Hashemite University
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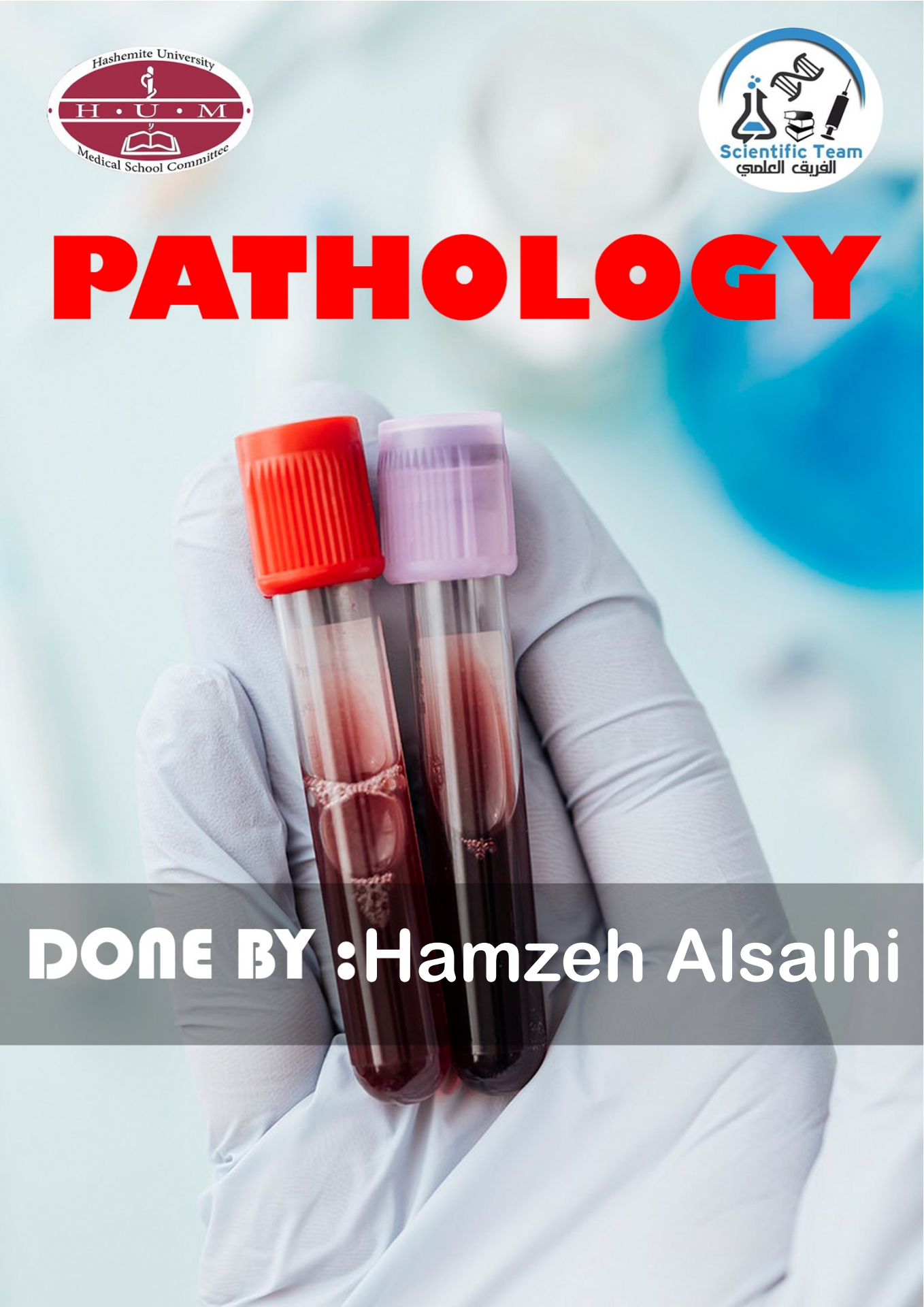
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY



DONE BY :Hamzeh Alsalhi

Clinically, ☺ **l-DOPA therapy is often extremely effective in symptomatic treatment,** but it does not significantly alter the progressive nature of the disease.
☹ **Over time, l-DOPA becomes less effective** at providing the patient with symptomatic relief & begins to cause fluctuations in motor function on its own.

▼The disease usually progresses over 10 to 15 years, with eventual severe motor slowing to the point of **near immobility**.
وبصير مُقعد.

☠ Death is usually the result of:
(1) **intercurrent infection** or
(2) **trauma from frequent falls caused by postural instability**
بسبب طريقة المشي

☹ About **10% to 15%** of Parkinson patients develop **dementia**, with the incidence ↑ with advancing age. While many affected individuals also have pathologic evidence of AD, the **dementia in other Parkinson disease patients is attributed to widely disseminated Lewy bodies in the cerebral cortex**.
سببين لحدوث الـ dementia

Huntington Disease (HD)

★**HD** is an **inherited autosomal dominant** disease characterized clinically by **progressive movement disorders (I) chorea & (II) dementia, with degeneration of the striatum (caudate & putamen).**

Chorea consist of jerky, hyperkinetic & involuntary movements **affecting all parts of the body;** patients may develop Parkinsonism with bradykinesia & rigidity. **HD** is relentless & progressive, resulting in ☠ **death** after an average of 15 years.

▶**All individuals with *HD have the same type of mutation-a trinucleotide repeat expansion* in a gene located on 4p16.3 that encodes a large protein (huntingtin).**

There is a polymorphic CAG trinucleotide repeat in the gene, encoding a polyglutamine tract in the protein.

☺ **Normal alleles contain 11 to 34 copies of the repeat;**

☹ In **HD** disease-causing alleles, the number of repeats is ↑, sometimes **into the hundreds.**

There is strong genotype-phenotype correlation, i.e., the larger the number of repeats, the earlier the onset of the disease.

😐 **Pathogenesis: although** not formally proved, it is possible that the **abnormal protein fails to fold properly**, & accumulation of misfolded protein triggers apoptosis in some neurons.

►**Grossly, the HD brain is small & shows • striking atrophy of the caudate nucleus &, sometimes less dramatically, the putamen (F23-31).** Pathologic changes develop over the course of the illness in a medial to lateral direction in the caudate & from dorsal to ventral in the putamen. The globus pallidus may be atrophied secondarily, & the lateral & third ventricles are dilated. • **Atrophy** is frequent in the **frontal lobe,** less often in the **parietal** & occasionally in the entire cortex.

Hydrocephalus exvacue. تؤدي إلى

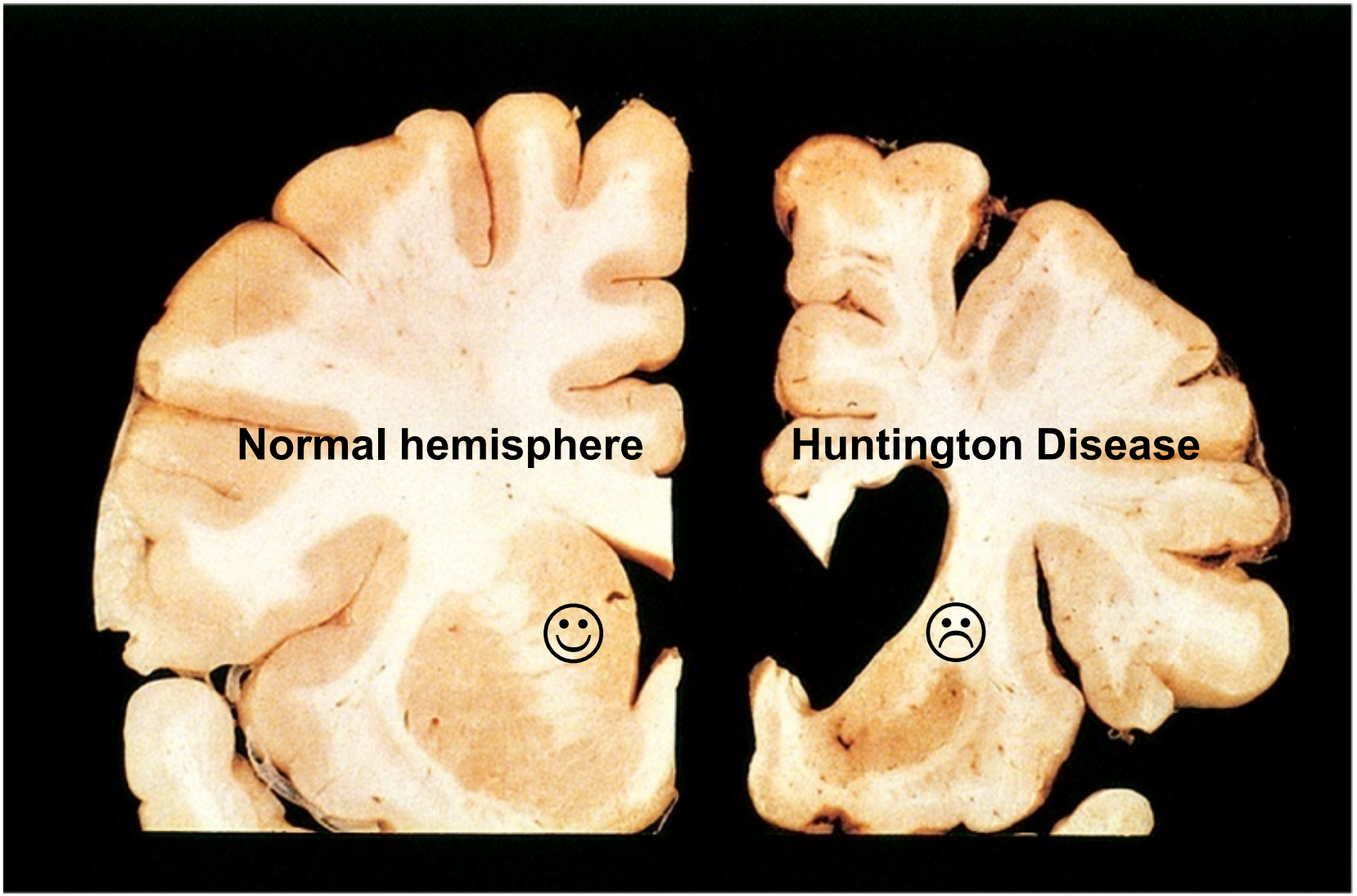
gliosis أي خلية ماتت بيع بتروح عنها بـ

■H, there is **(I) severe loss of neurons from these regions of the striatum,** with extensive fibrillary gliosis, & **(II)** in the remaining striatal neurons & in the cortex, there are **intranuclear inclusions that contain aggregates of ubiquitinated huntingtin protein.**

not in cytoplasm.. مهم انتبه

The size Hydr

F23-31: **Huntington disease.** Normal hemisphere on the left compared with the hemisphere with Huntington disease on the right showing atrophy of the striatum & ventricular dilation and



Clinically, HD onset is commonly in the 4th & 5th decades & is related to the length of the CAG repeat. **When repeat lengths exceed 70 copies**, the disease can present in adolescence or even earlier **(juvenile HD)**. There is:

(I) motor symptoms **choreiform** ↑ involuntary jerky movements of all parts of the body with writhing (Tangling) movements of the extremities; often precede the (II) symptoms of higher cortical dysfunction which may progress to a severe **dementia.**

☠ HD patients have an ↑ **risk of suicide**; **intercurrent infection** is the common natural cause of death.

Spinocerebellar ataxia (***Friedreich ataxia***)

★**Autosomal recessive progressive** illness that affect the **cerebellum ,** begin in the **1st decade** of life with **gait ataxia**, followed by **hand clumsiness & dysarthria.** There are ↓ or absent deep tendon reflexes; positive Babinski sign; impaired joint position & vibratory sense; & loss of pain, temperature sensation, & light touch. ☹ There is a **high incidence of cardiac disease & diabetes**. Most patients become wheelchair bound within 5 years of onset. ☠The cause of death is **intercurrent pulmonary infections & cardiac disease.**

Diseases of Motor Neurons

★These are a numbers of diseases that affect the:
(I) **lower** motor neurons in the spinal cord (**SC**) & in the brain stem, loss of which results in denervation of muscles, with resulting **muscular atrophy, weakness, & fasciculations;** & (II) **upper** motor neurons (Betz cells) in the motor cortex, the loss of the projection of upper motor neurons onto the lower motor neurons results in **paresis, hyperreflexia, spasticity, & positive Babinski sign.** Sensory systems & cognitive functions are usually unaffected, but types with dementia do occur.

ارتجافات.

ضعف العضلات.

ALS.

Amyotrophic Lateral Sclerosis (Motor Neuron Disease)

- **ALS is the most common form of neurodegeneration affecting the motor system**; (1) "lateral sclerosis" refers to the degeneration of the corticospinal tracts in the lateral portion of the **SC** (■ 4.25) as a result of loss of upper motor neurons, resulting in **Hyper-reflexia; while (2) the muscle atrophy** ("amyotrophy") **result from** loss of lower motor neurons.

- **ALS** affect men slightly more frequent than women.

- **ALS** manifest clinically in the 5th decade or later.
- 90% of **ALS** cases are **sporadic**.
- 10% of **ALS** are **familial, mostly autosomal dominant**, develop symptoms earlier; but the clinical course is comparable with the sporadic with a 50% 5-year survival. → sporadic or familial . سواء
- **ALS** disease locus is on chromosome 21, involving the **gene encoding a form of superoxide dismutase, SOD1.** Mutations in this gene cause 50% of the familial cases of **ALS**, & as with huntingtin, the **mutation may cause misfolding of the protein, leading to apoptosis.**

►**Grossly**, **ALS** most evident changes are found in:

(1) **anterior roots of the SC, which are thin & gray (rather than white, F9-25) &,** in especially severe cases, the

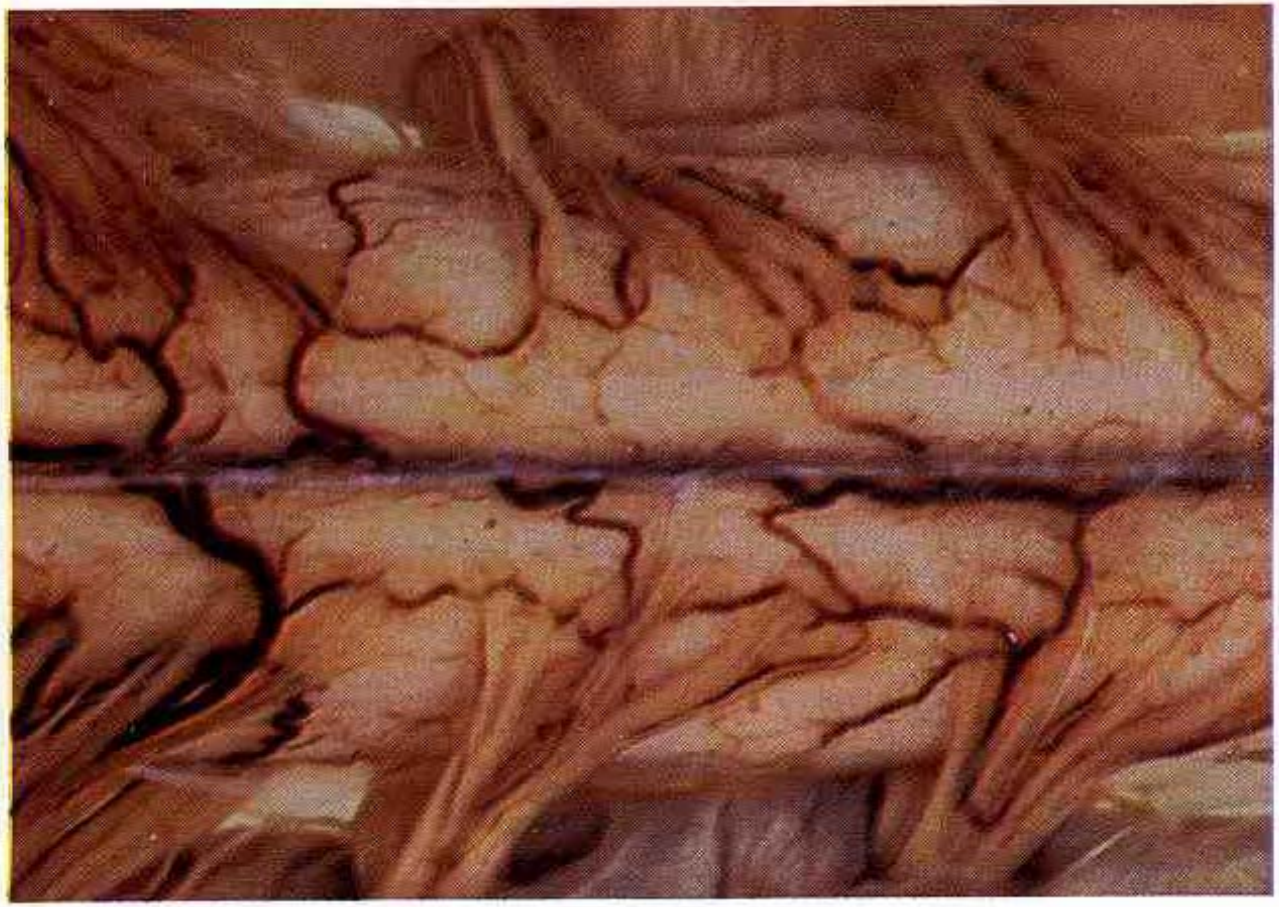
(2) **motor cortex** (precentral gyrus) **may be atrophic.**

◘H, there is a **reduction in the number of anterior horn cell throughout** the length of the **SC** with **loss of anterior root myelinated fibers** (◘ 4.25 & 26) & reactive gliosis**.**

◘ **Similar** findings are found with involvement of motor cranial nerve nuclei, always sparing those of the extraocular muscles.

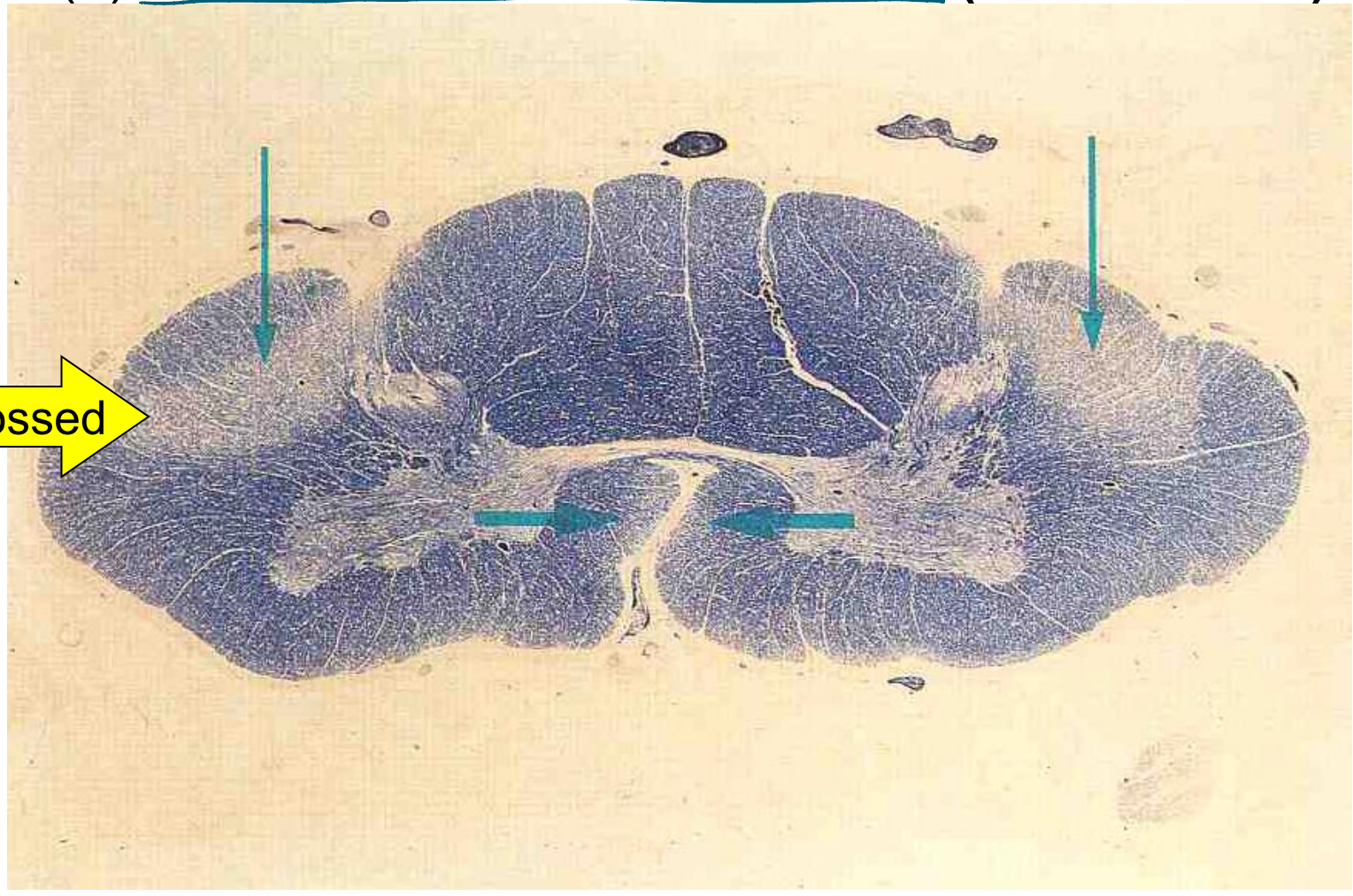
F9-25: **Motor neuron disease: Ventral surface of spinal cord**

☹ The anterior spinal nerve roots are *atrophic & thin* due to **reduction in the number of anterior horn cell neurons** throughout the length of the SC, with loss of anterior root myelinated fibers & reactive gliosis.



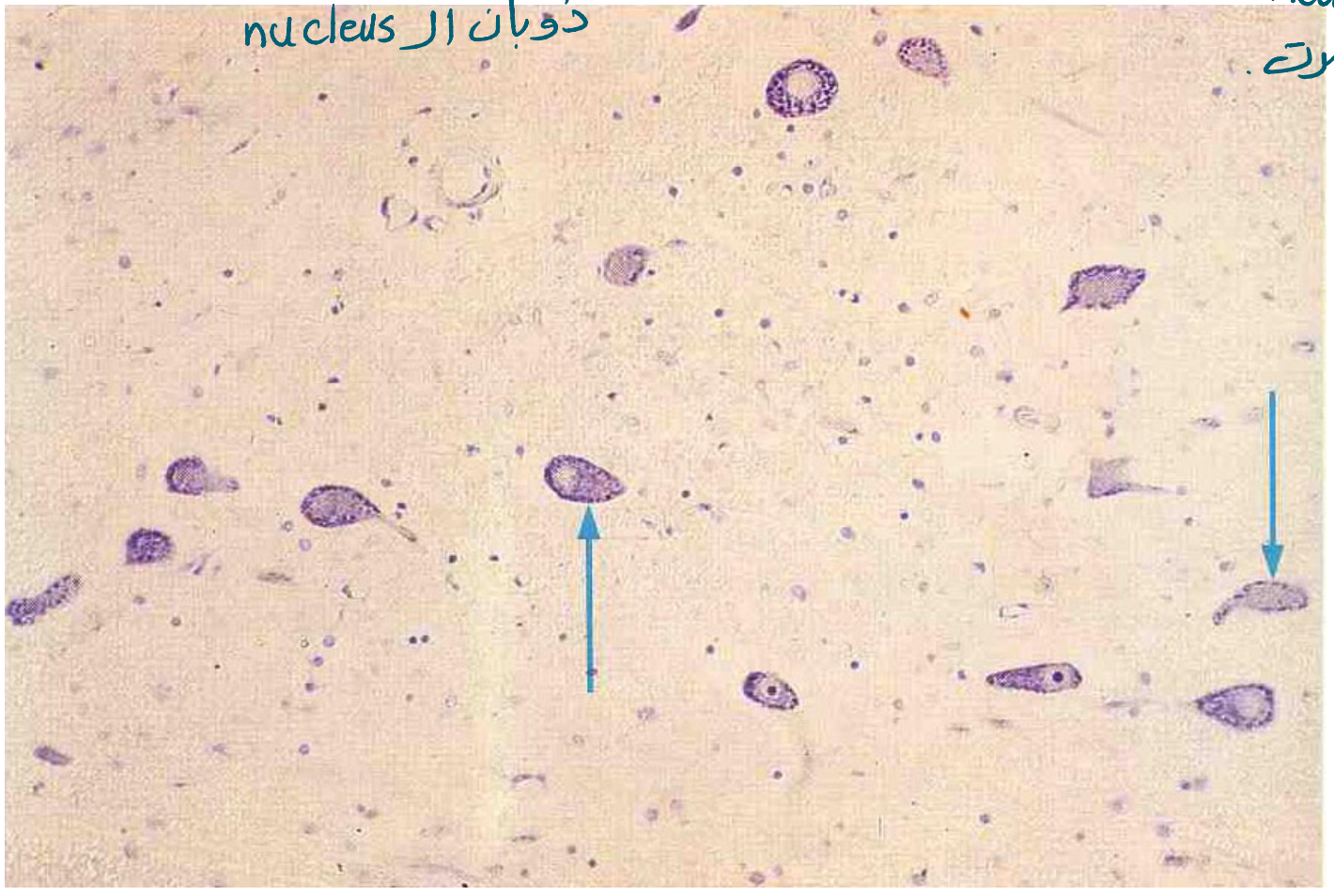
9.25 Motor neuron disease: spinal cord

◘ 4.25: **Motor neuron disease (ALS): Spinal cord** section stained deep blue for myelin. There is loss of staining (demyelination with pallor) affecting both the **(I) lateral crossed cerebrospinal tracts (thin arrows),** which is more pronounced than the (II) **anterior columns direct tracts (thick arrows)**



◘ 4.26: **Motor neuron disease (ALS): Spinal cord** section, showing anterior horn from a patient, who had progressive muscular atrophy, stained with thionin to demonstrate the motor neurons selectively. The number of motor neurons is much less than normal & the few which remain are degenerated, shrunken (arrows) showing chromatolysis & karyolysis. فراغ حول النواة 80-90% of motor neurons تتكون تدمرت

ذوبان ال nucleus



In ALS (I) Death of **upper** motor neurons, causes degeneration of the descending corticospinal tracts, **easily seen** in the **SC**, **& (II)** Death of anterior horn cells [**lower** motor neurons] with loss of innervation causes **neurogenic atrophy** of skeletal muscles.

▲ *Clinically, early* symptoms include **asymmetric weakness of the hands,** manifested by **dropping objects** & difficulty performing fine motor tasks.
Later, muscle strength & bulk diminish and ***fasciculations*** {involuntary contractions of individual motor units) occur.

☠ Eventual, **respiratory muscles weakness** cause recurrent pulmonary infection, which is the usual cause of ☠ **death**.

★In some patients, degeneration of the **lower brain stem cranial motor nuclei** occurs early & progresses rapidly, a pattern of disease referred to as ***bulbar*** **ALS**, in which, abnormalities of swallowing & speaking dominate.

Bulbospinal Atrophy (Kennedy Disease)

★This X-linked, adult-onset disease, affecting **lower motor neurons; is characterized by distal limb amyotrophy** & bulbar signs such as dysphagia & atrophy & fasciculations of the tongue. Affected individuals manifest **androgen insensitivity** with **gynecomastia, testicular atrophy & oligospermia**.

😐 This is a trinucleotide-repeat disorder, similar to Huntington disease; in this case, the polyglutamine repeat is in the **androgen receptor**.

Spinal Muscular Atrophy

مش مرض واحد بل مجموعة أمراض.

★These are a distinctive group of autosomal recessive motor neuron diseases that begin in childhood or adolescence. There is loss of lower motor neurons, muscle atrophy & weakness, often involves entire fascicles (panfascicular atrophy)

The most common form is **Spinal Muscular Atrophy (SMA1)** (Werdnig-Hoffmann disease), has its onset at birth or within the first 4 months of life & usually leads to death within the first 3 years of life. All forms of the disease are associated with mutations in the same gene (*SMN*) on chromosome 5.

SUMMARY

Degenerative Diseases: Neurodegenerative diseases cause symptoms depend on the pattern of involvement of the brain.

- Diseases that affect primarily the cerebral cortex (e.g., **Alzheimer** disease) are more likely to cause cognitive change, alterations in personality, & memory disturbance. Accumulation of the Aß petide, derived from amyloid precursor protein (APP) is central to the pathogenesis of Alzheimer disease.

- Diseases that affect basal ganglia (e.g., **Huntington or Parkinson disease**) have motor symptoms as prominent clinical features. Parkinson disease is caused by loss of dopaminergic neurons, & Huntington disease is caused by trinucleotide repeat expansions in the gene encoding huntingtin protein , resulting in **disease-causing gain of function**.