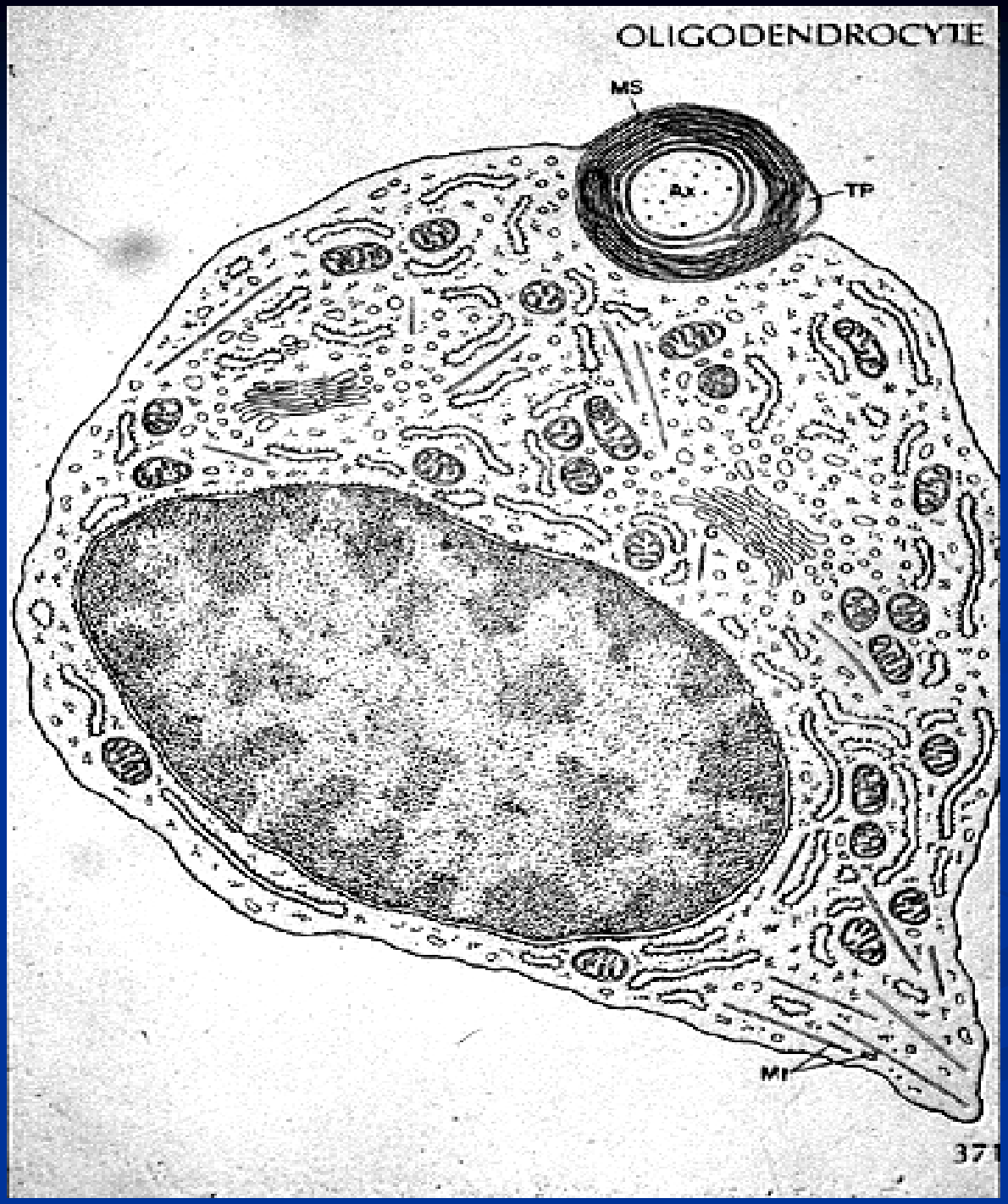
- Herpes simplex / zoster virus
- Papova/JC (progressive multifocal leuko-encephalopathy)
- Paramyxovirus (measles)
- Cytomegalovirus

Cytoplasm

- Negri / Lyssa bodies (Rabies)


Negri body


Tay-Sachs


OLIGODENDROCYTE
MS
Ax
TP
MI

Oligodendroglial Reactions

Viral replication	inclusions
Protein aggregation	inclusions
lysosomal activation	lysosomal storage

demyelination

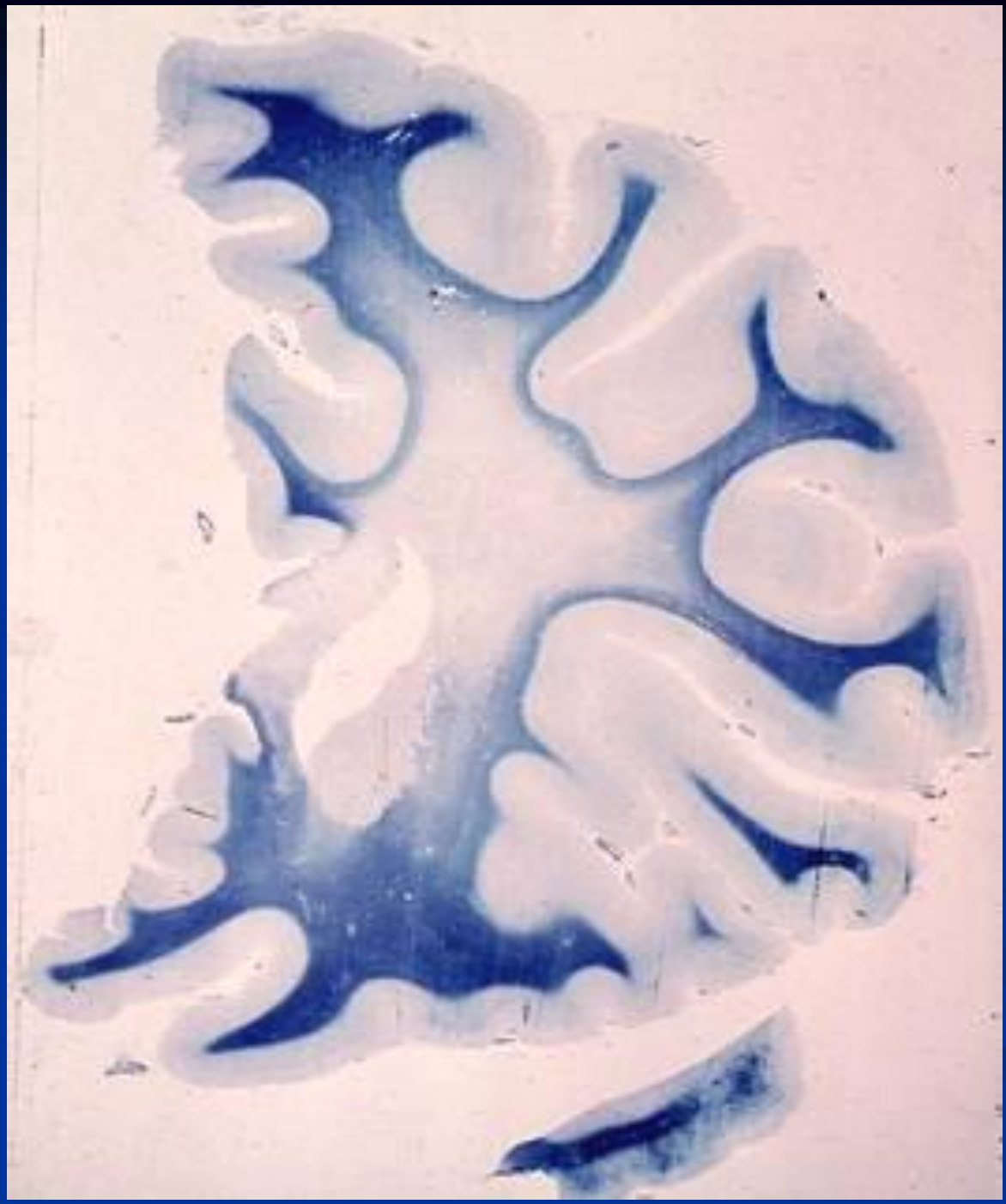
Primary and secondary Demyelination

Types of Demyelination

Diffuse - metabolic, toxic

Focal - unifocal: traumatic, neoplastic

multifocal: inflammatory




S.–Nr.: 92, 1911

TABLE 5. MOLECULAR MECHANISMS OF OLIGODENDROCYTE INJURY AND DEMYELINATION.

AGENT	ACTION	STUDY
Cytokines		
Interferon gamma	Apoptosis of oligodendrocytes Demyelination or hypomyelination	Vartanian et al.,[36] Corbin et al.,[37] Horowitz et al.[38]
Fas or fas ligand	Apoptosis of oligodendrocytes	D'Souza et al.[39]
Tumor necrosis factor α	Apoptosis of oligodendrocytes	Selmaj and Raine[40]
Reactive oxygen intermediates	Apoptosis of oligodendrocyte precursors Necrosis of oligodendrocytes	Yonezawa et al.[41] Merrill et al.[42]
Complement acting alone or through complement-fixing antibody	Apoptosis of oligodendrocytes	Wren and Noble[43]

CLASSIFICATION OF PRIMARY MYELIN DISEASES

Allergic and infectious diseases

Hereditary (metabolic) diseases

Toxic diseases

Nutritional diseases

Traumatic diseases

Vascular diseases


Multiple Sclerosis

Glia reactions

Microglia

Astrocytes

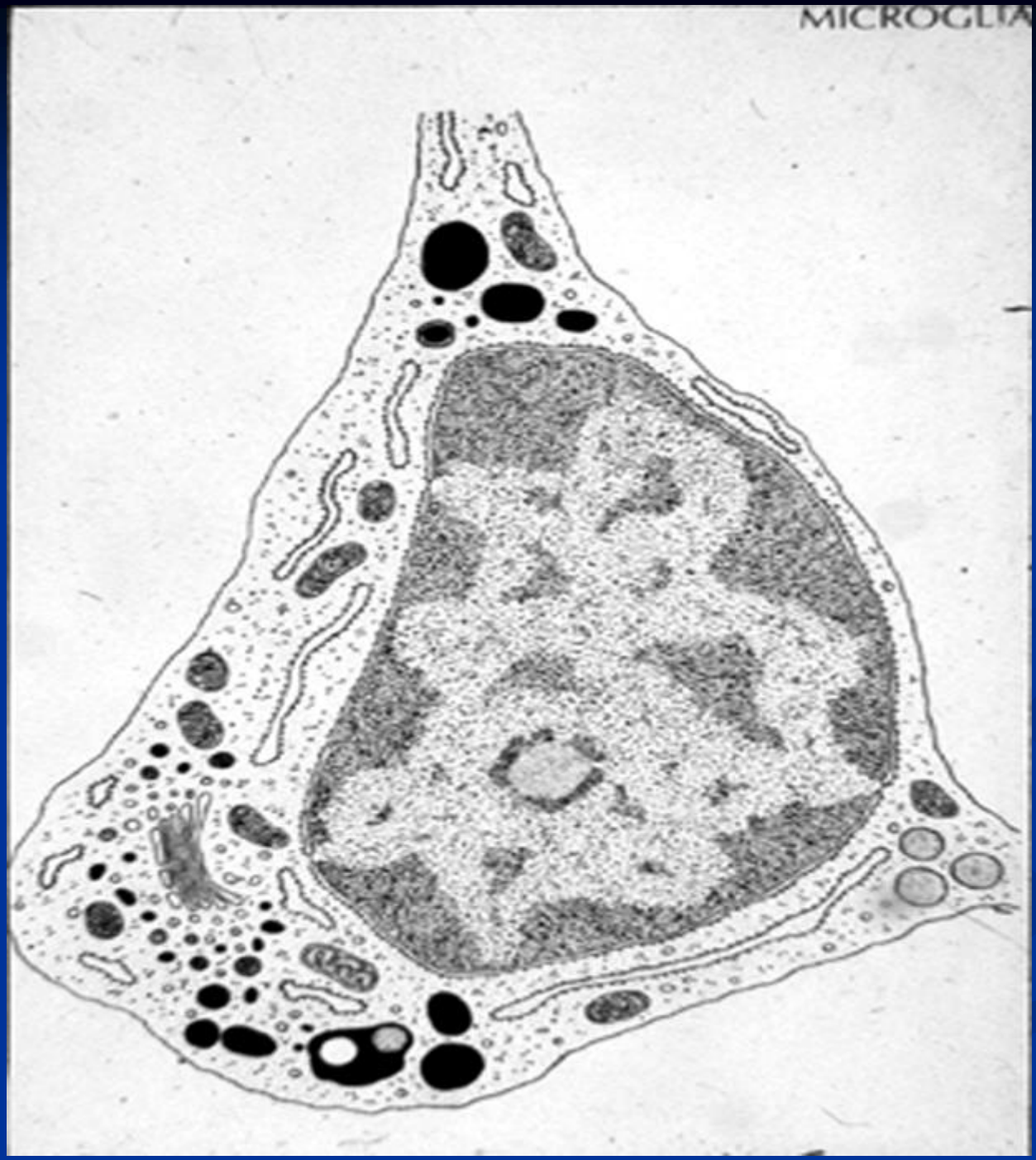
(Glial scar)

Mesenchymal reactions

Vessels

Fibroblasts

Scar


MICROGLIA

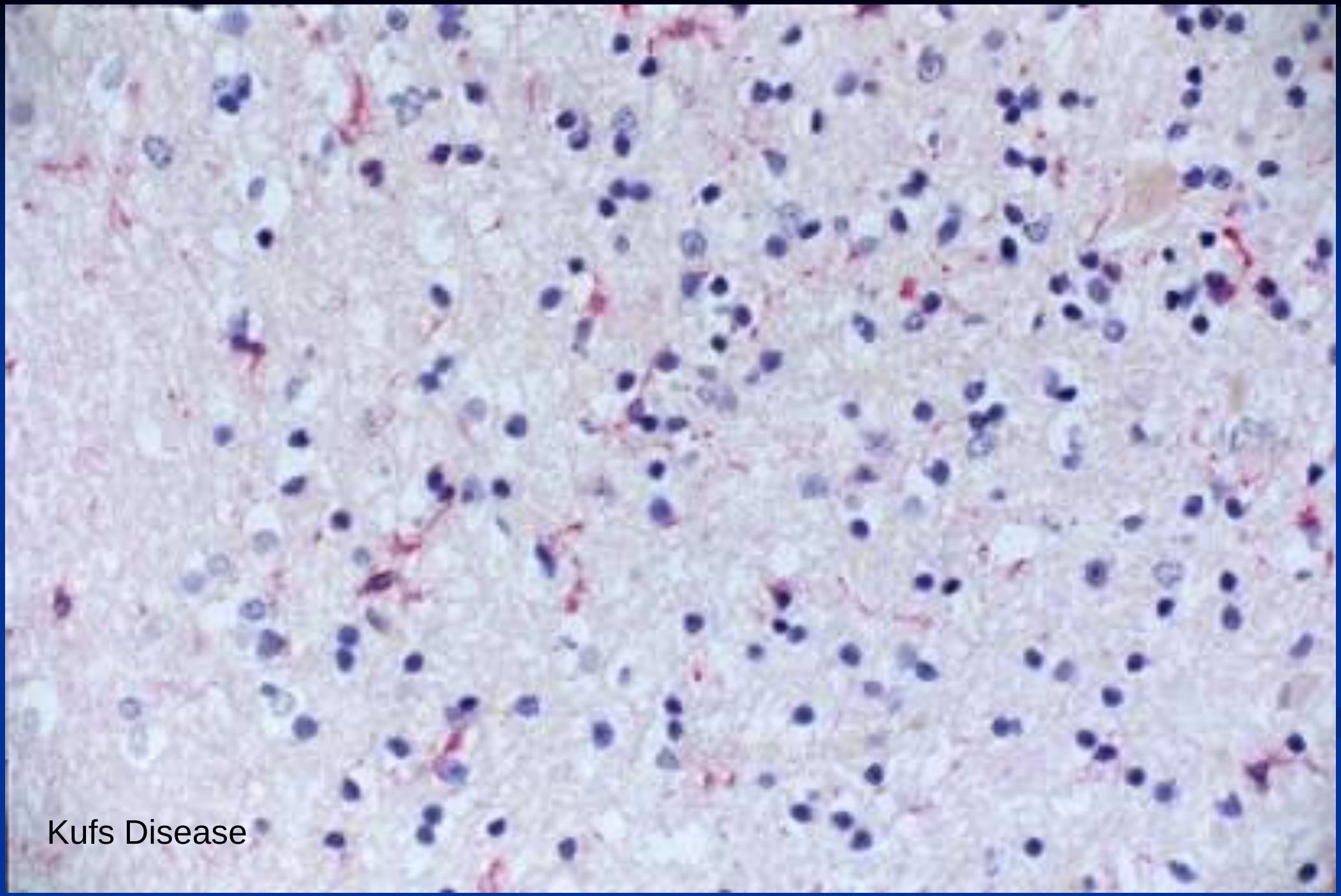
Microglia-rapid reaction

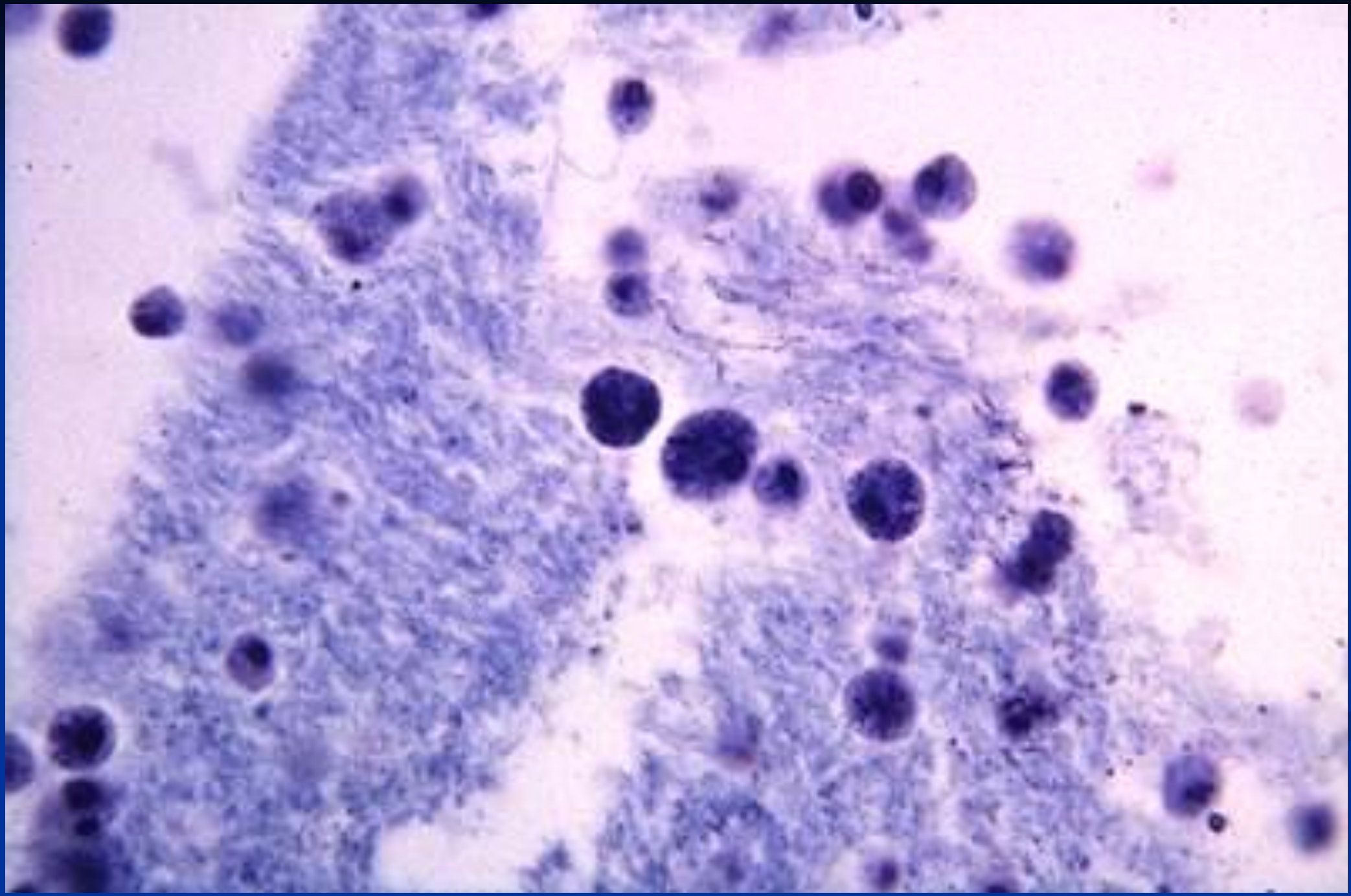
phagocytes

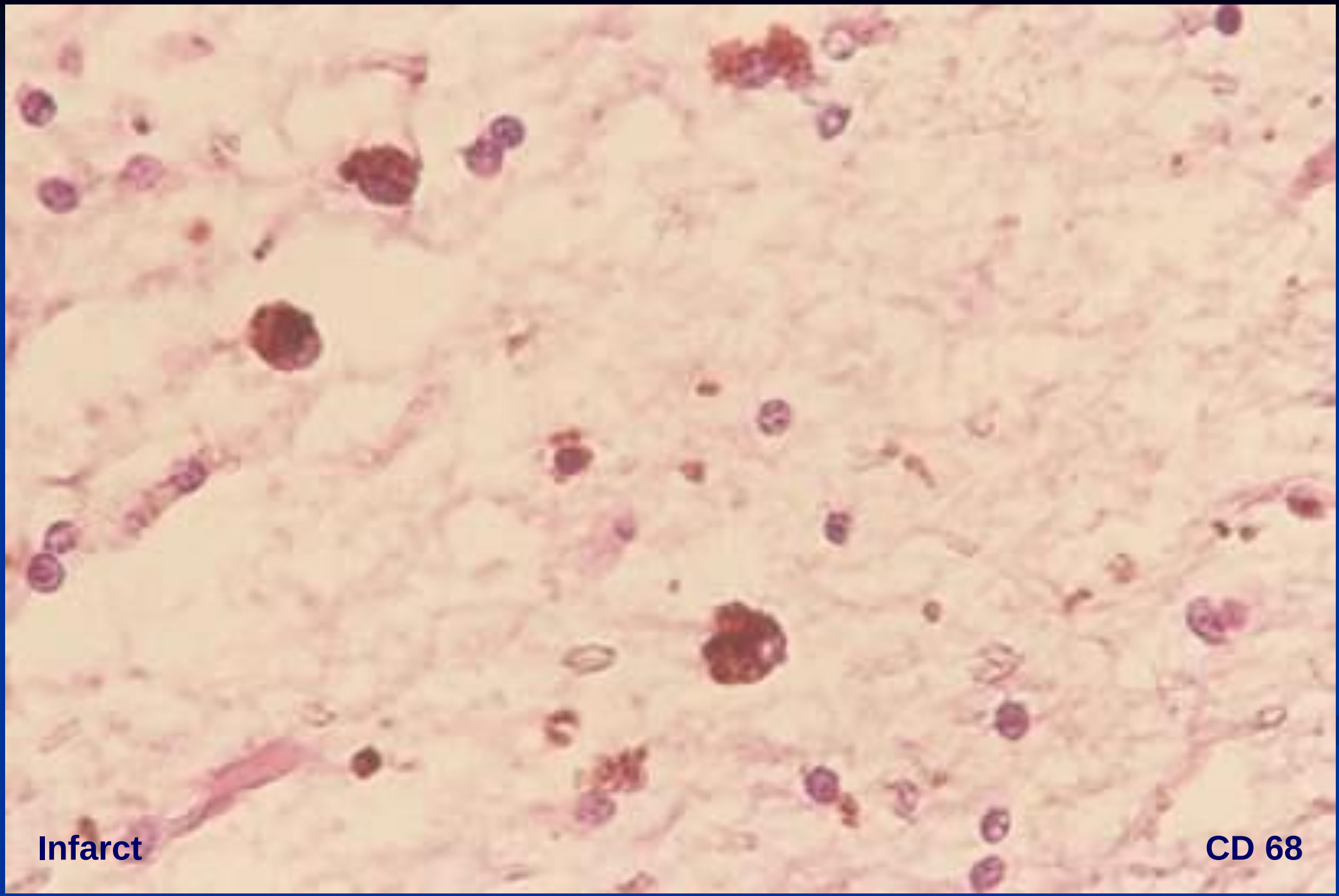
MHC I + II positive

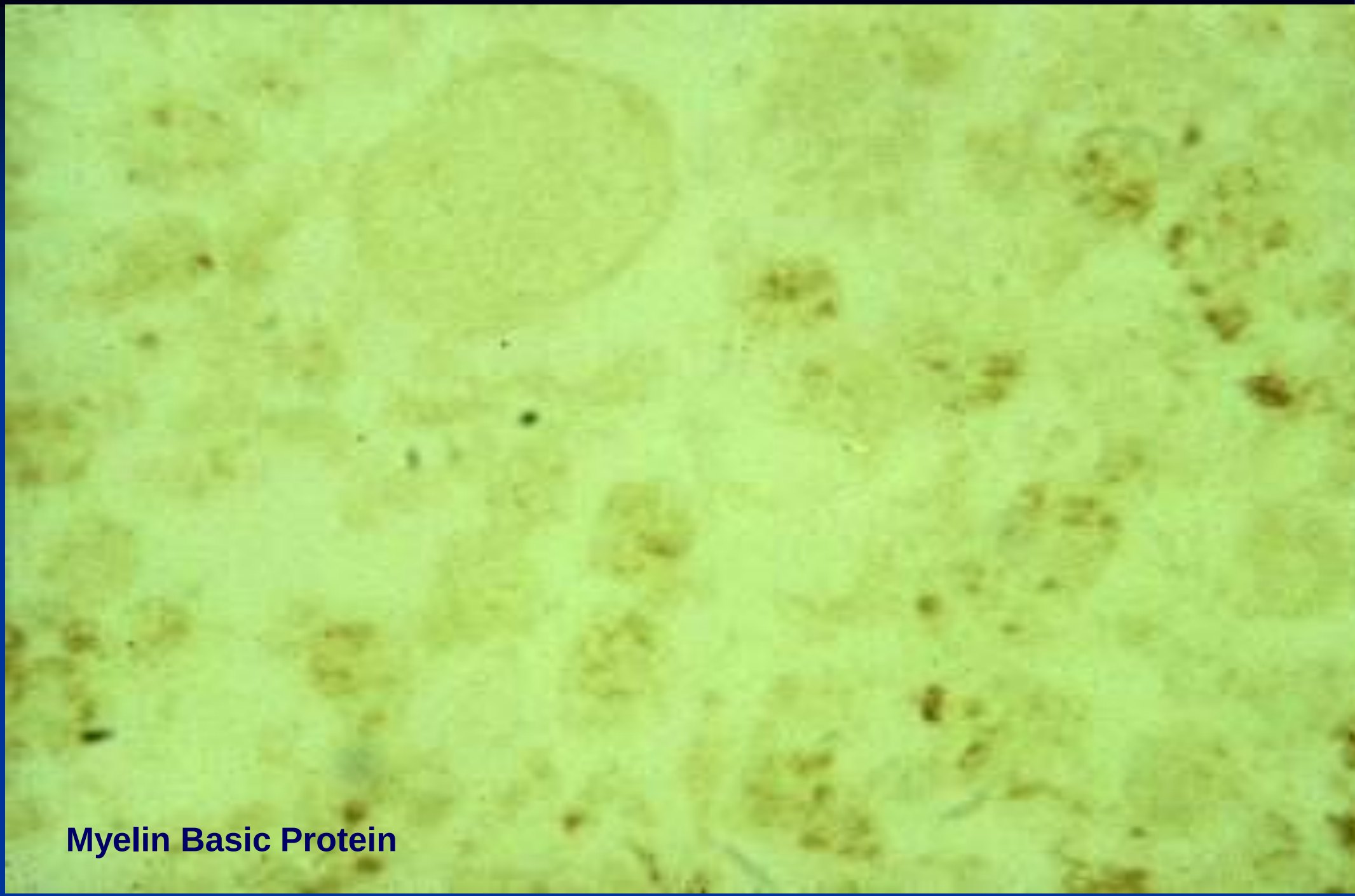
express	APP, complement receptor
produce	cytokines, NO
present	antigens

Synaptic stripping by microglia

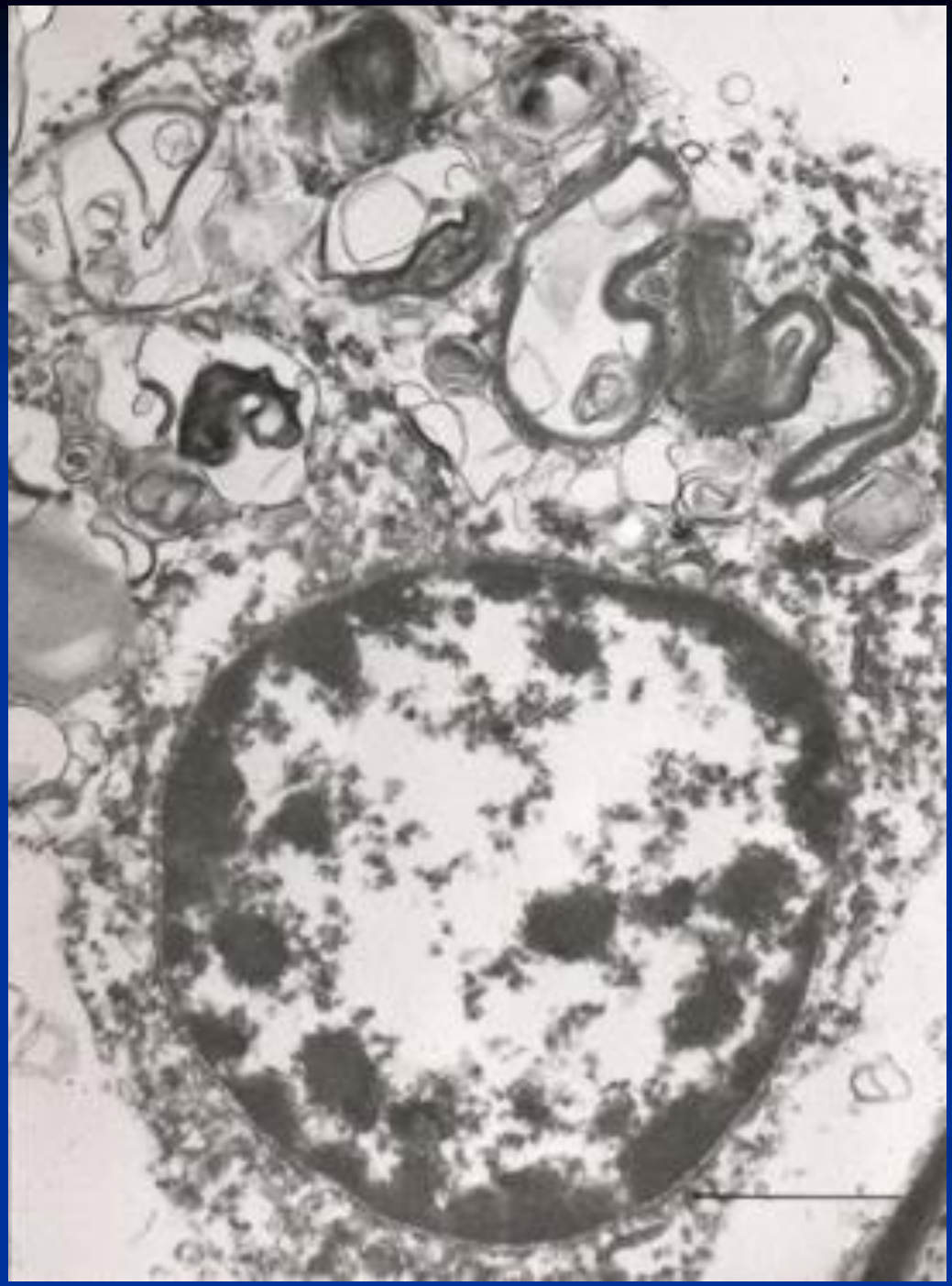

Kufs Disease

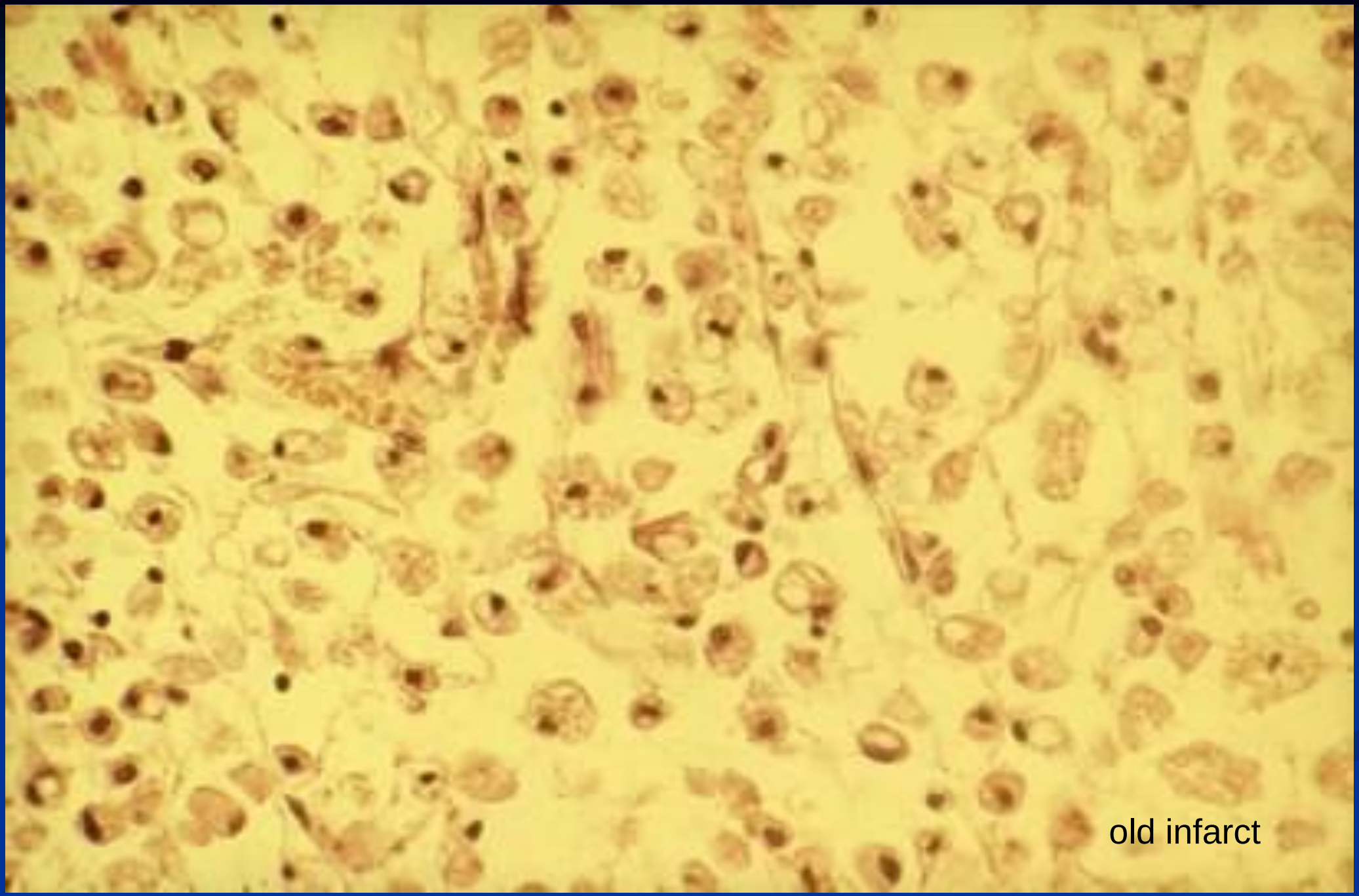


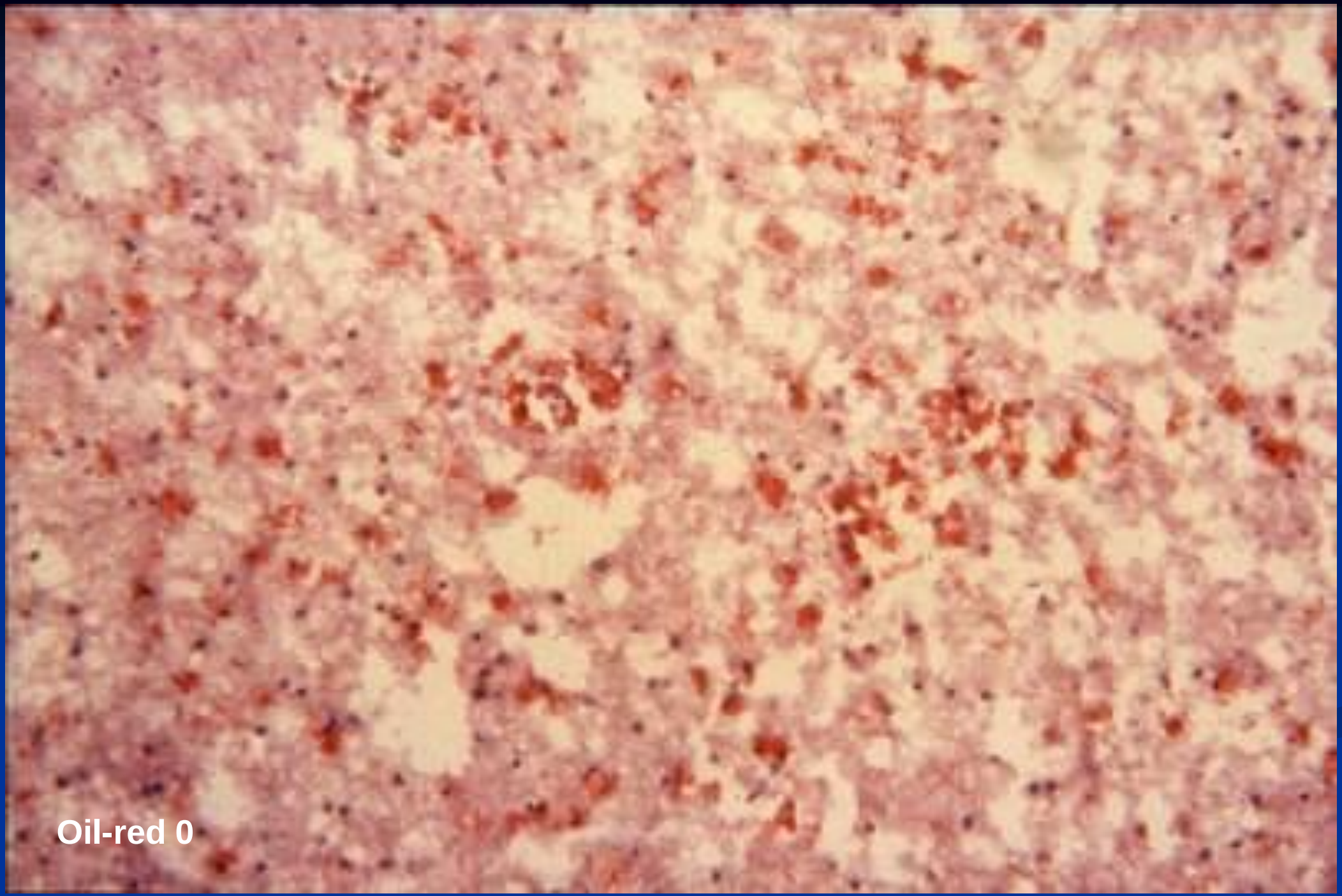

Infarct
CD 68



Myelin Basic Protein

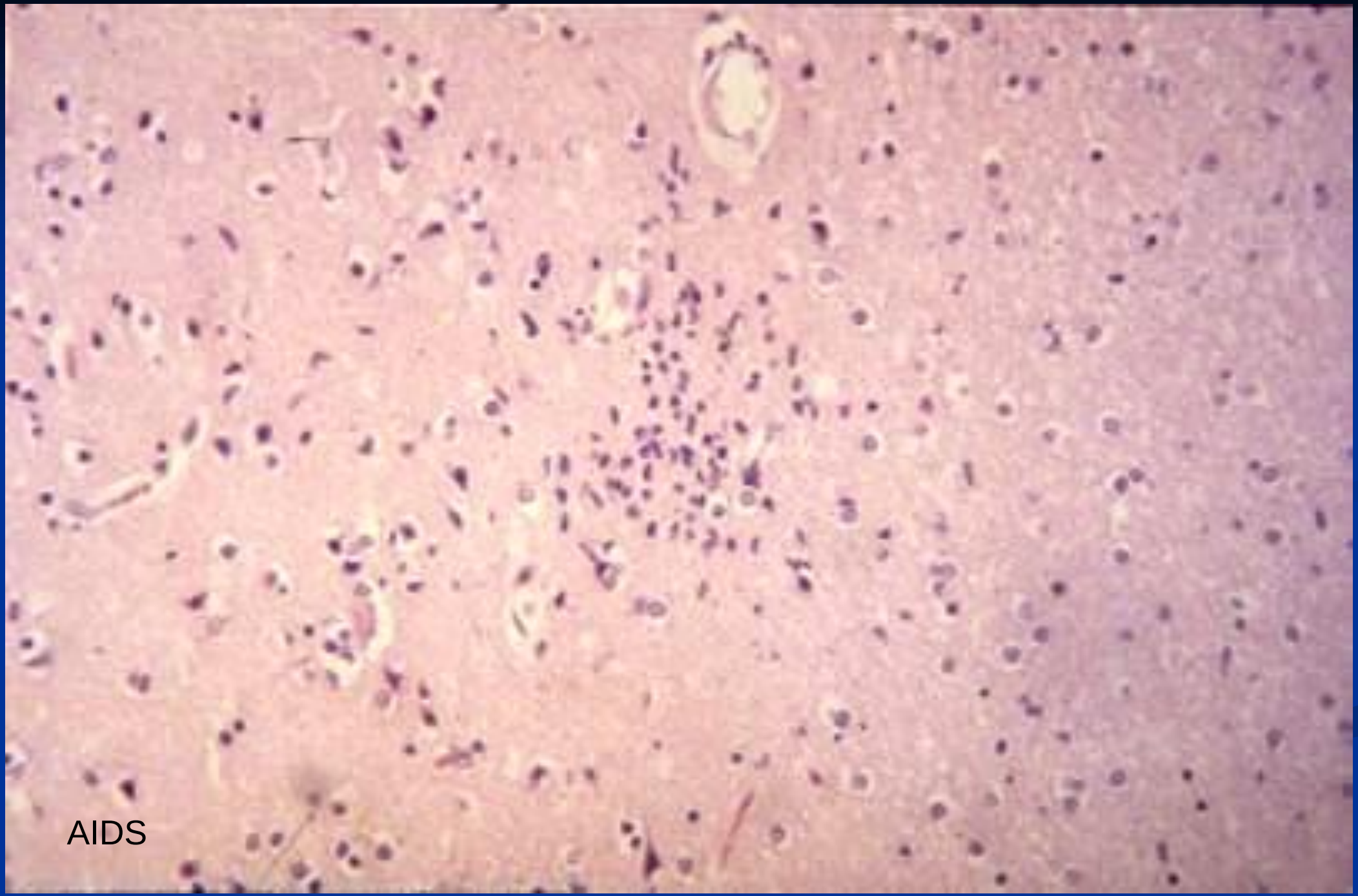


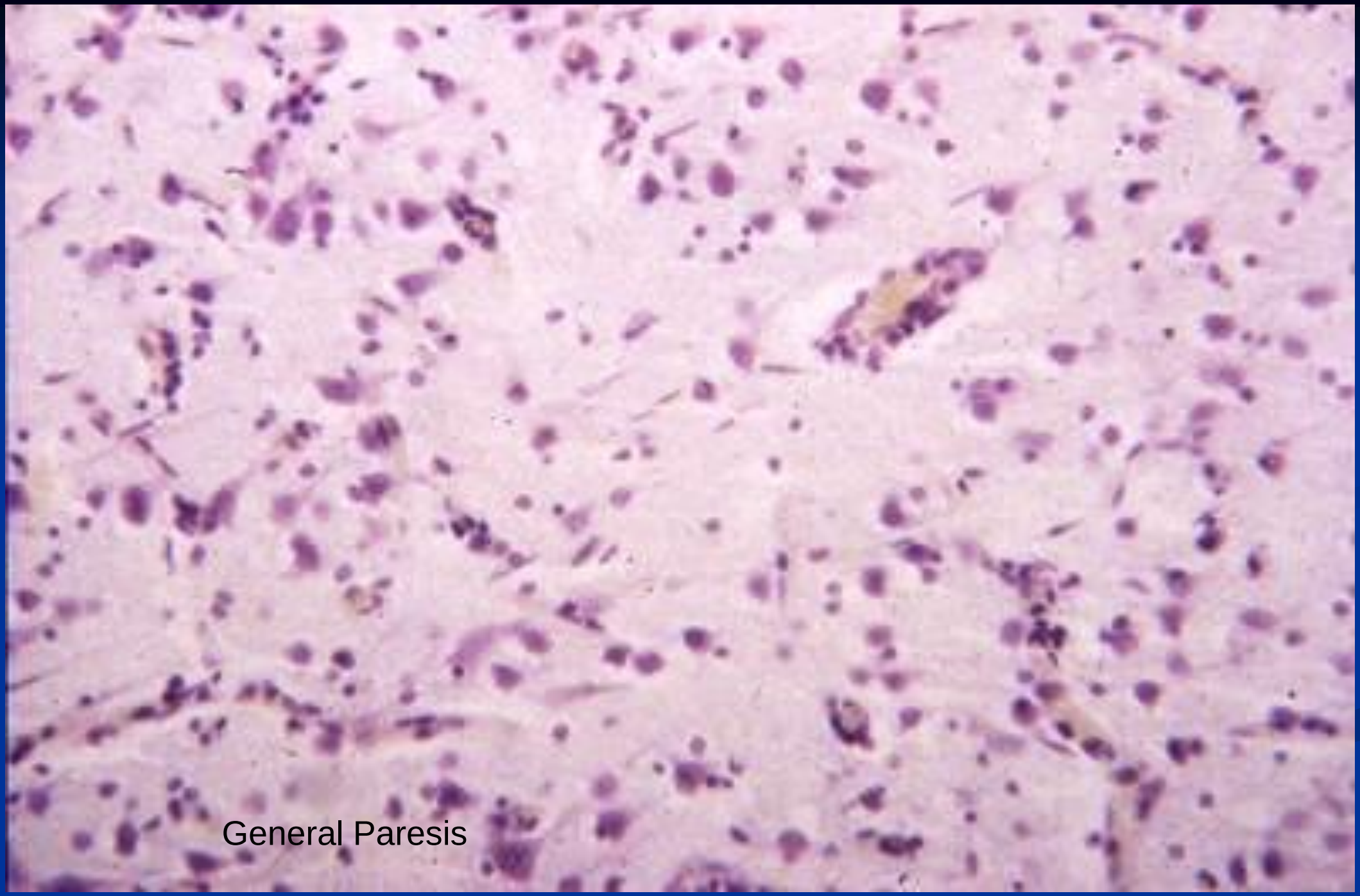

old infarct


Oil-red 0

Orthochromatic (sudanophilic) Degradation

metachromatic Degradation


AIDS


General Paresis

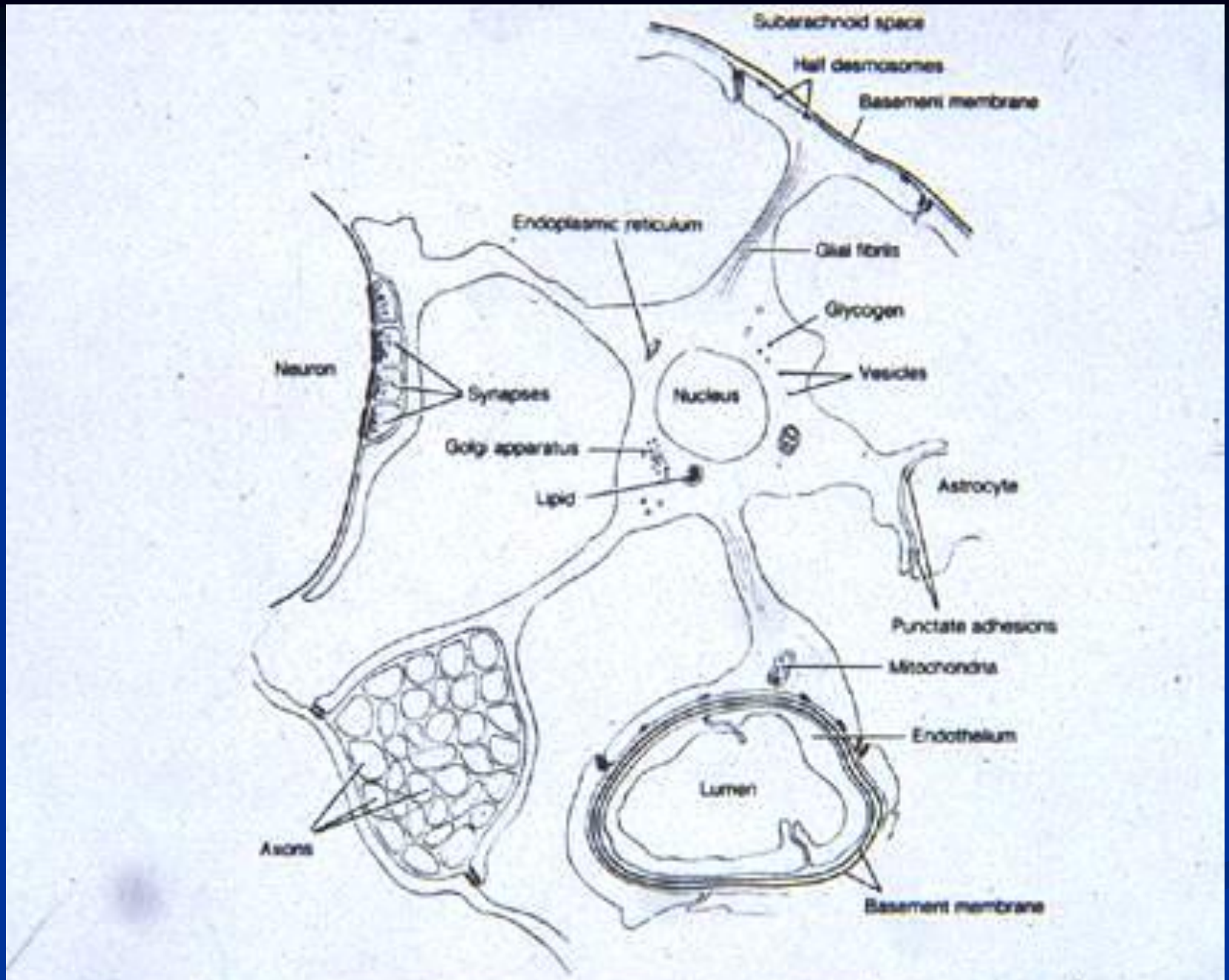


Figure 1.54. A diagram of the possible configurations of the astrocytic processes. (From A. Hirano

Hepatic Glia

Hypertrophy of astrocytic nuclei

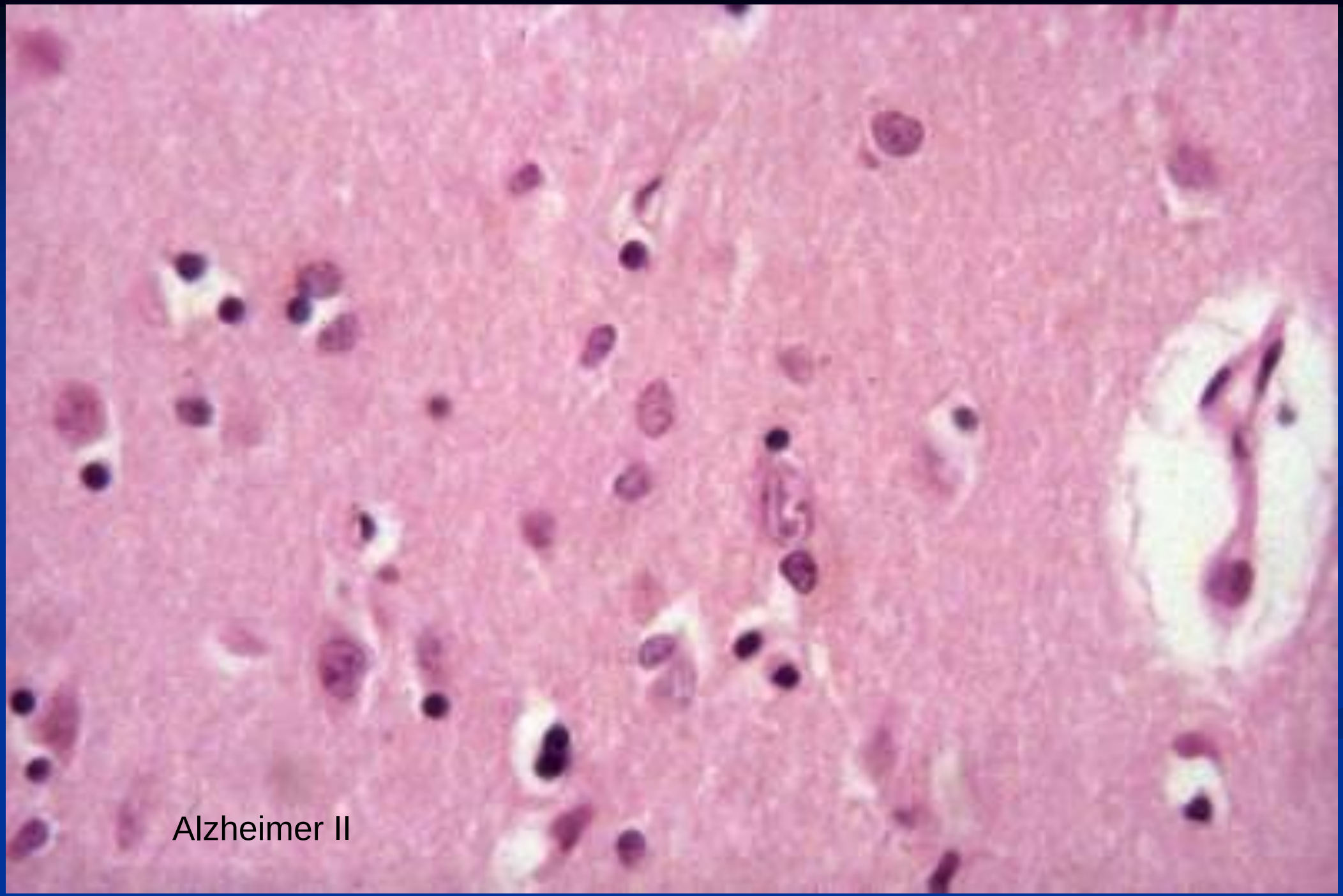
Alzheimer type I	=	Wilson disease (hepato-lenticular degeneration)
Alzheimer Type II	=	hepatic and uremic encephalopathies

Alzheimer type I glia:

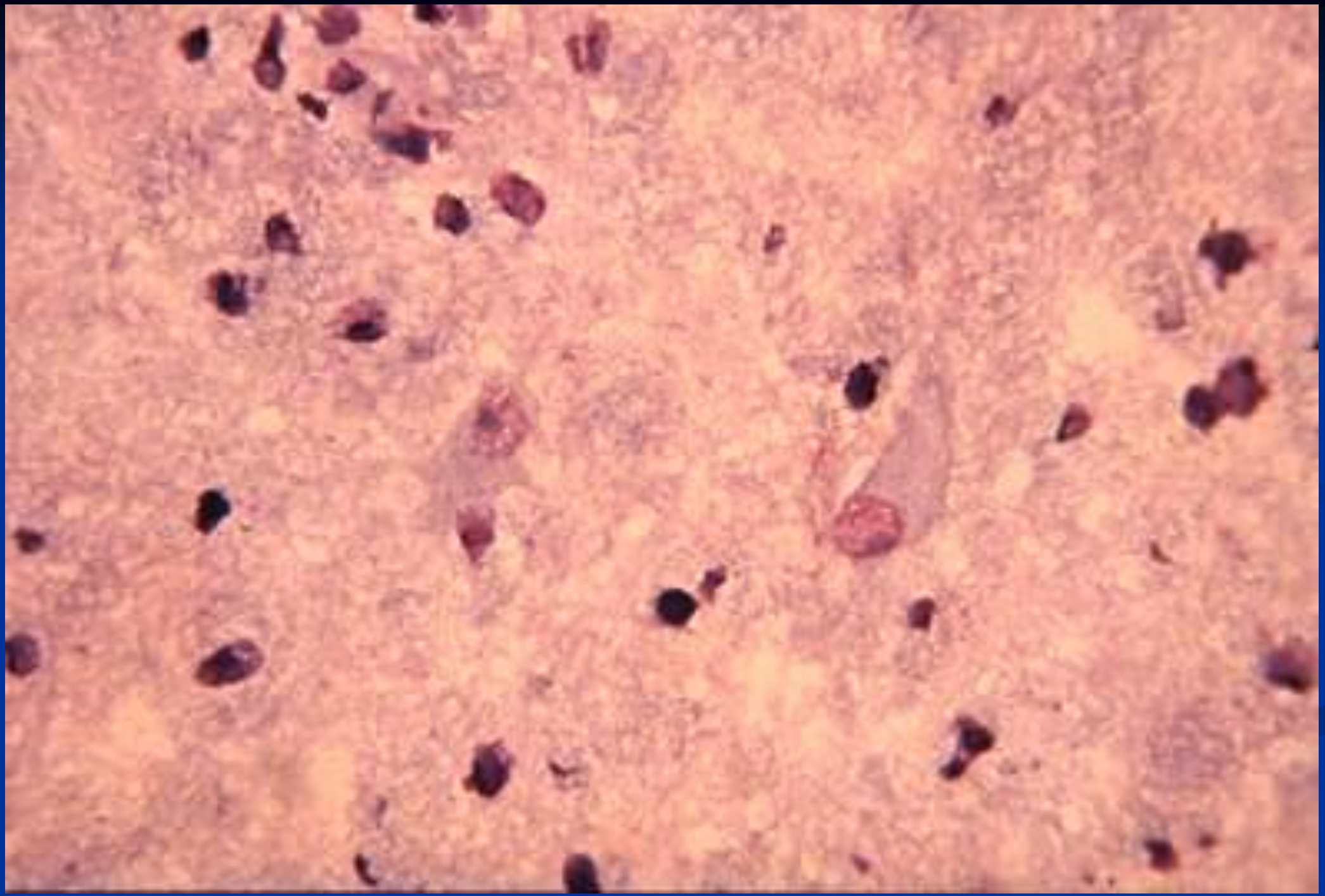
M. Wilson = hepatolenticular degeneration

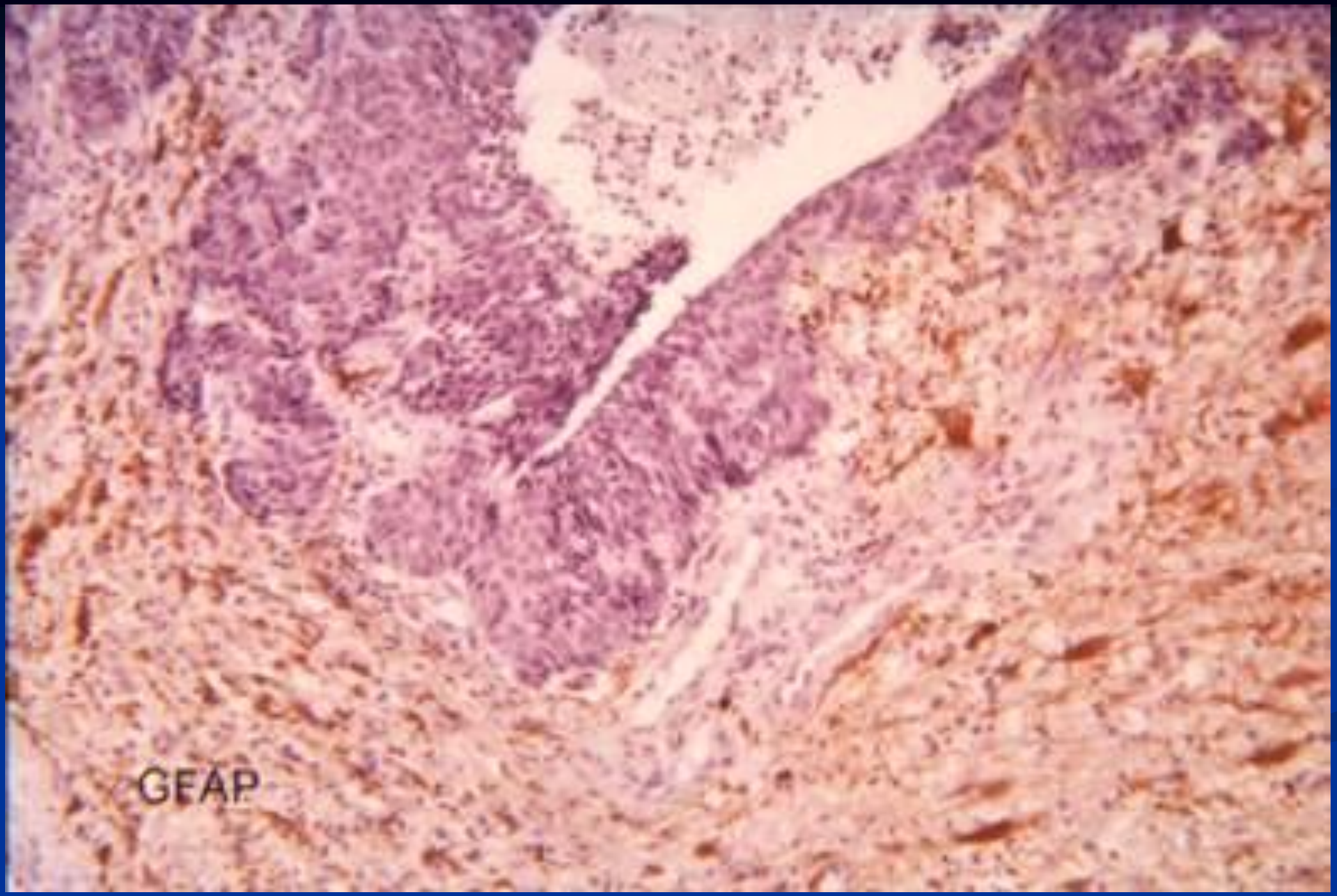
Alzheimer type II glia:

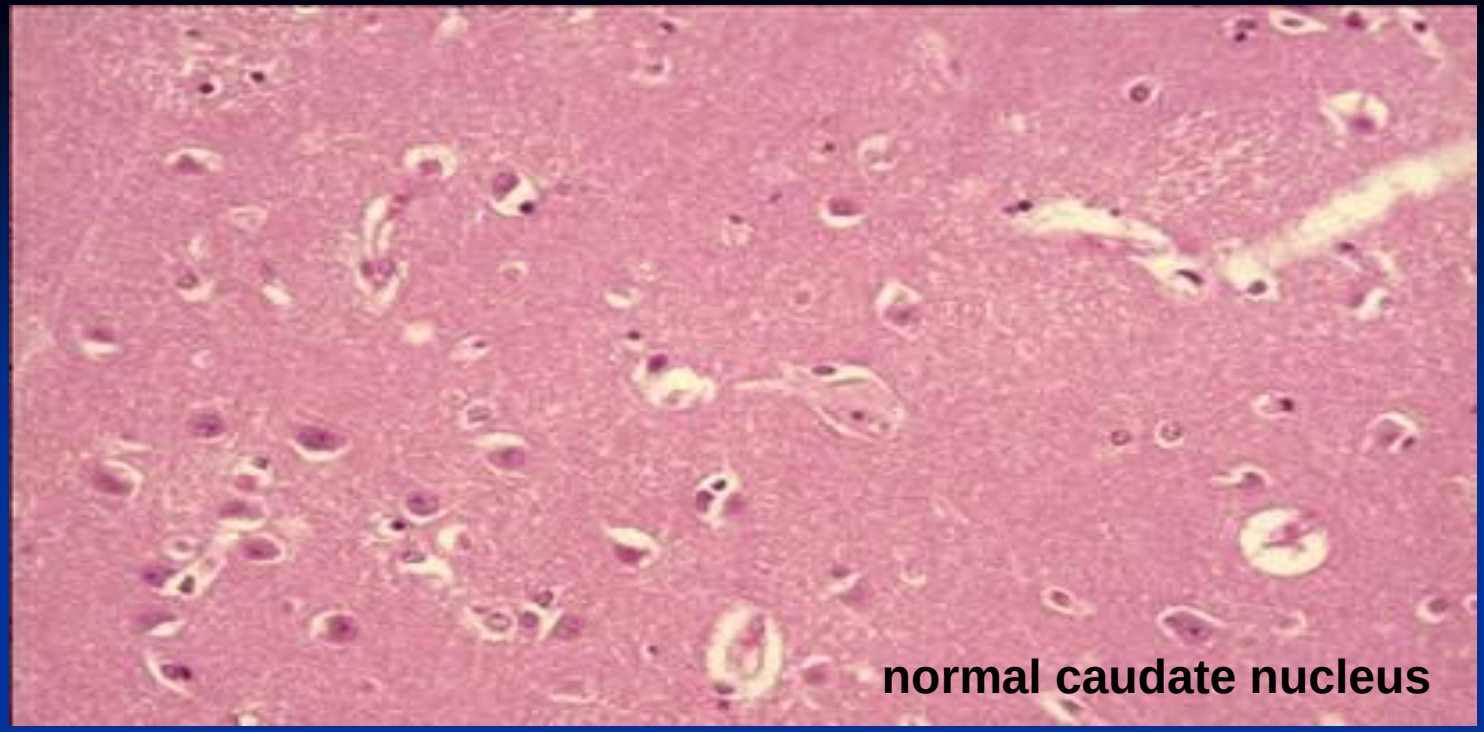
hepatic encephalopathy

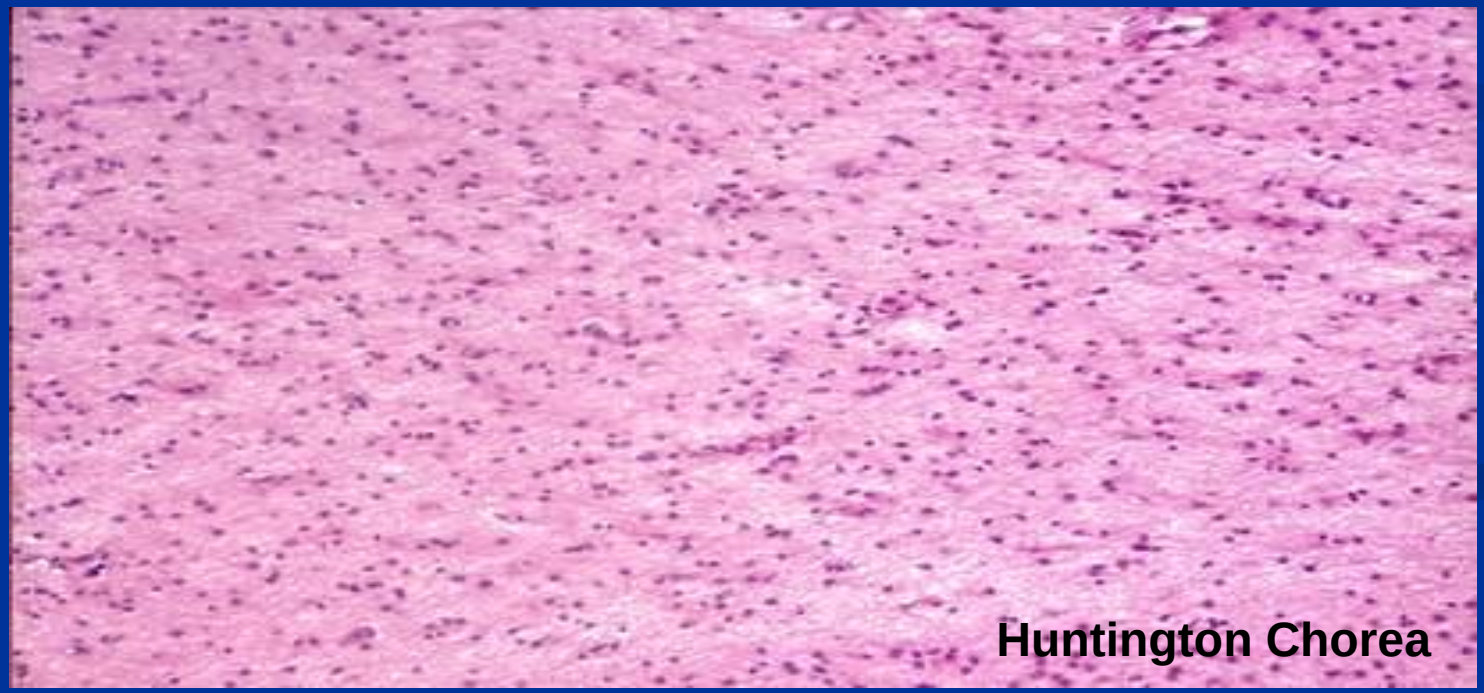

Alzheimer II

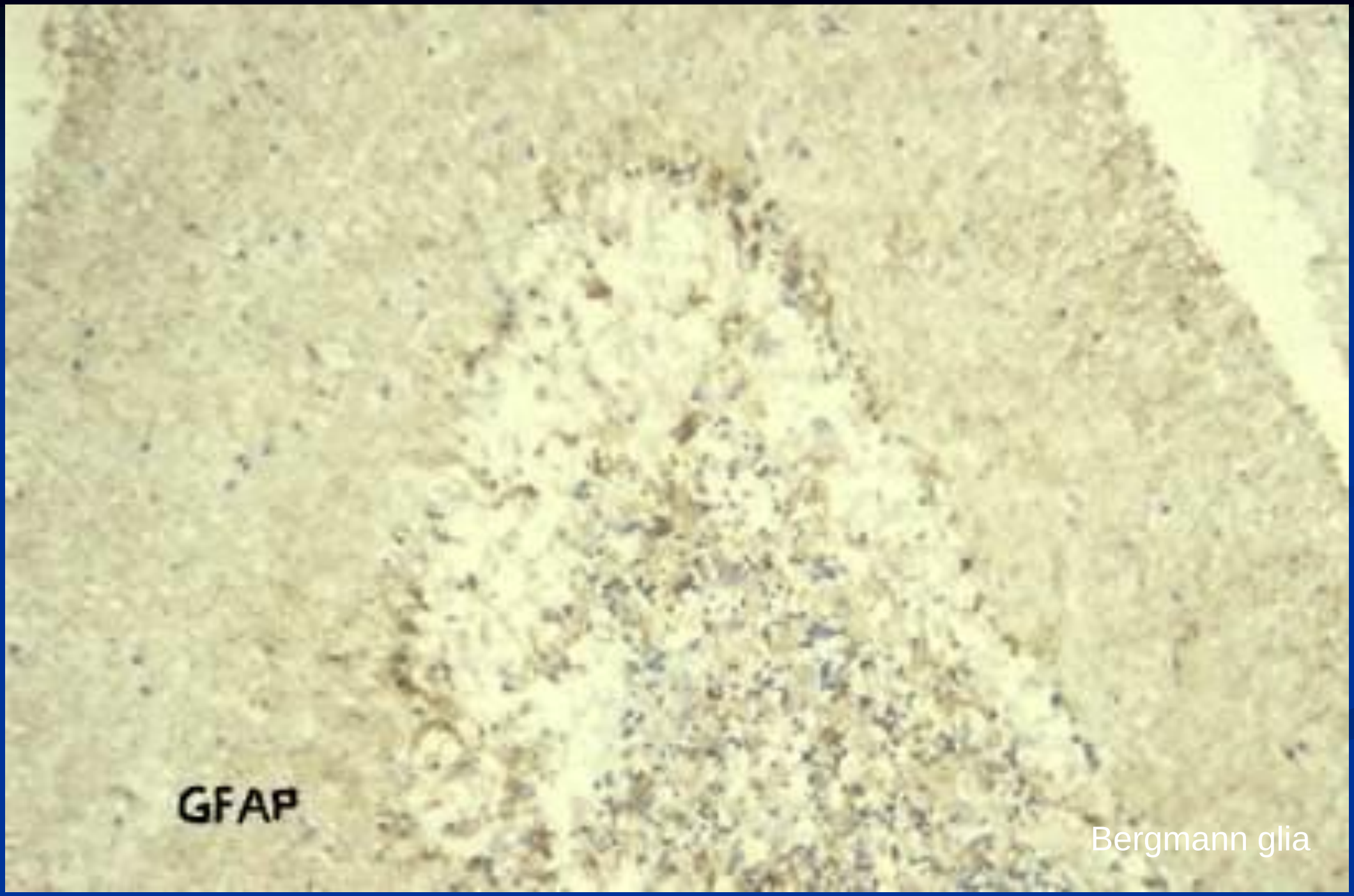
Gemistocytes



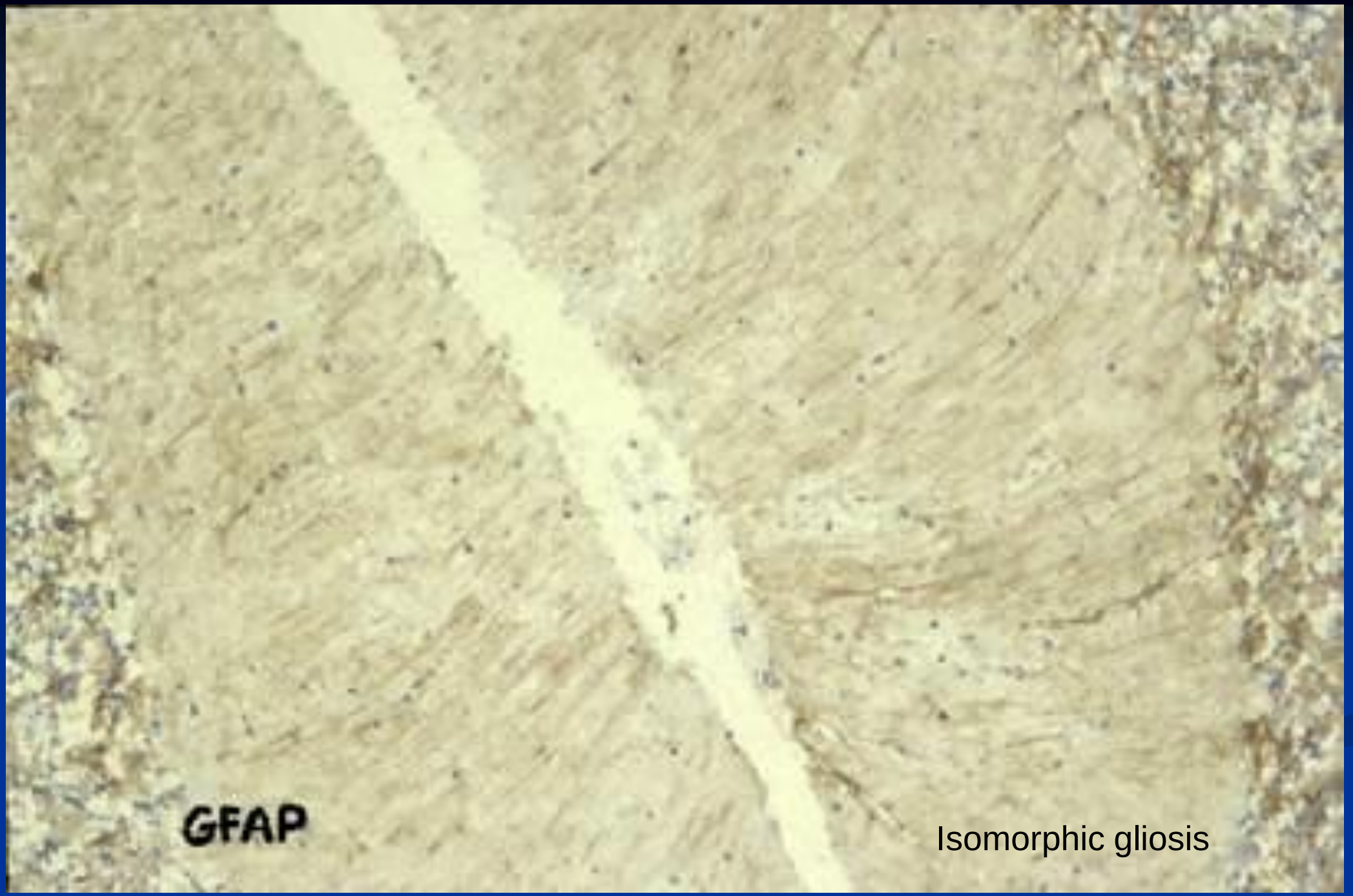

GFAP


normal caudate nucleus

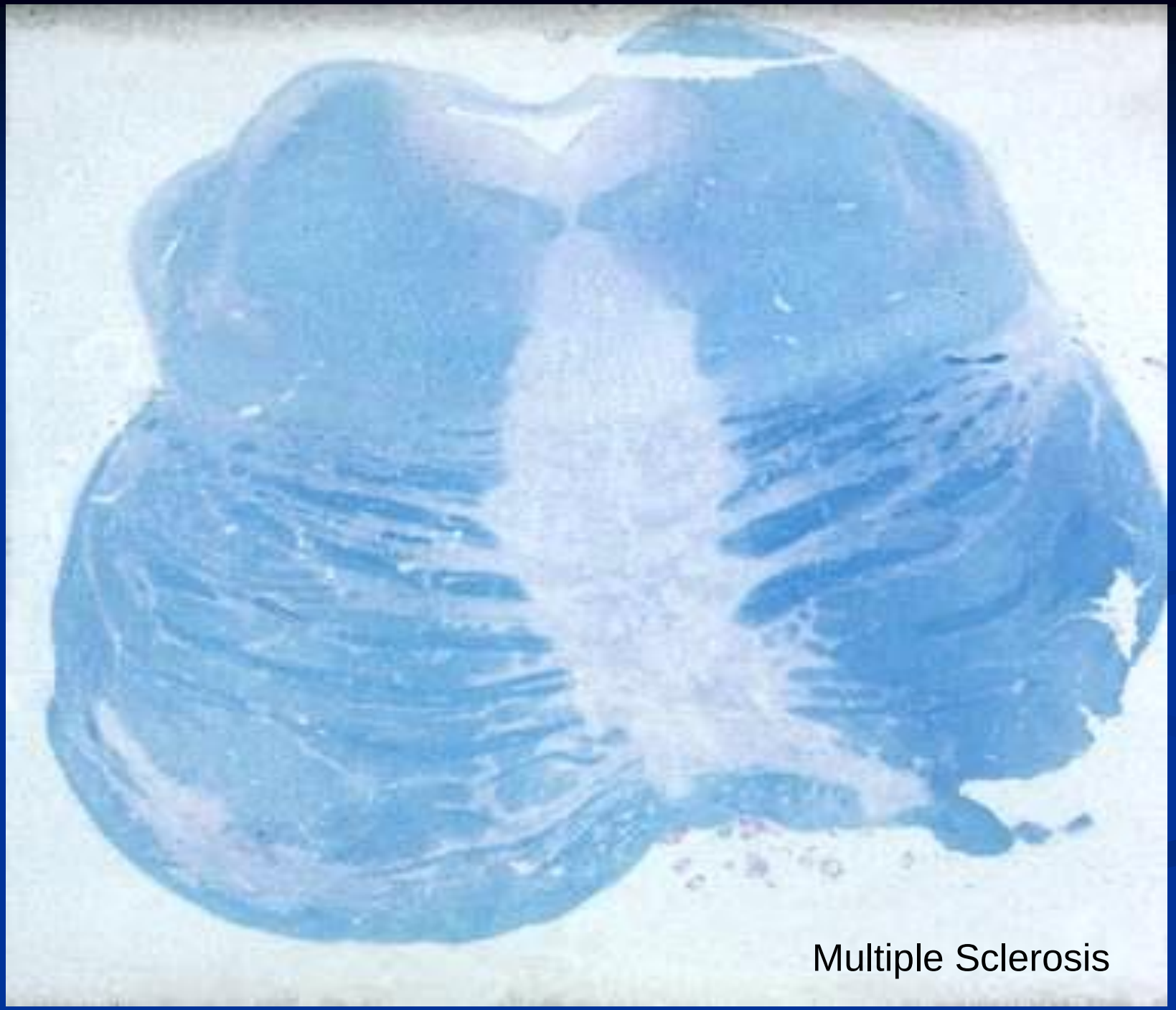

Huntington Chorea



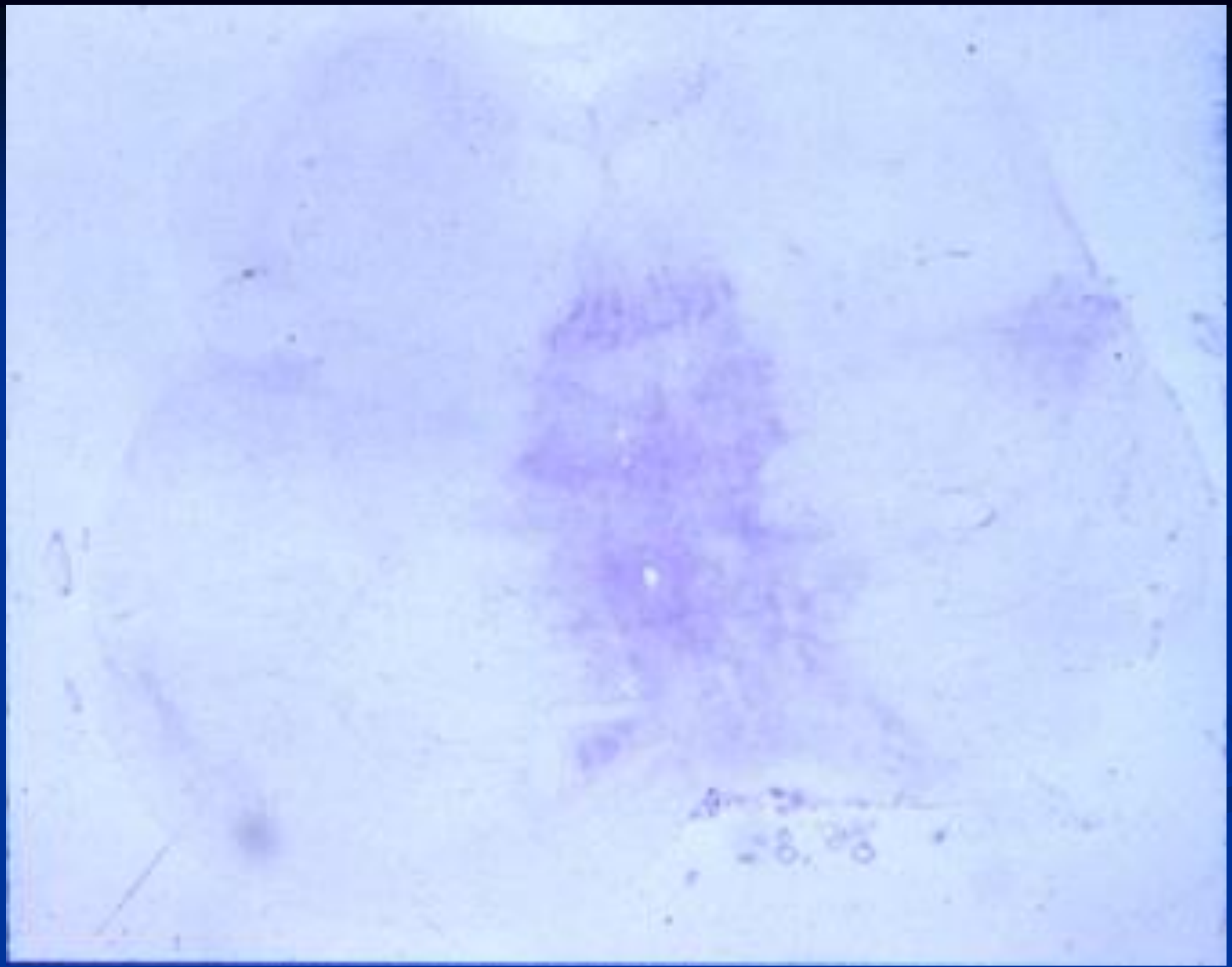
Bergmann glia



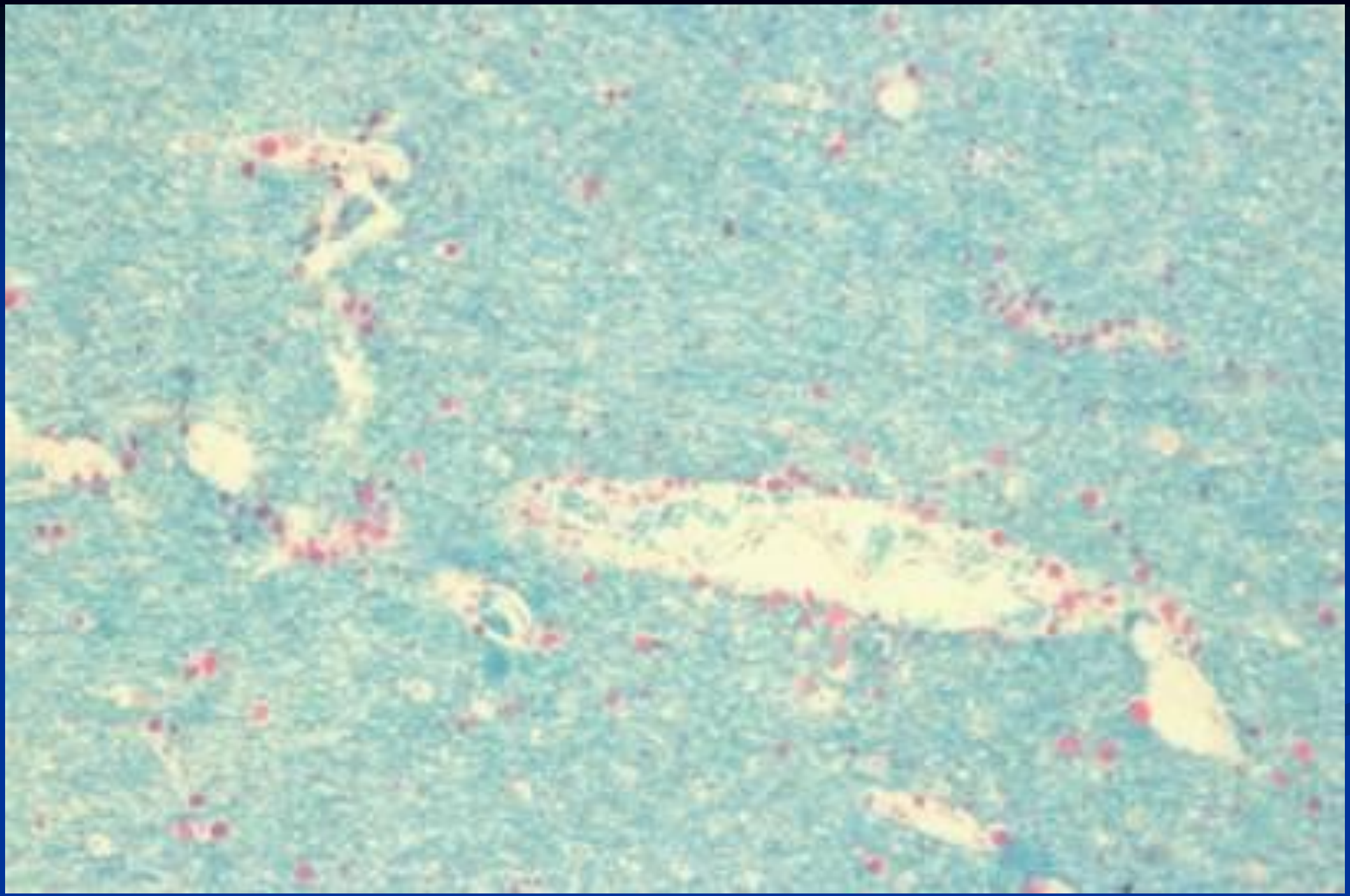
Isomorphic gliosis



Multiple Sclerosis



Corpora amylacea

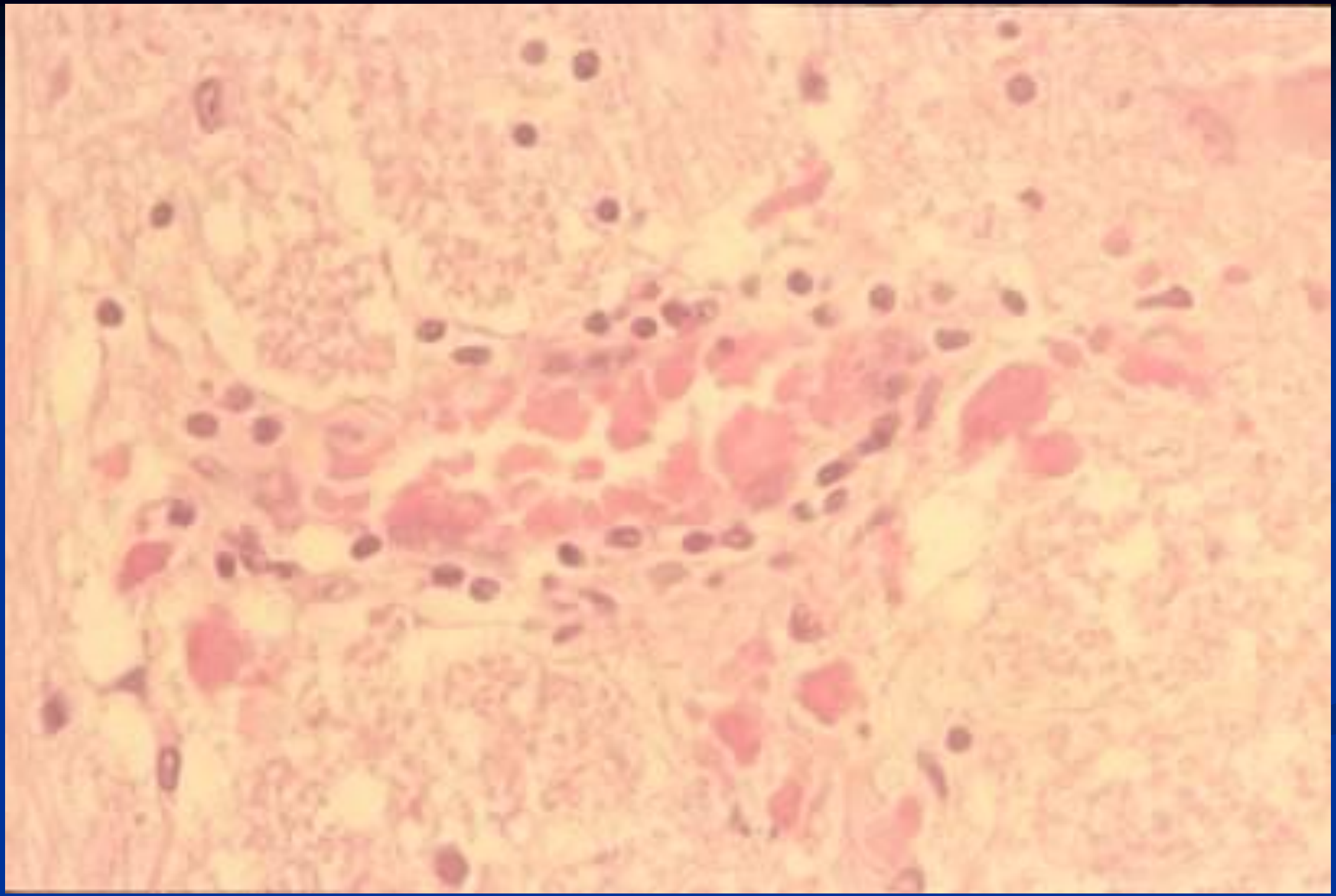


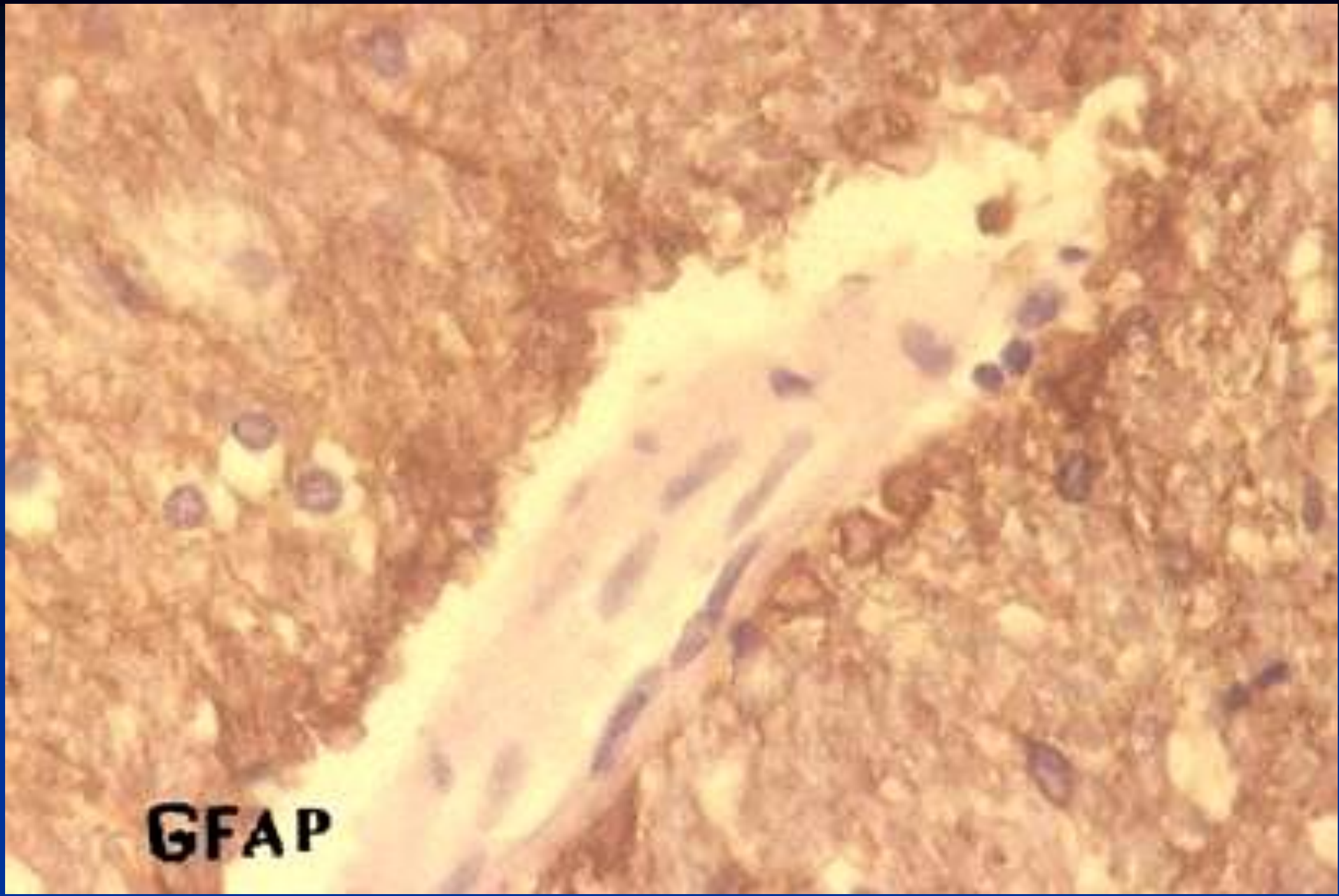
Rosenthal fibers: occurrence

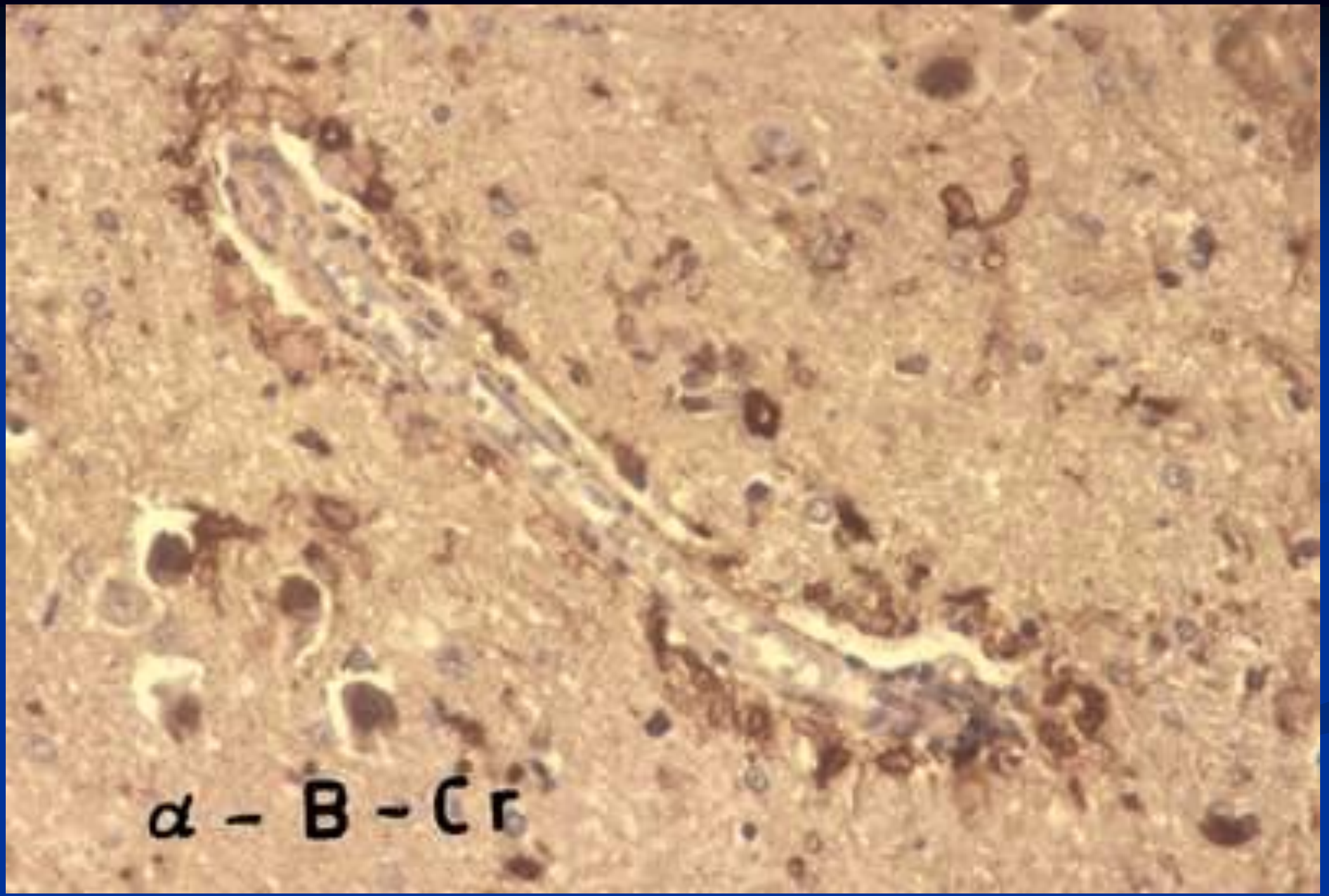
reactive
- around craniopharyngeoma
- around MS plaques

neoplastic (?)
- pilocytic astrocytoma

genetic
- Alexander disease
- giant axonal neuropathy




GFAP


α - B - Cr

Types of reaction

Cell types	Regressive/ degenerative	Progressive/hyper- trophic- hyperplastic
neuron	many specific and nonspecific alterations	none
oligodendroglia	limited	none (limited)
astrocyte	limited	astrocytosis
microglia	limited	inflammation phagocytosis

Space occupying Lesions

Contents of the Cranial Cavity

- 70 % brain tissue
- 12 % cerebrospinal fluid
- 15 % blood

Intracranial Pressure

normal adult	0-10 mm (upper limit 15 mm)
5-year old child	0-5 mm
newborn	0-3 mm
elevated	
mild	-25 mm
moderate	-30 mm
marked	-37,5 mm (electrical activity ceases, ischemia)
death	-60 mm

Causes of space-occupying lesions

tubors

haemorrhages

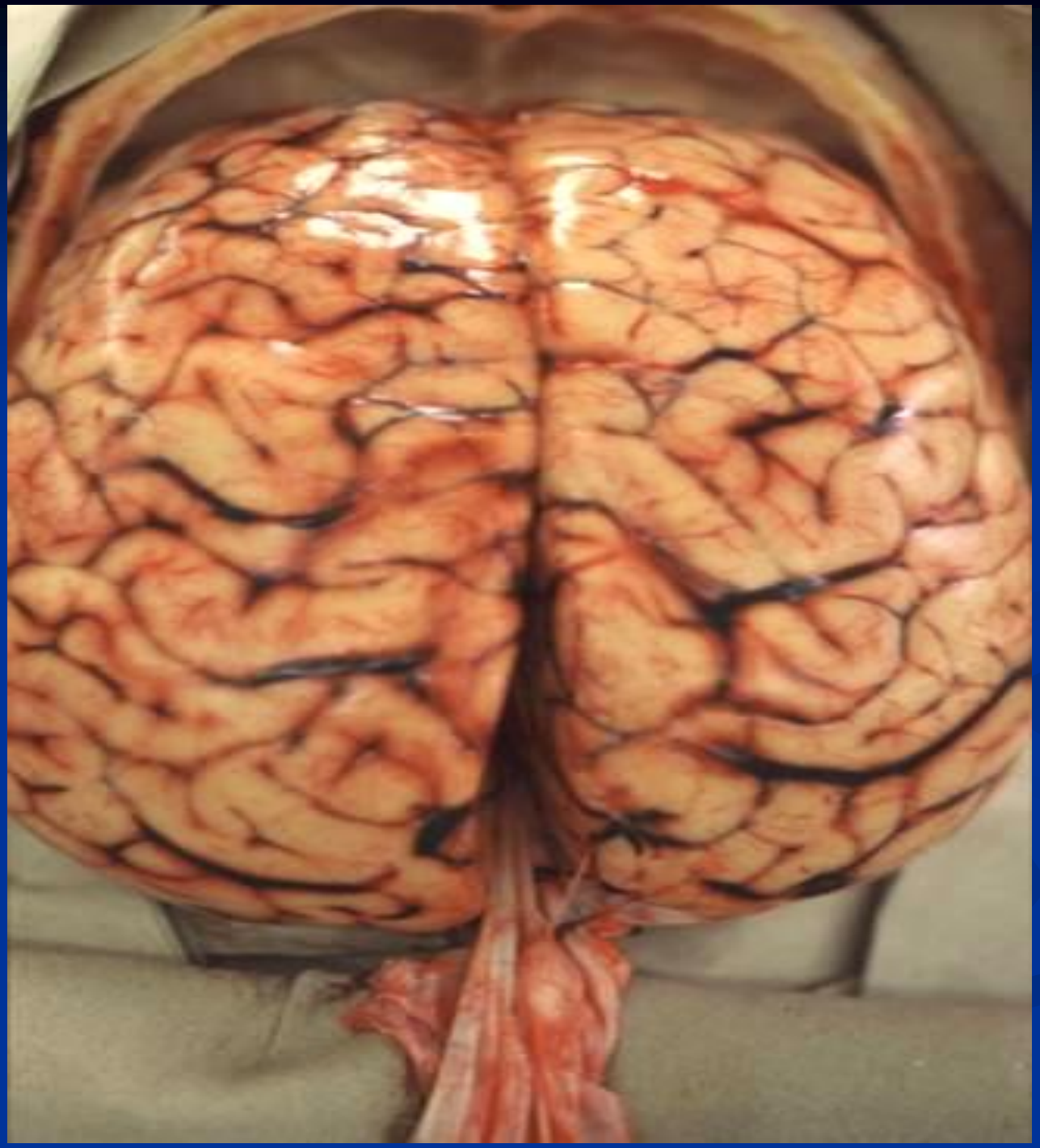
inflammatory processes

blockage of CSF (hydrocephalus)

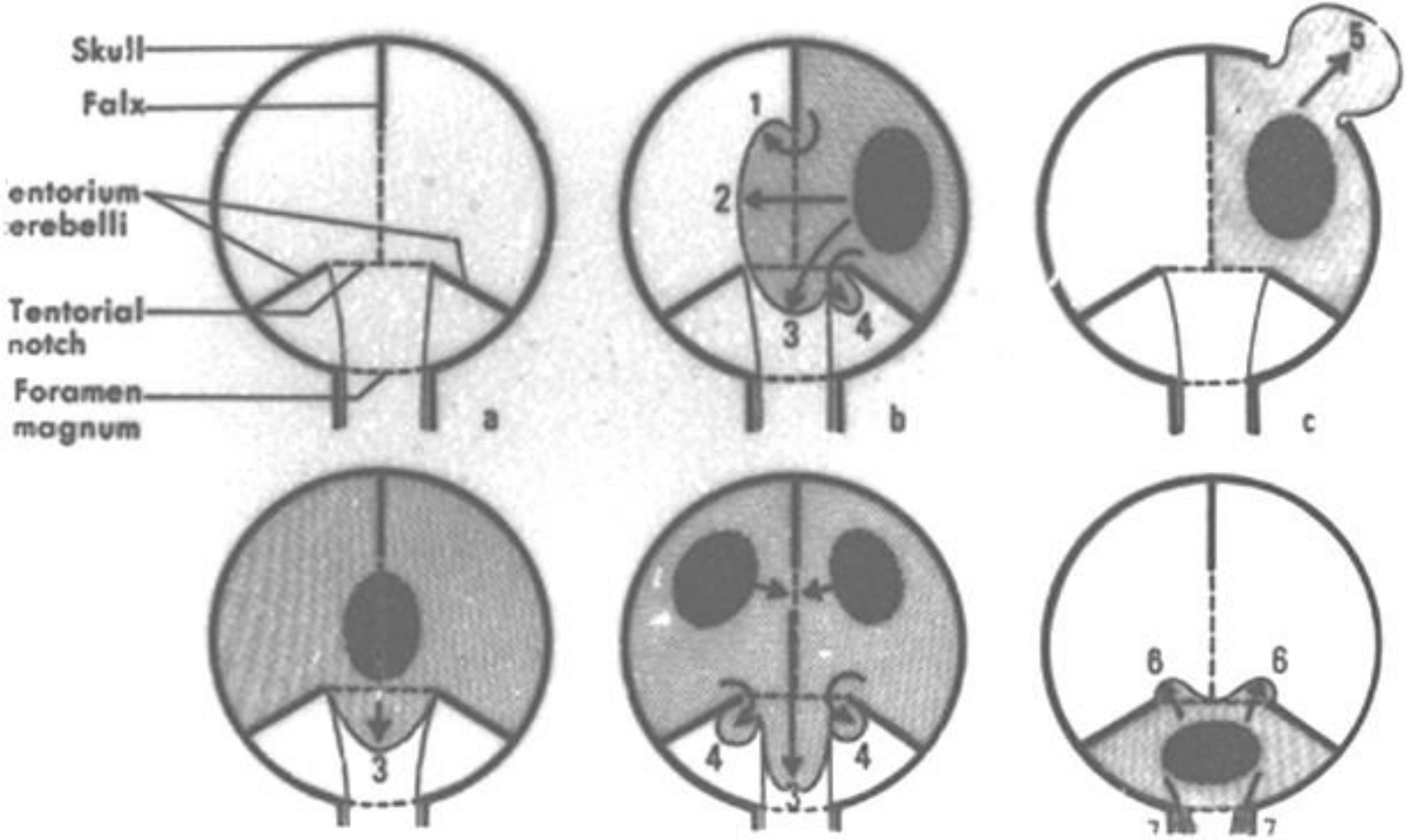
brain edema

trauma

ischemia / anoxia



TUMORS OF THE CENTRAL NERVOUS SYSTEM



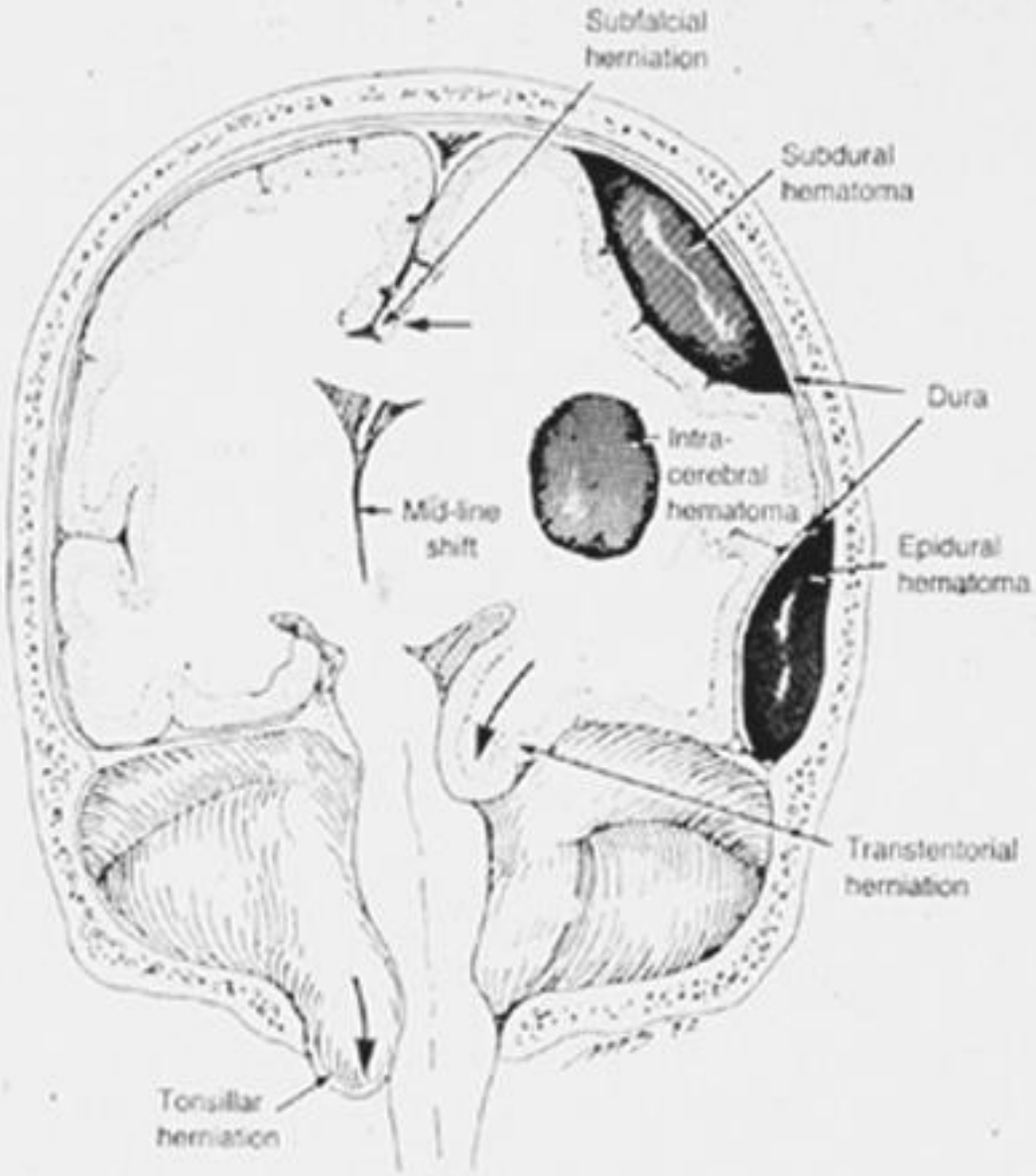
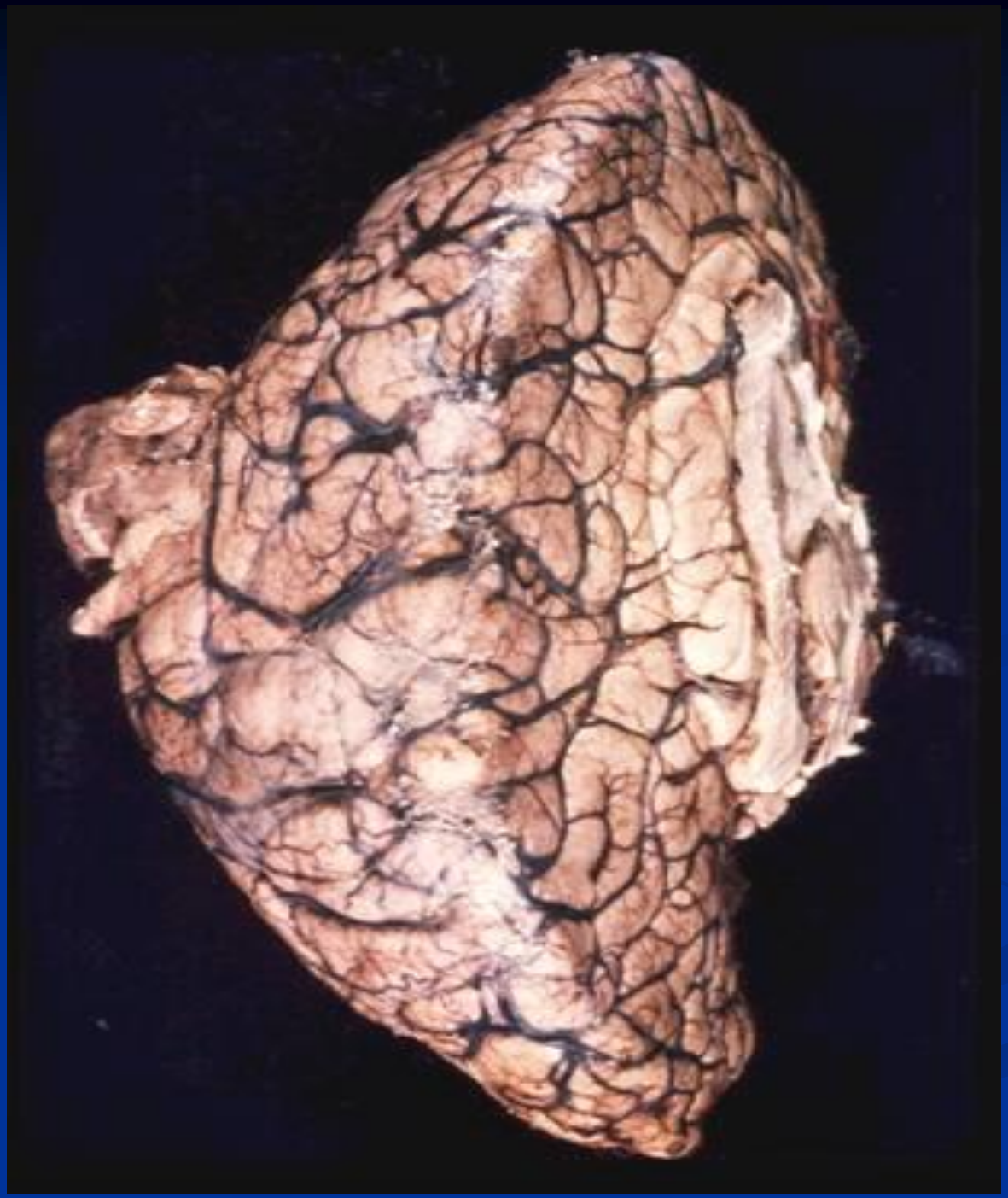


Figure 1. Types of Intracranial Hemorrhage and Brain Herniation. Adapted from Bullock and Teasdale,[4] with the permission of the publisher.



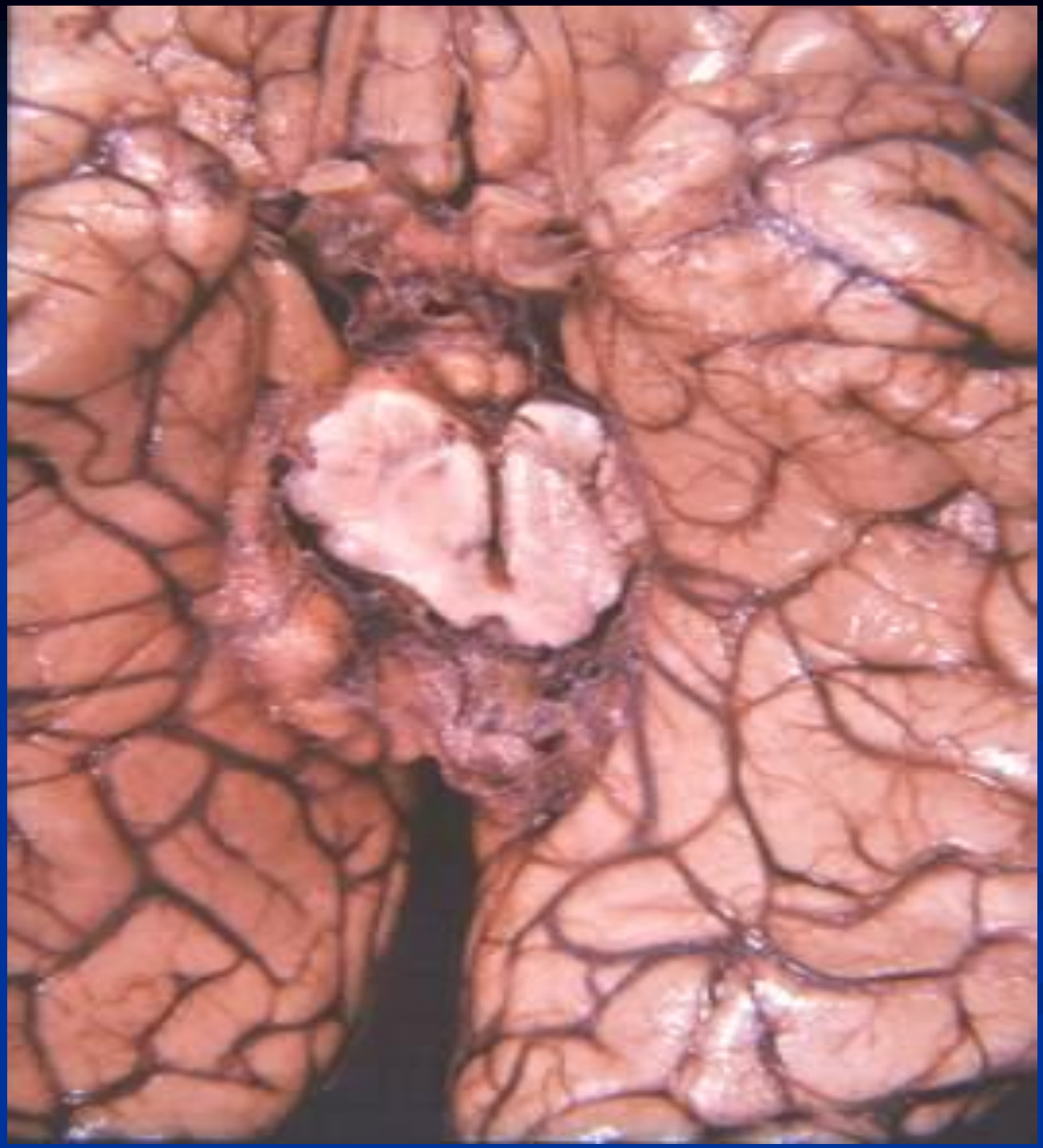
Herniations

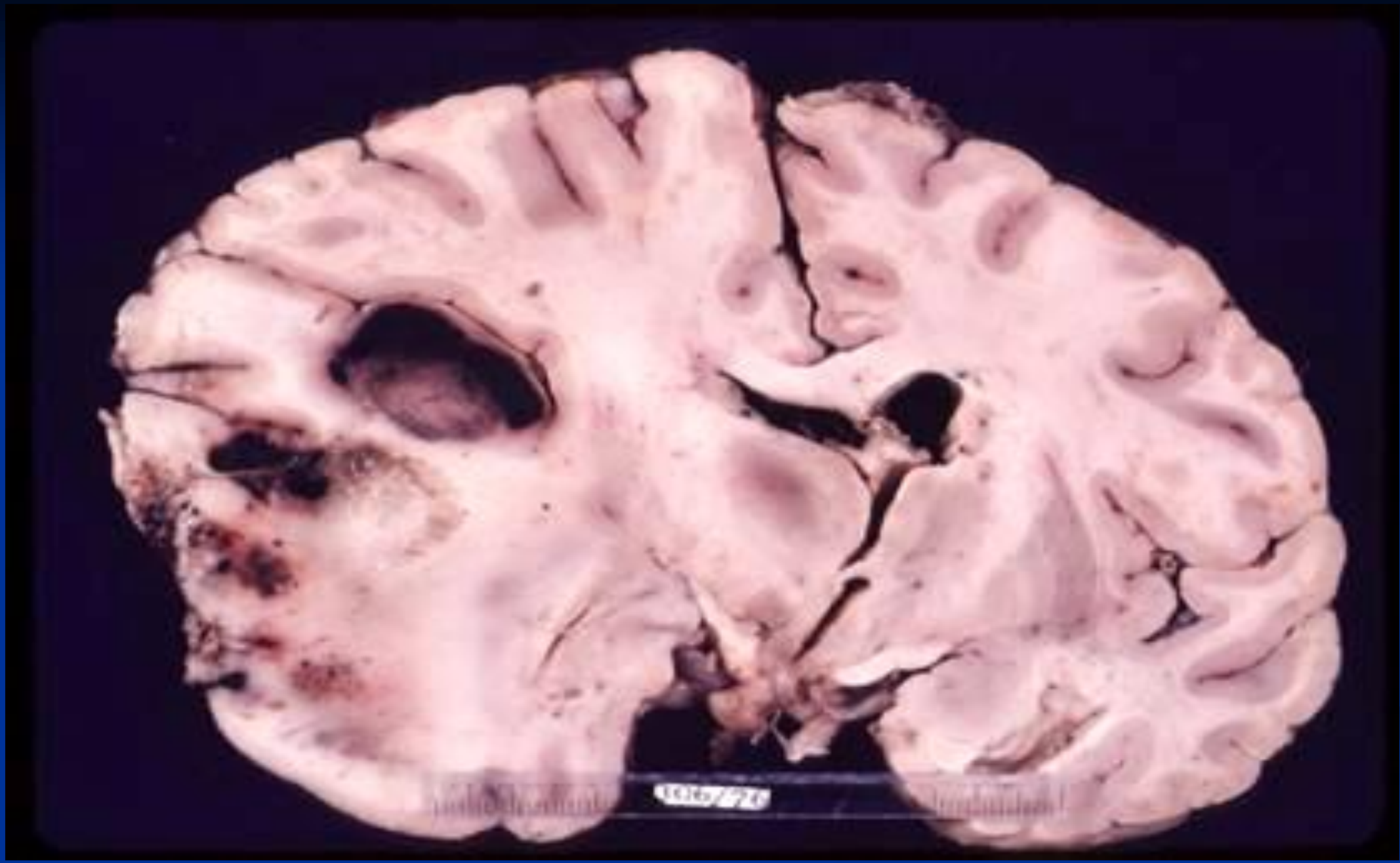
Subfalcial herniation
right and left supratentorial cavities

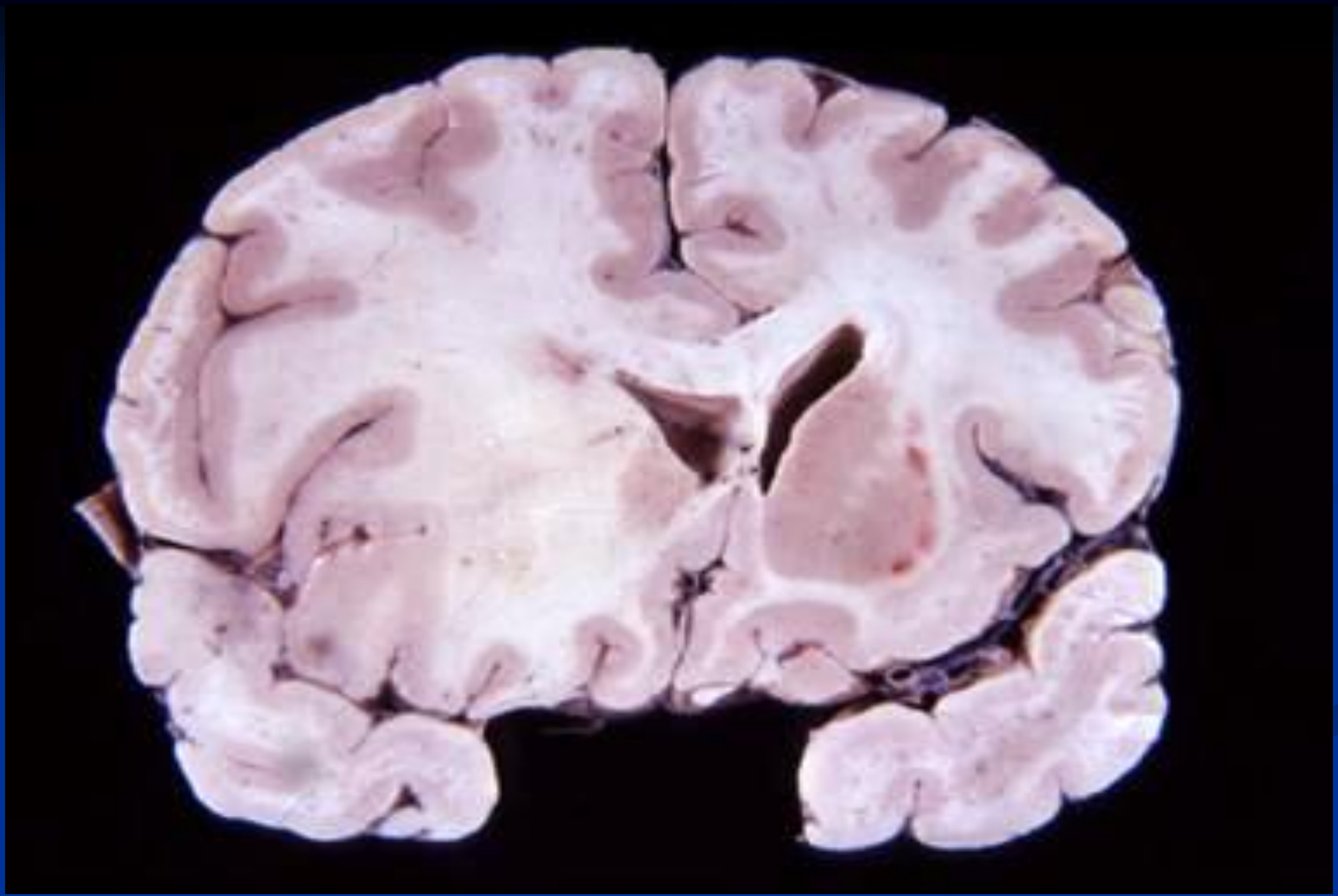
Uncus herniation
supratentorial cavities → infratentorial cavity

tonsillar herniation
infratentorial cavity → spinal canal

Retrograde: cerebellum
infratentorial cavity → supratentorial cavity







Walther Wagner

MAINZ