

THE PHAKOMATOSES

James G. Smirniotopoulos, M.D.

Uniformed Services University
4301 Jones Bridge Road
Bethesda, MD 20814
Voice: 301-295-3145
FAX: 301-295-3893

Visit us on the WEB:
<http://rad.usuhs.mil>

Learning to Care for Those in Harm's Way

SPEED
BUMPS

STREET SIDE STAFF ONLY
ALL VISITORS REPORT
TO SECURITY OFFICE

511



THE PHAKOMATOSES

Neuro - Ectodermal

- or -

Nerves and Skin

Dorland's Medical Dictionary

the matter into a cytostome, with invagination of the matter by the cell membrane to form a food vacuole, a process of food intake occurring in ciliate protozoa.

phagotype (fag'o-tīp) phage type; see under *type*.

phakitis (fa-ki'tis) [Gr. *phakos* lens + *-itis*] inflammation of the crystalline lens.

phako- [Gr. *phakos* a lentil, or lentil-shaped object; a spot on the body, a freckle] for words beginning thus, see also those beginning *phaco-*.

phakoma (fah-ko'mah) [*phaco-* + *-oma*] 1. an occasional small, grayish white tumor seen microscopically in the retina in tuberous sclerosis. 2. a patch of myelinated nerve fibers seen very infrequently in the retina in neurofibromatosis.

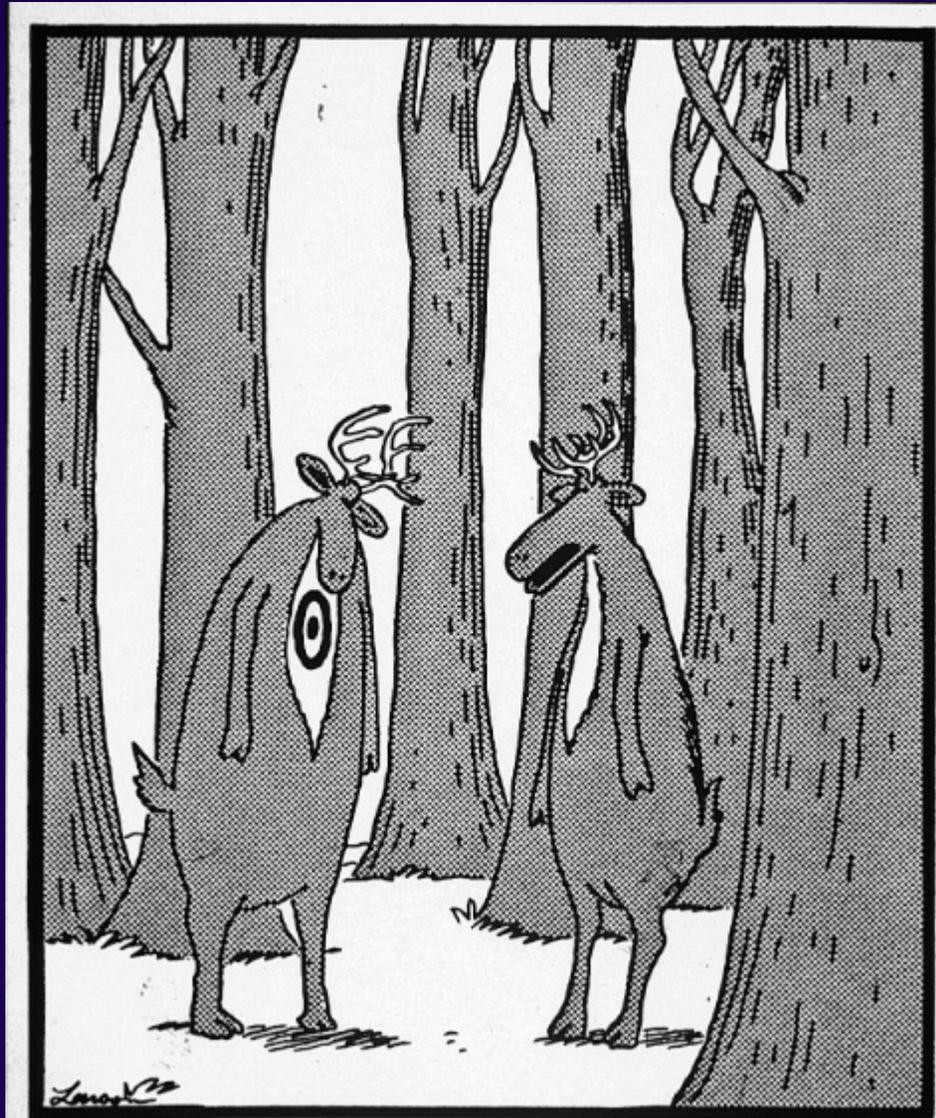
phakomatosis (fak'o-mah-to'sis), pl. *phakomato'ses* [Gr. *phakos* mother spot] an ophthalmologic term for any of four hereditary syndromes (neurofibromatosis, tuberous sclerosis, encephalotrigeminal angiomatosis, and cerebroretinal angiomatosis) characterized by disseminated hamartomas of the eye, skin, and brain.

phalacrois (fal'ah-kro'sis) [Gr. *phalakrōsis* baldness] alopecia.

phalangeal (fah-lan'je-al) pertaining to a phalanx.

phalangectomy (fal'an-jek'to-me) excision of a phalanx of a finger or toe.

Birthmarks



"Bummer of a birthmark, Hal."

THE PHAKOMATOSES

- Neurofibromatosis Type 1
- Neurofibromatosis Type 2
- Encephalo-Trigeminal Angiomatosis
- Tuberous Sclerosis
- Cerebello-Retinal Angiomatosis

PHAKOMATOSES: Why Study Them?

- They are COMMON diseases
- DIAGNOSED by Imaging
- GENETIC Implications
- SCREEN Relatives
- SURVEILLANCE of Affected

Phakomatoses Mnemonic Tool

- NF-1 (von Reck's)
 - TRUE Neurofibromatosis #17
- NF-2 (Bilateral. VIII Syndrome)
 - M.I.S.M.E. #22
- STURGE-WEBER (Dimitri) Syndrome
 - Congenital Vascular Lesion, perhaps NOT inherited
- TUBEROUS SCLEROSIS
 - Pringle's "HAMARTOMA" Disease

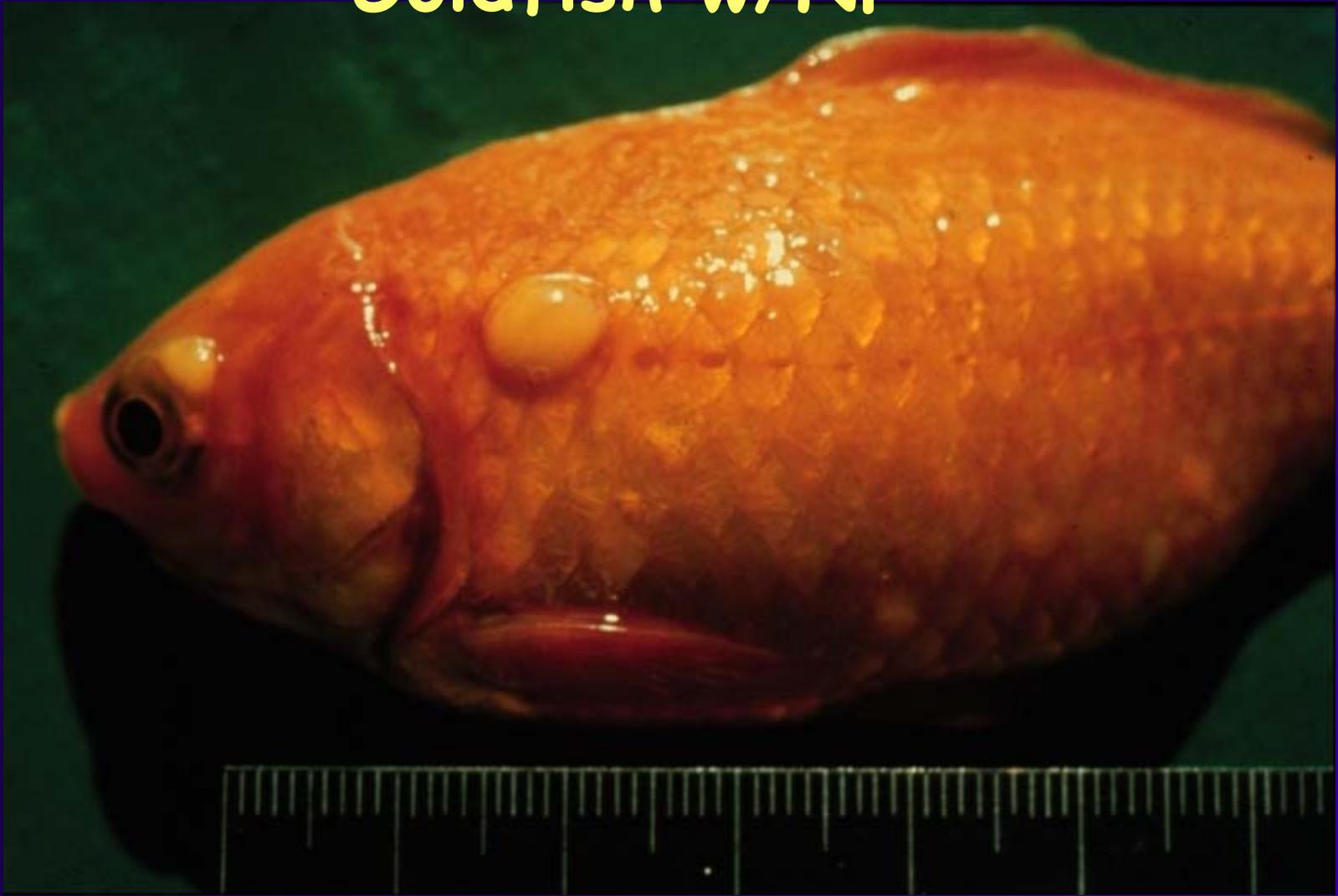
NEUROFIBROMATOSIS - TYPES

- Neurofibromatosis Type 1 (NF-1)
 - von Recklinghausen Disease
 - "True" Neurofibromatosis
 - Prominent Cutaneous Signs
 - Chromosome 17q
- Neurofibromatosis Type 2 (NF-2)
 - Bilateral Acoustic Schwannoma
 - "Central Neurofibromatosis"
 - Minimal Skin Manifestations
 - Chromosome 22q

NEUROFIBROMATOSIS

- Species Affected
 - MAN
 - GOLDFISH
 - TURKEYS
 - CATTLE

Goldfish w/NF



NIH Diagnostic Criteria

- Cafe-Au-Lait spots
 - - 6 or more
 - - 5 mm child, 15 mm adult
- Neurofibromas - 2 or more
- Plexiform Neurofibroma - 1
- Axillary (Intertriginous) Freckling
- Optic Glioma
- Lisch Nodules (Iris) - 2 or more
- "Distinctive Bone Lesions"
- Relative with NF-1

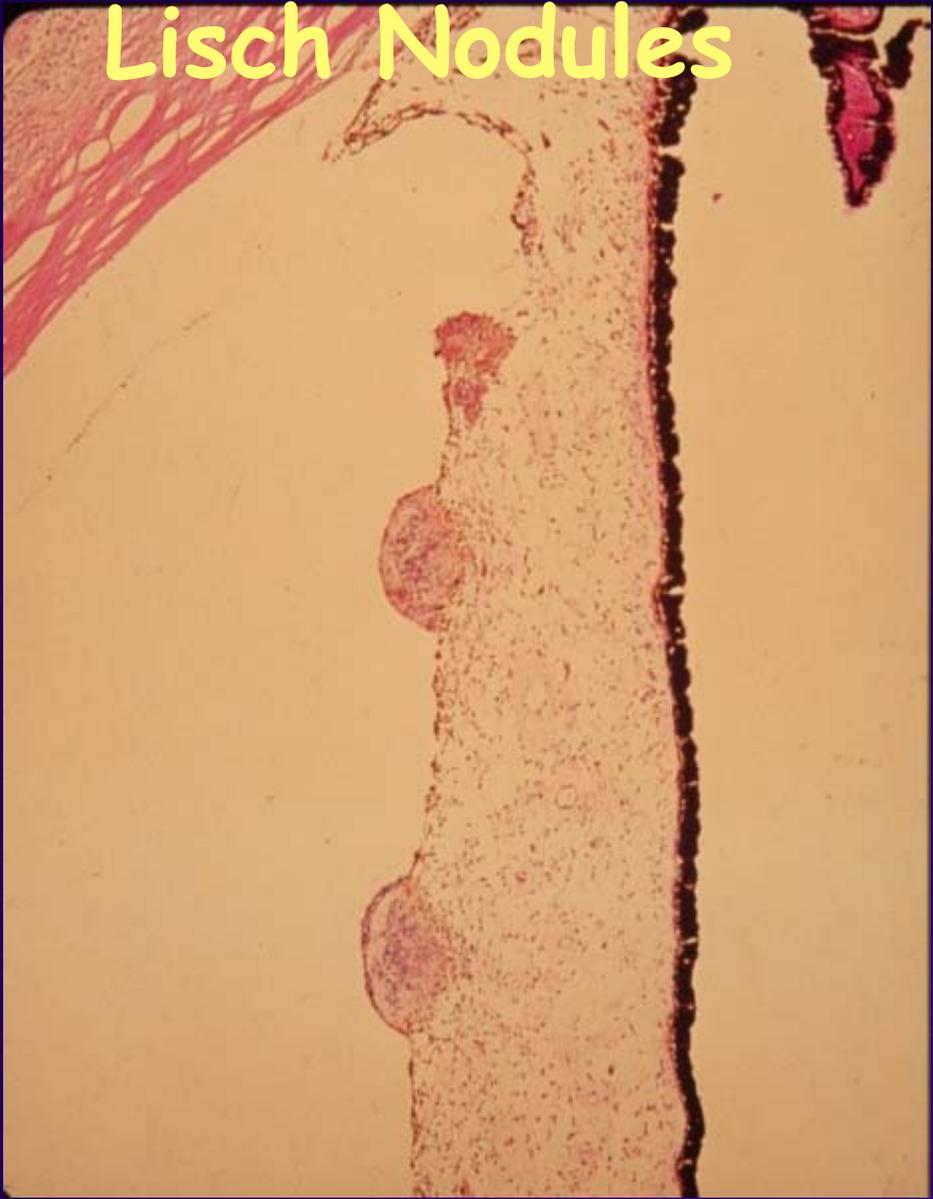
NF-1: EYE MANIFESTATIONS

- LISCH Nodules (Iris Hamartomas)
 - Penetrance > 90%
 - Specificity > 90%
 - Translucent/pigmented
 - Small (< 3mm.), Slit-Lamp Exam
- OPTIC GLIOMA
 - Pilocytic Astrocytomas
 - Benign ("Hamartoma-like"), Tx?
 - True Neoplasms, spread along SAS
 - up to 1/2 of Childhood ONG w/NF-1

Lisch Nodules

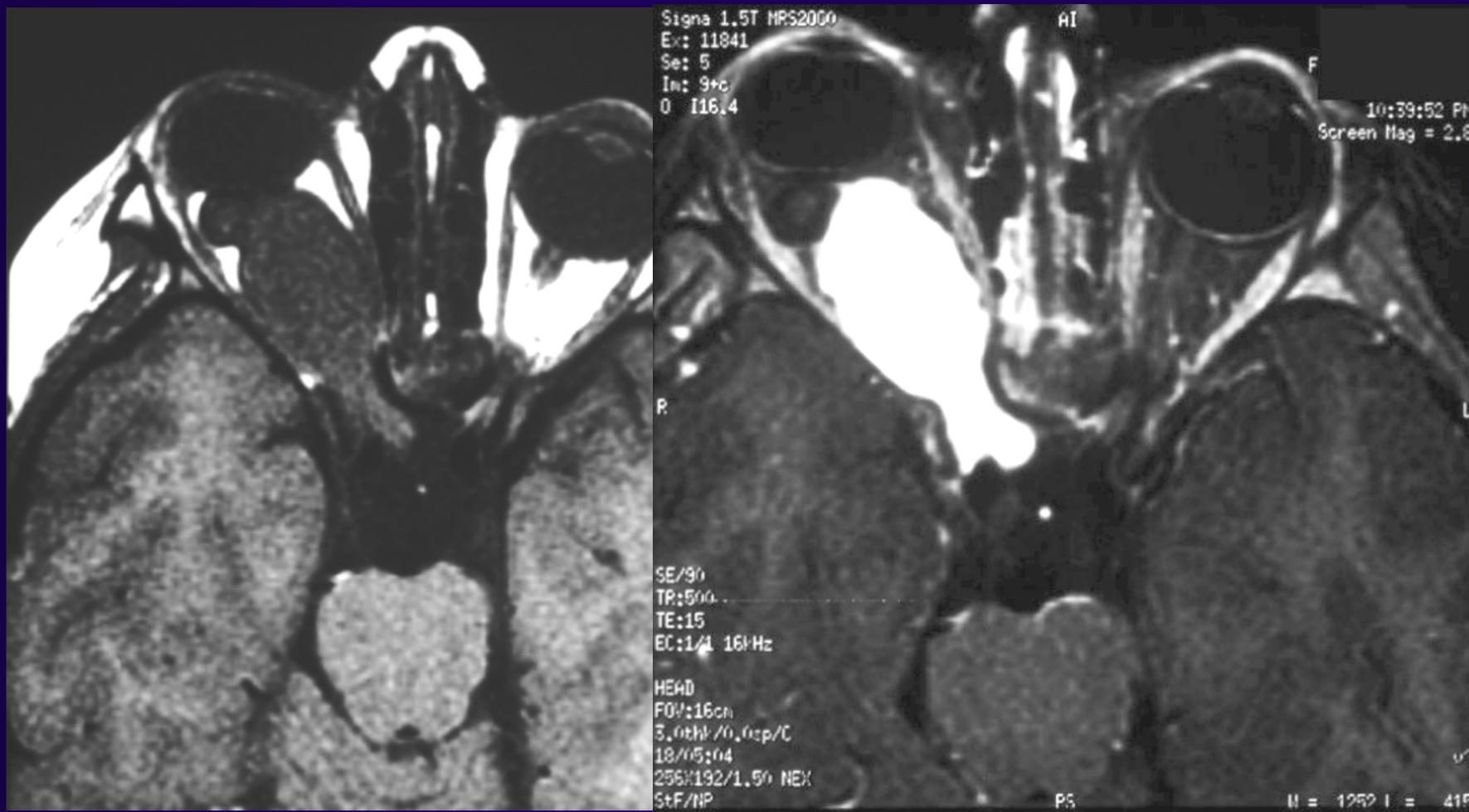


Lisch Nodules



Optic Nerve Glioma

Radiology - <http://rad.medpix.net>

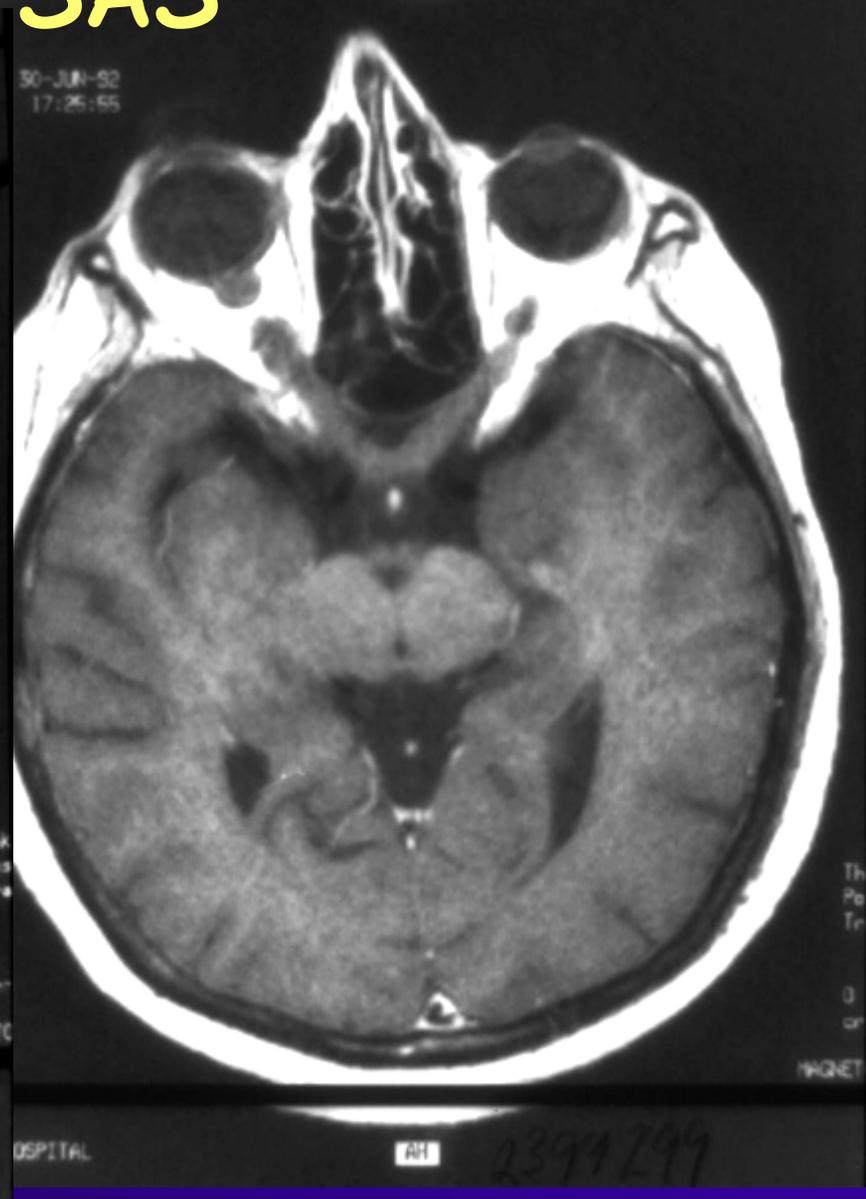
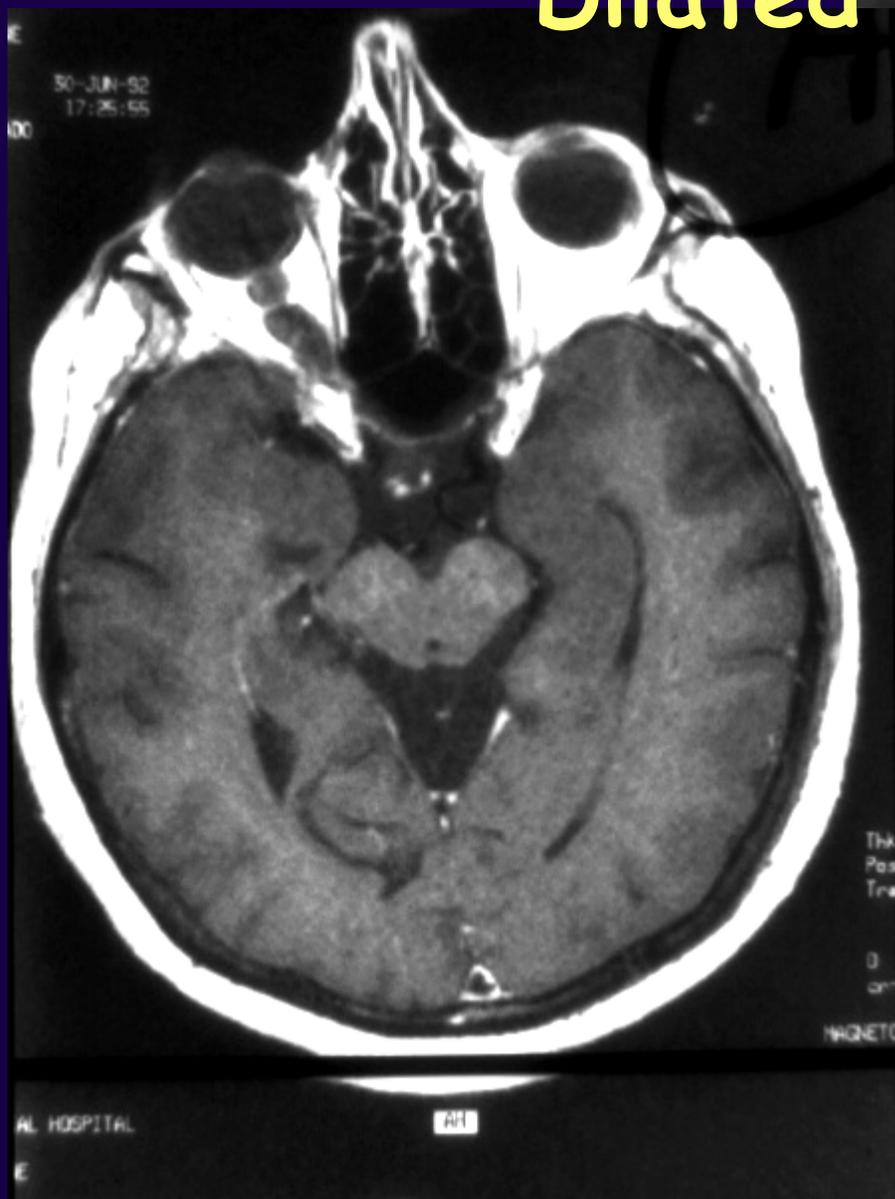


Optic Nerve Glioma



Radiology - <http://rad.medpix.net>

Dilated SAS



Radiology - <http://rad.medpix.net>

NEUROFIBROMATOSIS - 1

- Cutaneous
- Cafe-au-Lait spots
- Intertriginous Freckling
- Neurofibromas (Skin and SubQ)
- Fibroma Molluscum (TNTC NFB)
- Elephantiasis Neuromatosa (diffuse skin thickening/plexiform NFB -or- focal gigantism)

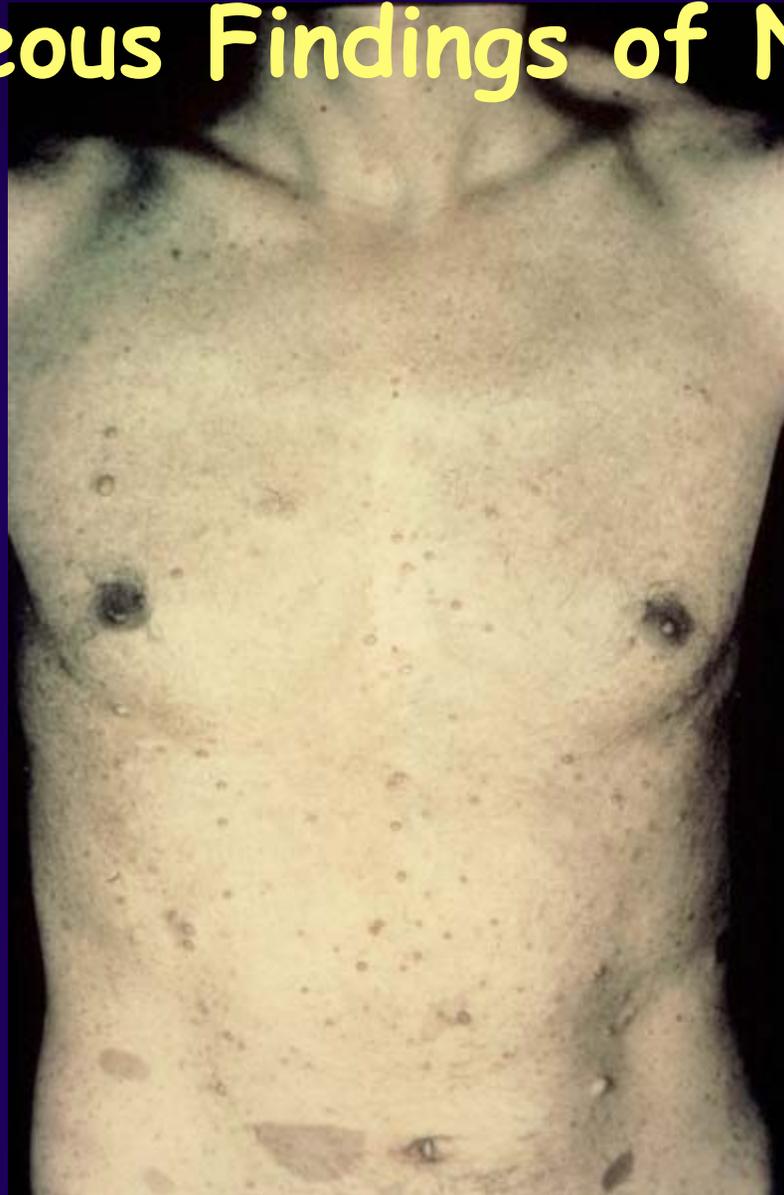
Café-au-lait spot



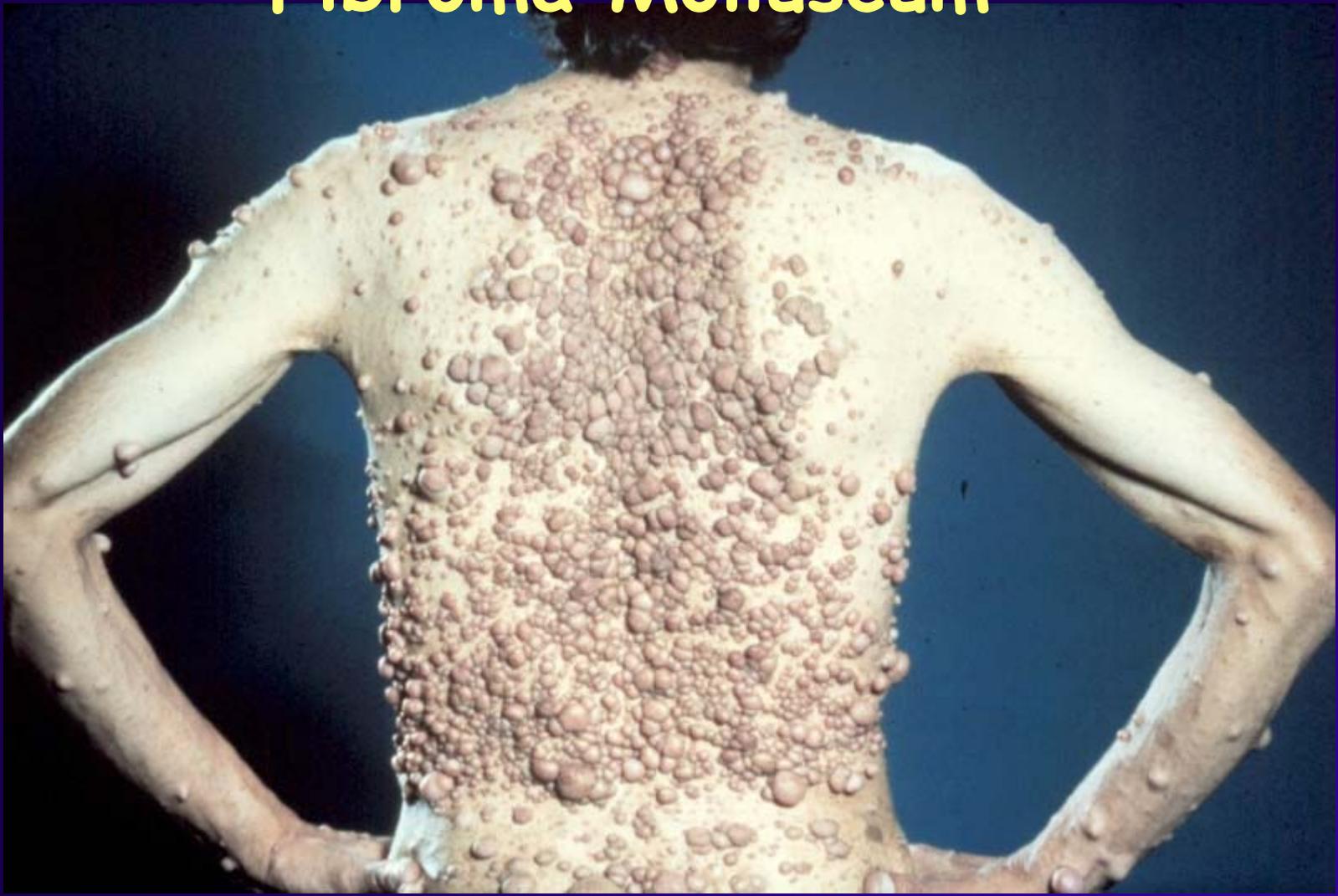
Axillary Freckle



Cutaneous Findings of NF-1



Fibroma Molluscum



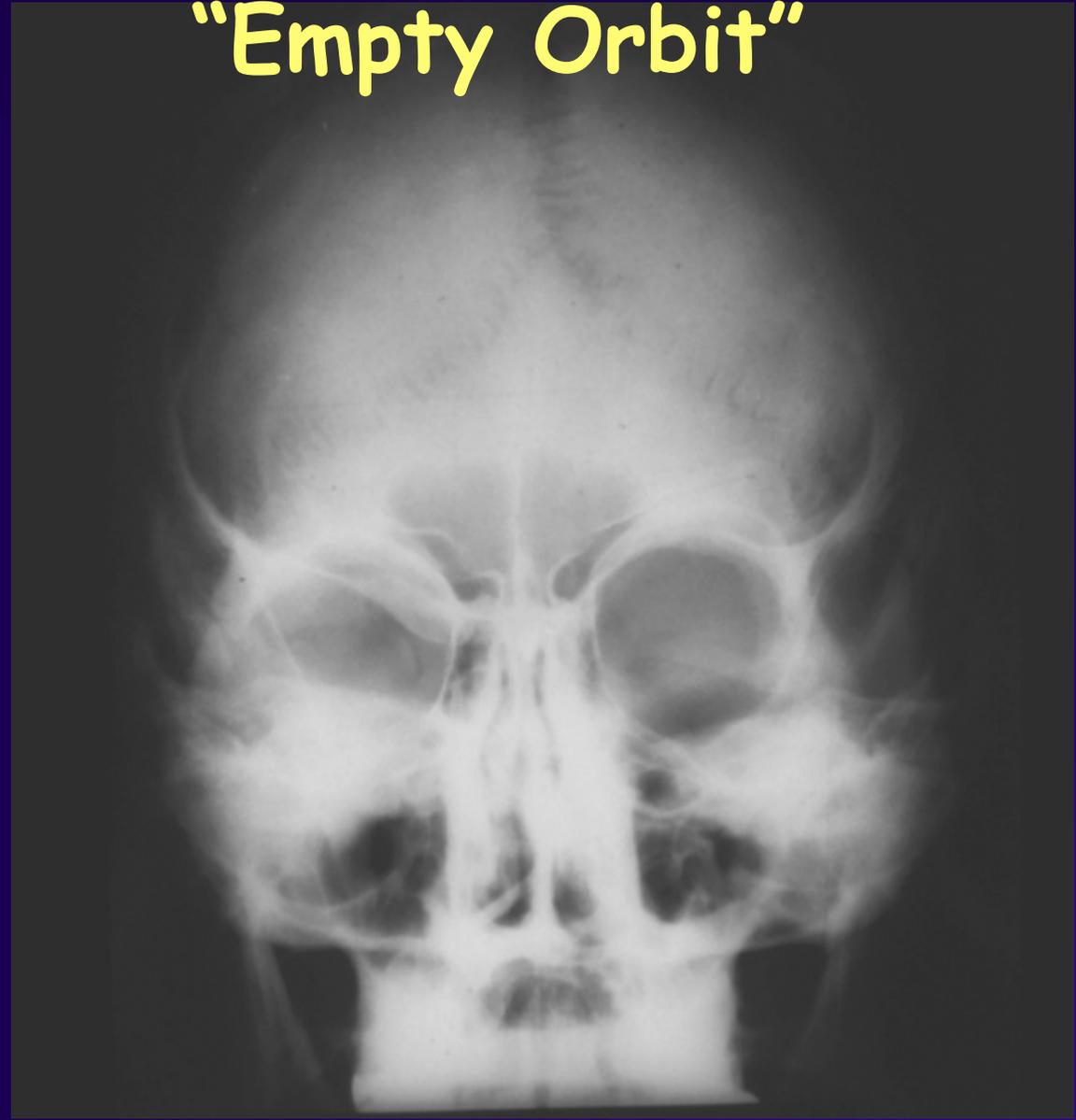
NEUROFIBROMATOSIS-I

- Skull and Spine Dysplasia
- Sphenoid Bone ("absent orbit")
- Lambdoid Suture at Temporal Bone
- Optic and Auditory Canals (enlarged)
- Scoliosis (Simple or Acute Cx Kyphosis)
- Vertebral Scalloping (usu. Lumbar)
- Enlarged Spinal Foramina

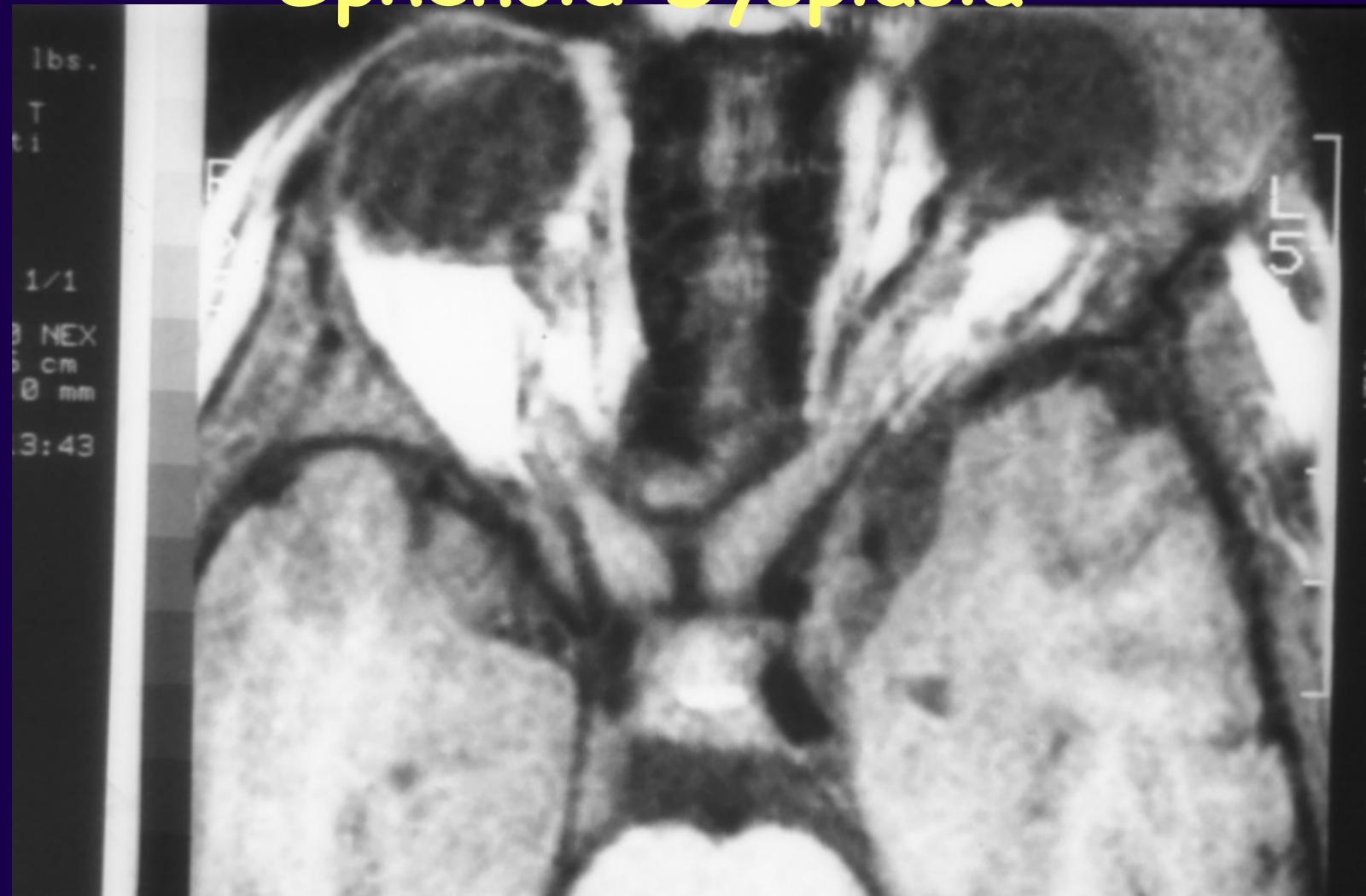
Lambdoid Suture Defect



"Empty Orbit"



Sphenoid Dysplasia



Pseudo-arthritis



Pseudo-arthritis



Focal Gigantism



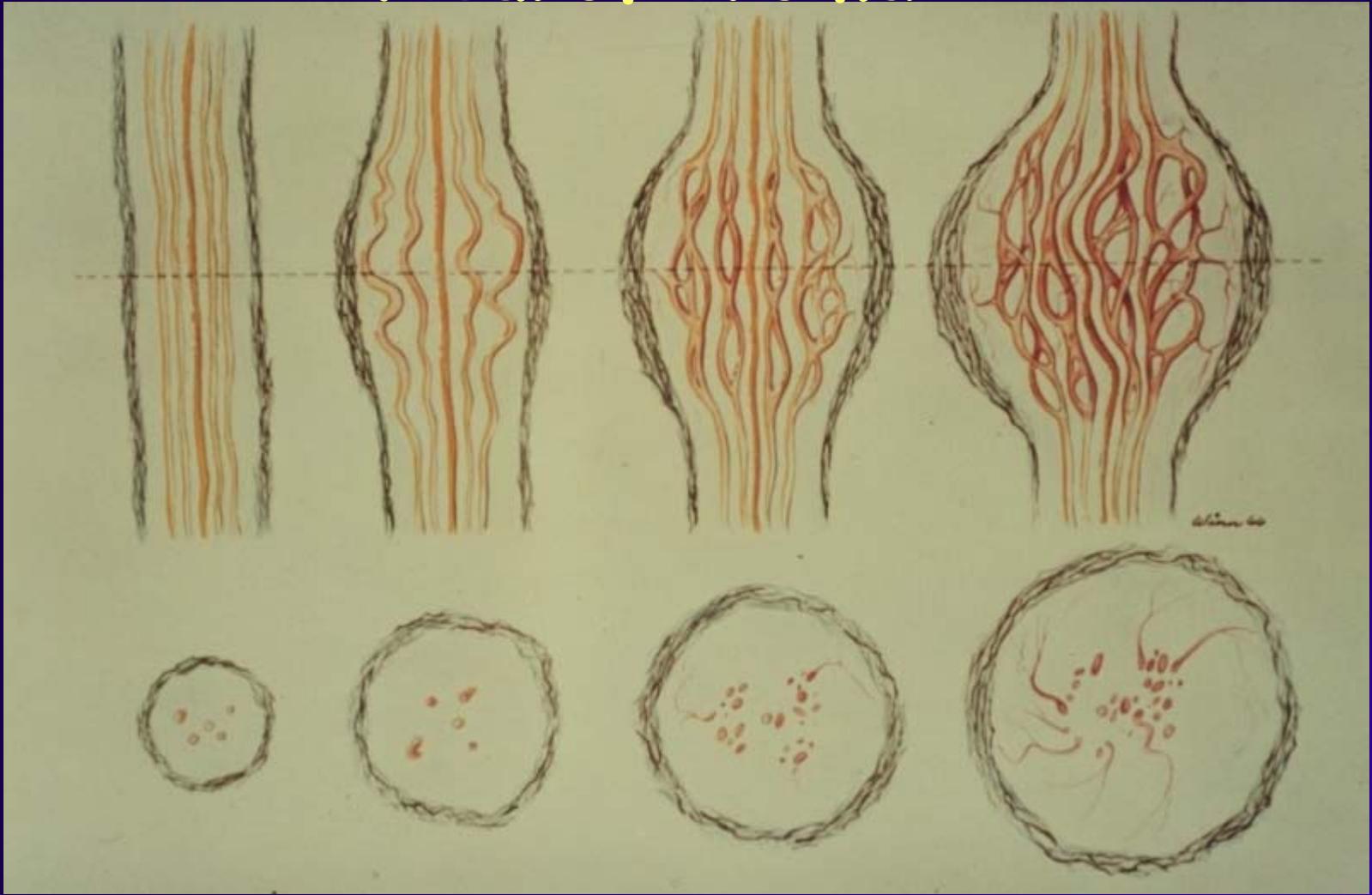
NERVE SHEATH TUMORS

- Schwannoma (Sporadic >> NF-2 > NF-1)
 - focal mass
 - usually sensory root, cranial and spinal nerves
- Neurofibroma
 - usually NF-1, esp. if spinal or paraspinal
 - spindle or dumb-bell lesion
- Plexiform Neurofibroma (usually NF-1)
 - diffuse or fusiform enlargement
- Malignant Peripheral Nerve Sheath Tumor
 - NF-1 or Sporadic

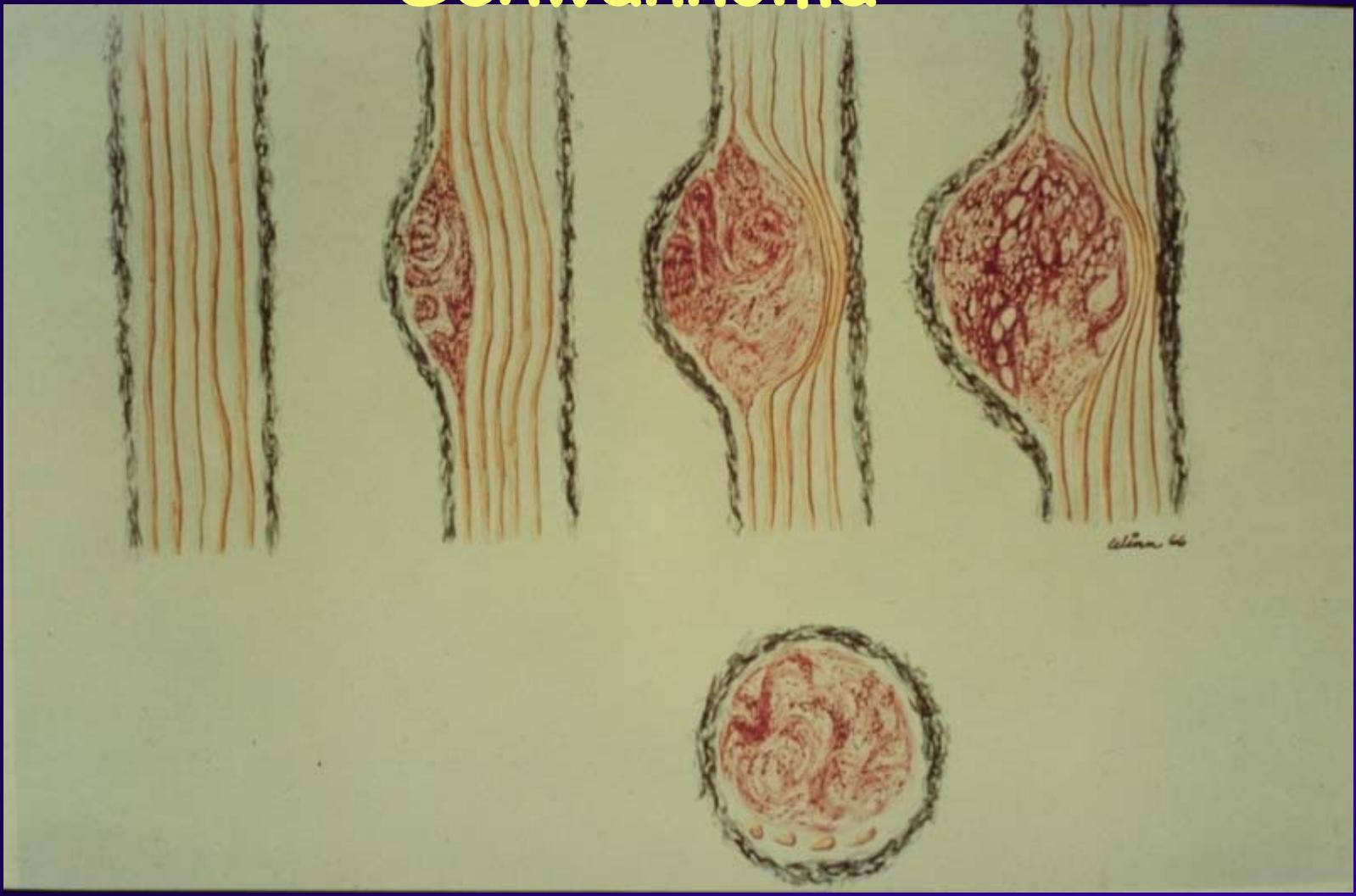
Neurofibroma vs. Schwannoma

- Neurofibroma
 - Schwann cells
 - Fibroblasts
 - Acellular material
 - Infiltrating
 - Resect Parent Nerve
- Schwannoma
 - Schwann Cell Neoplasm
 - Secondary vascular changes
 - Mostly cellular
 - Encapsulated
 - Nerve Sparing Surgery

Neurofibroma



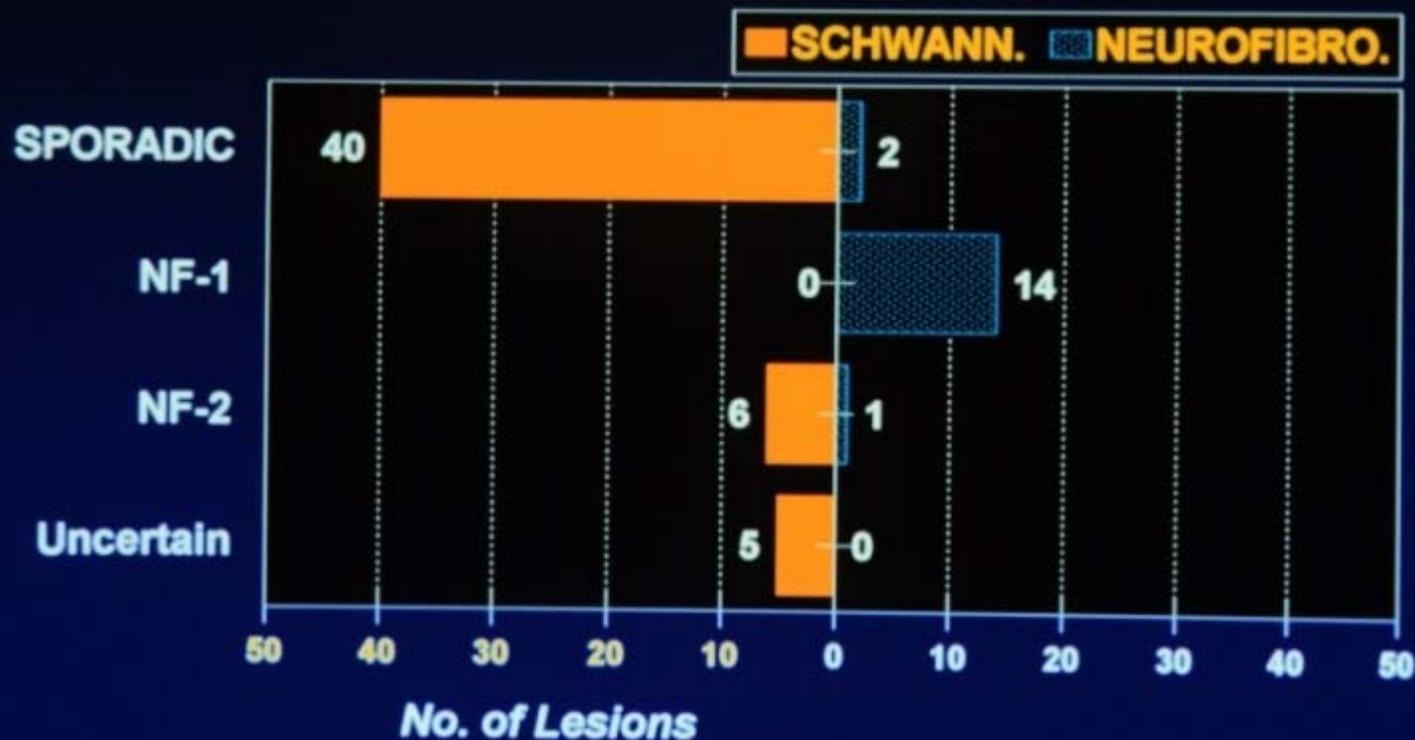
Schwannoma



Intraspinal Neoplasms

INTRASPINAL NEOPLASMS

68 Pts. - J NEUROSURG 74:248-253, 1991



James G. Smirniotopoulos, M.D. - Slide 26

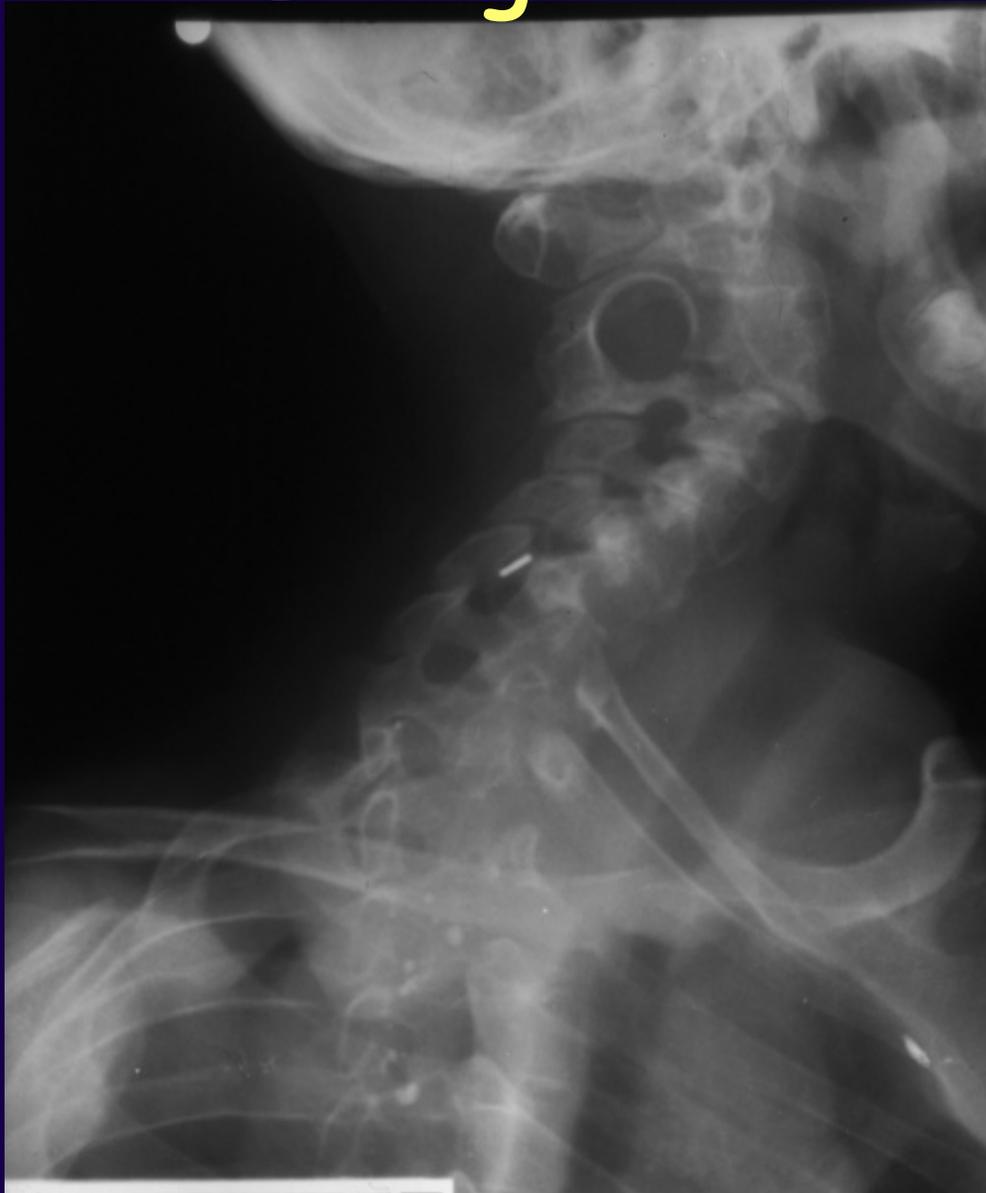
DISTRIBUTION of Nerve Sheath Tumors

- Cranial - Schwannoma (Sporadic >> NF-2)
- Spinal - Both Types (S >> N)
- Dumbbell - Both (N >> S)
- PNS - Both
- Cutaneous - Neurofibroma (usu. NF-1)

NEUROFIBROMATOSIS: Spine

- Scoliosis (NF-1, only?)
 - Simple ("idiopathic")
 - Acute Cervical Kyphosis
- Dural Ectasia (NF-1, only?)
 - Vertebral Scalloping
 - Arachnoid "cysts"
 - Lateral meningocele

Enlarged Neural Foramen



DDx:

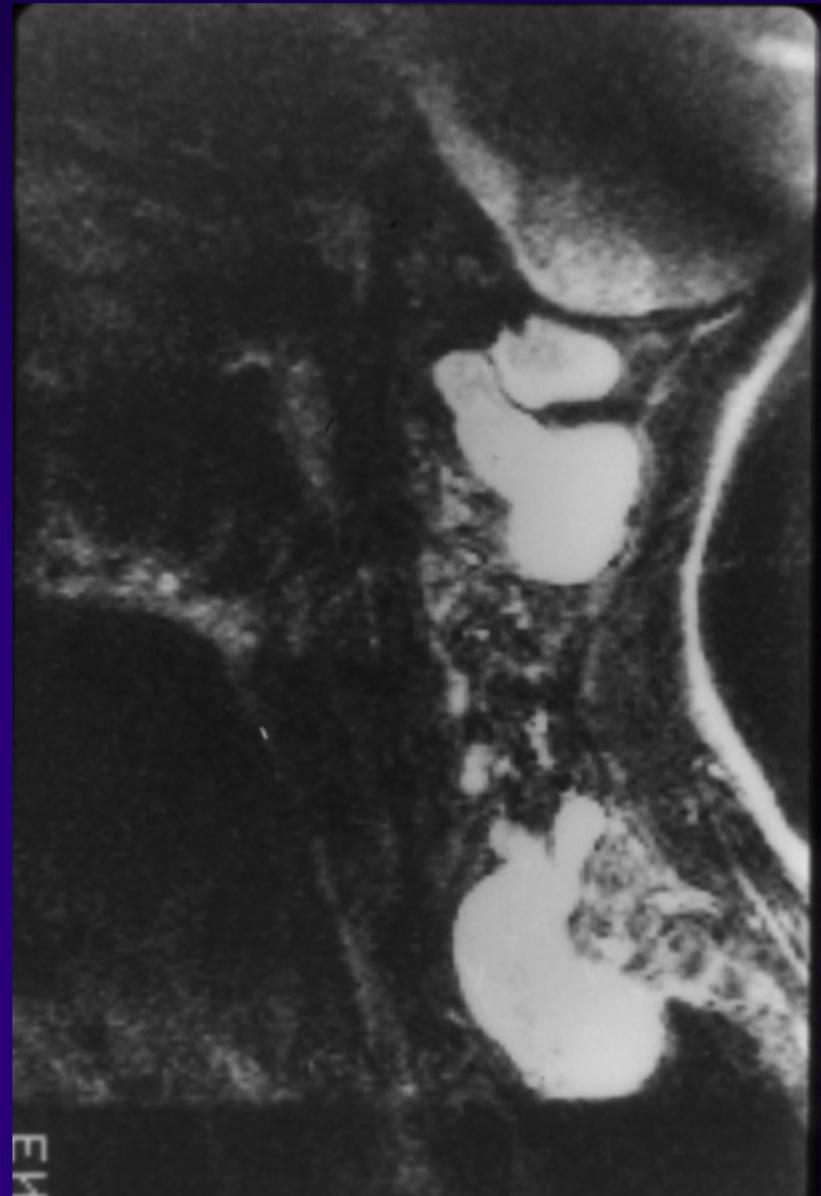
Nerve Sheath Tumor

- Neurofibroma
- Schwannoma

Arachnoid Cyst

Bone Dysplasia

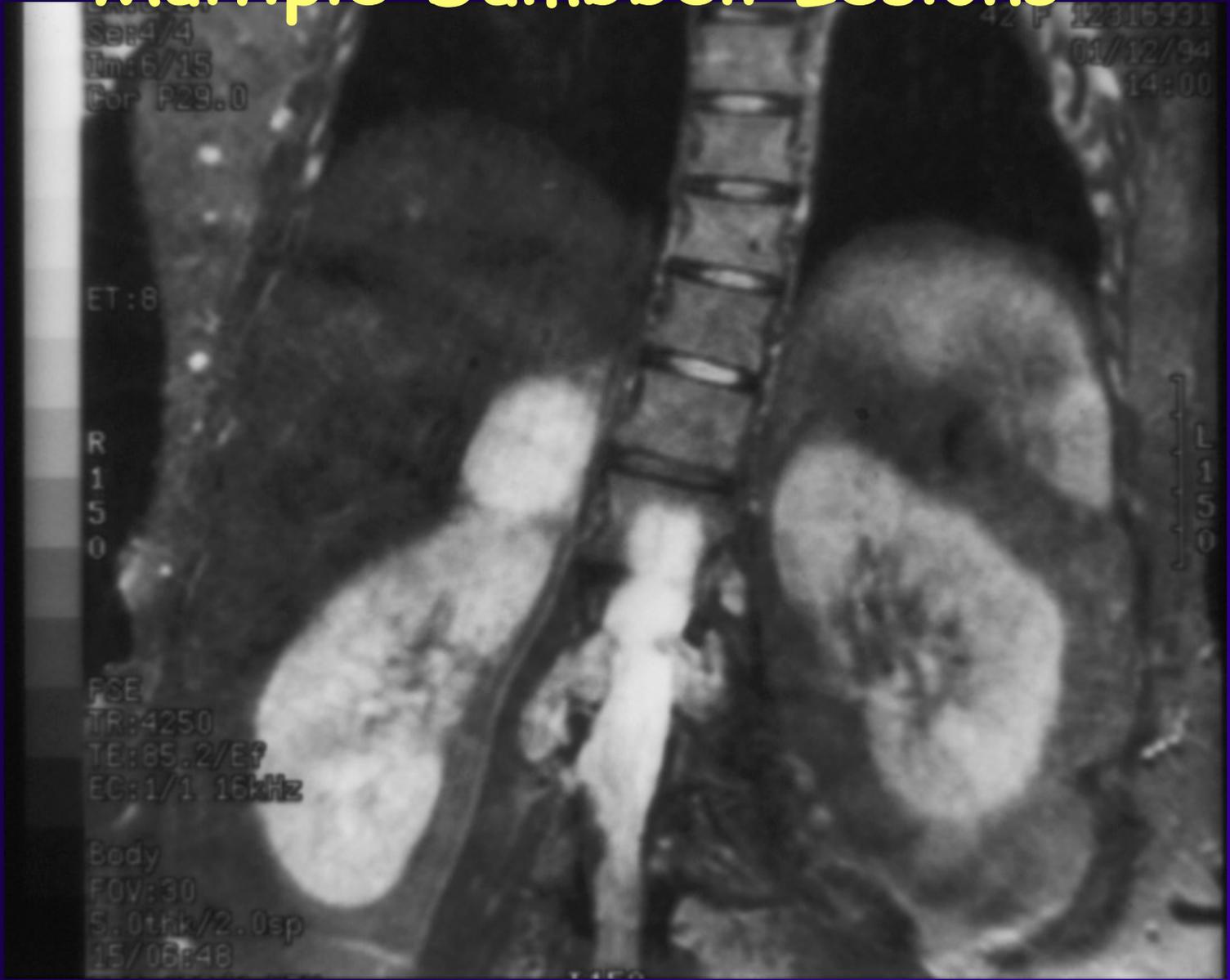
Enlarged Neural Foramen



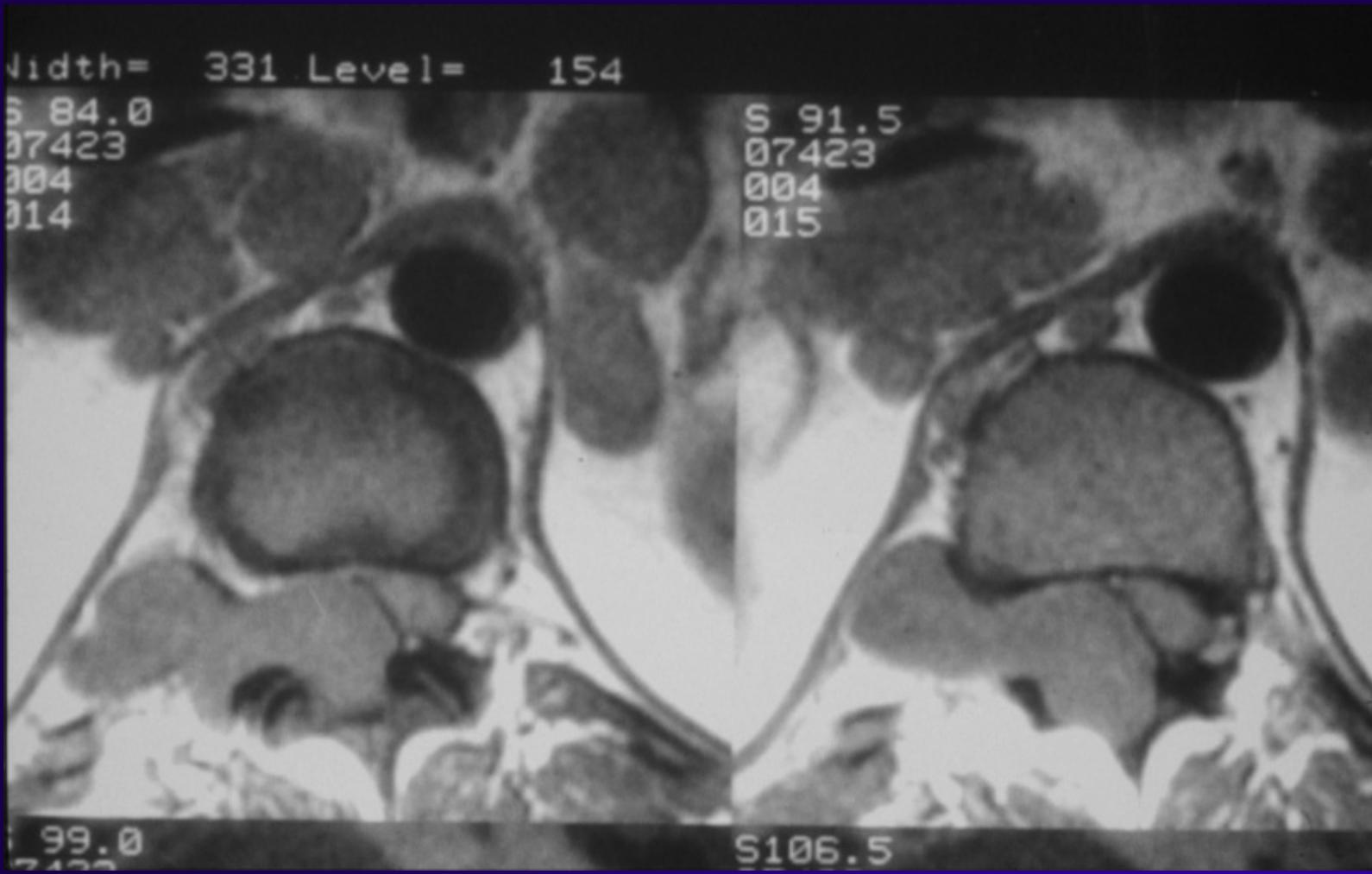
Multiple Dumbbell Lesions



Multiple Dumbbell Lesions



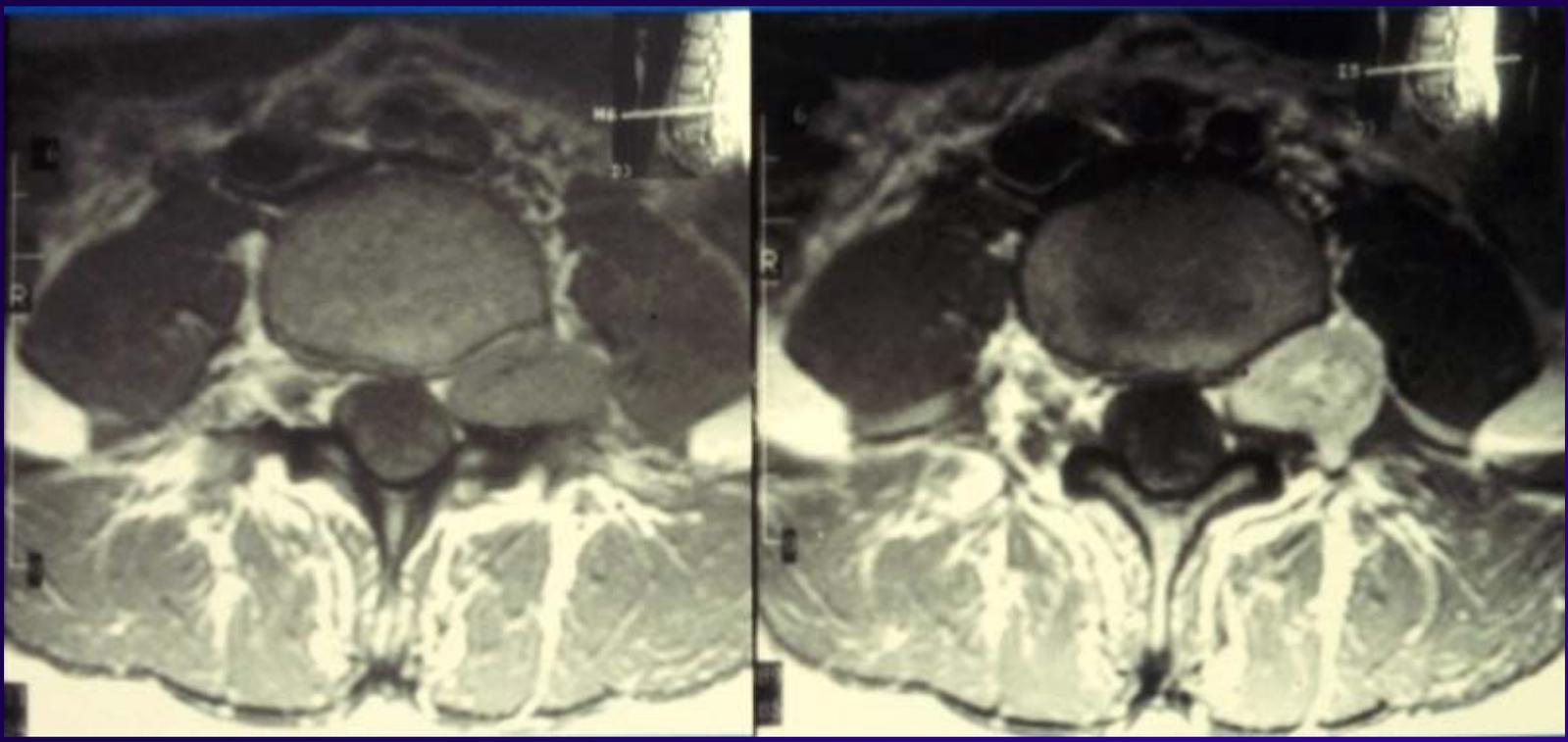
Dumbbell NF



Dumbbell NF



Schwannoma



Schwannoma

Schwannoma: Myelogram & Gross



Rib Notching



Plexiform NF



Multiple Neurofibromas

Radiology - <http://rad.medpix.net>

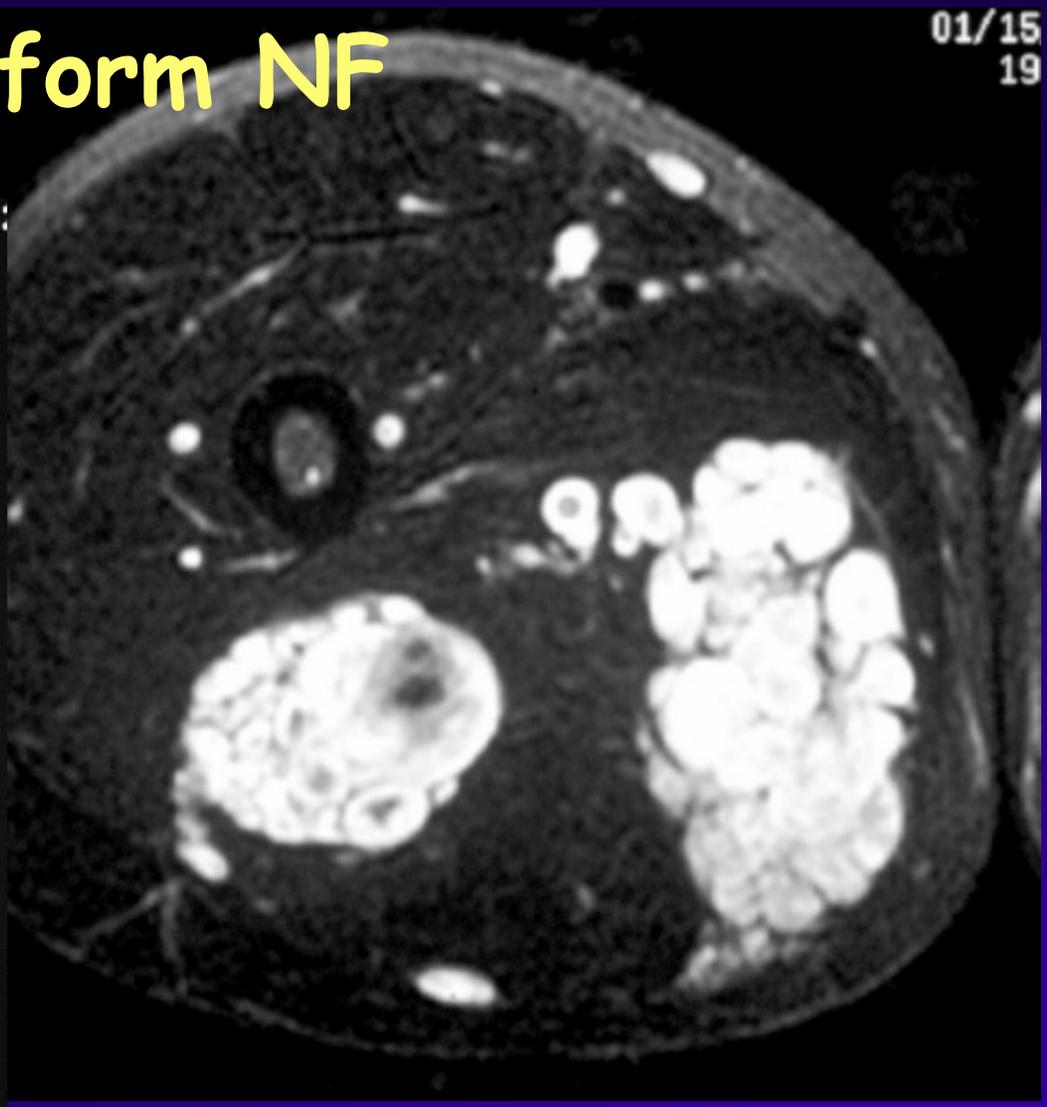
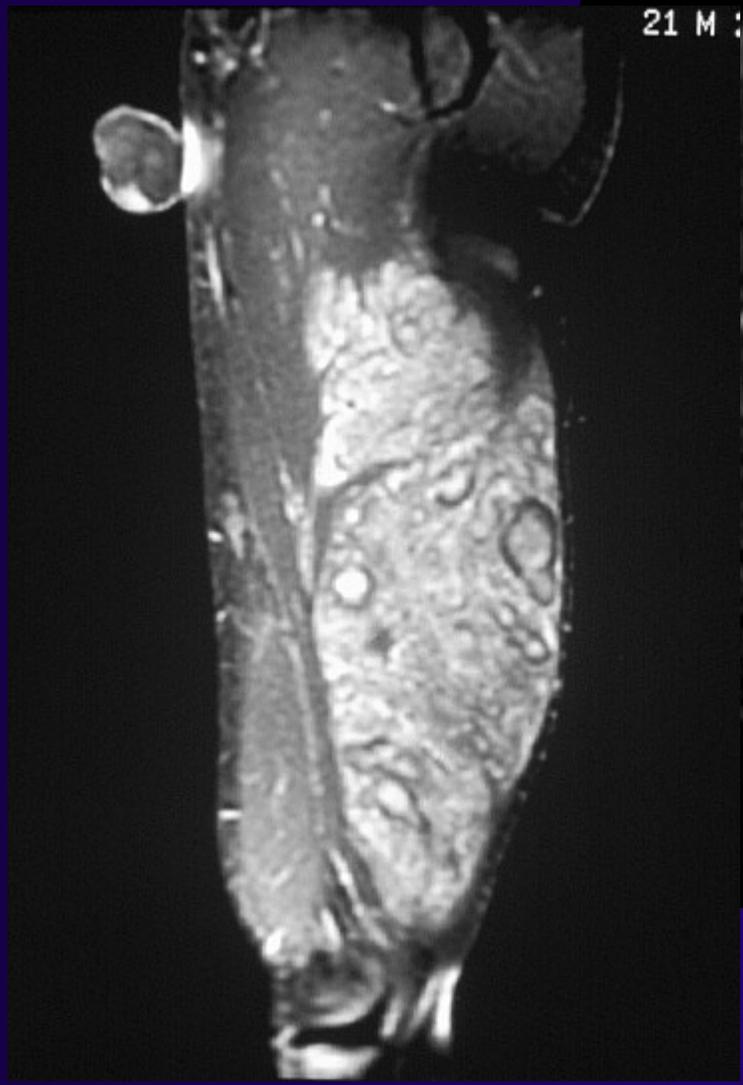


Plexiform Neurofibroma

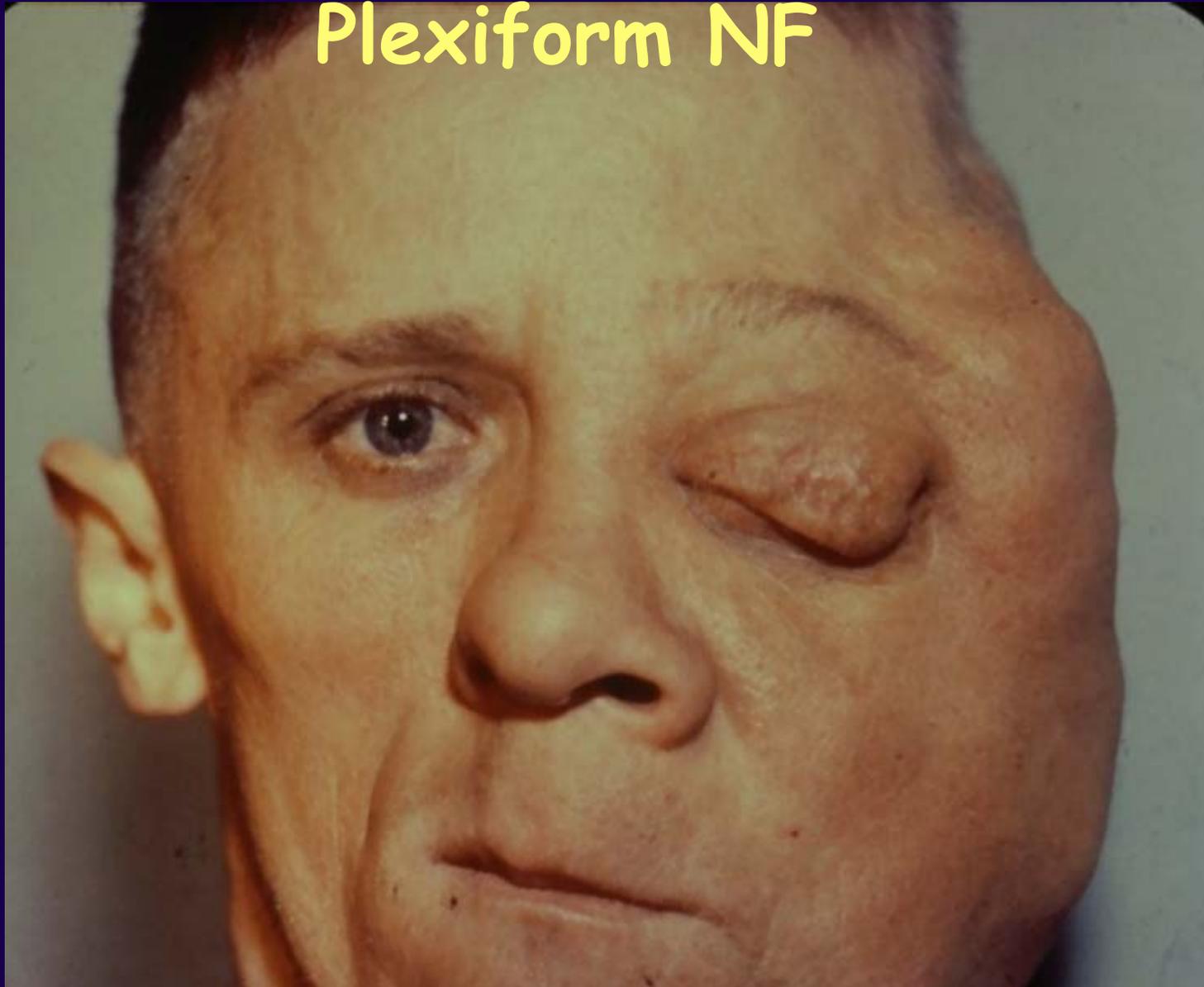


Plexiform NF

01/15
19



Plexiform NF





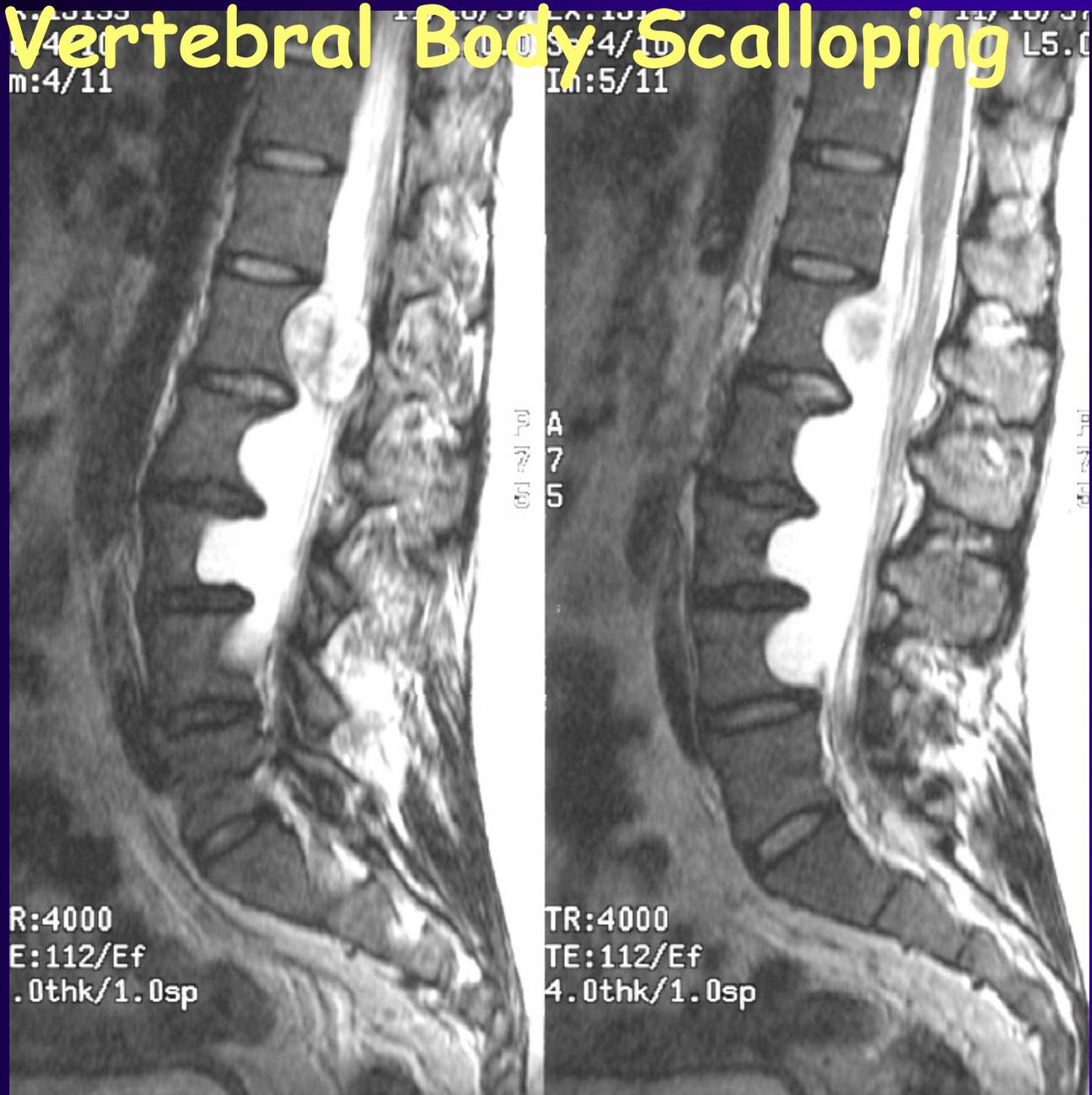
NEUROFIBROMATOSIS-1: Spine

- Scoliosis (Acute Cx Kyphoscoliosis)
- Vertebral Scalloping
- Enlarged Neural Foramina
- Lateral Thoracic Meningocele

Vertebral Body Scalloping



Vertebral Body Scalloping



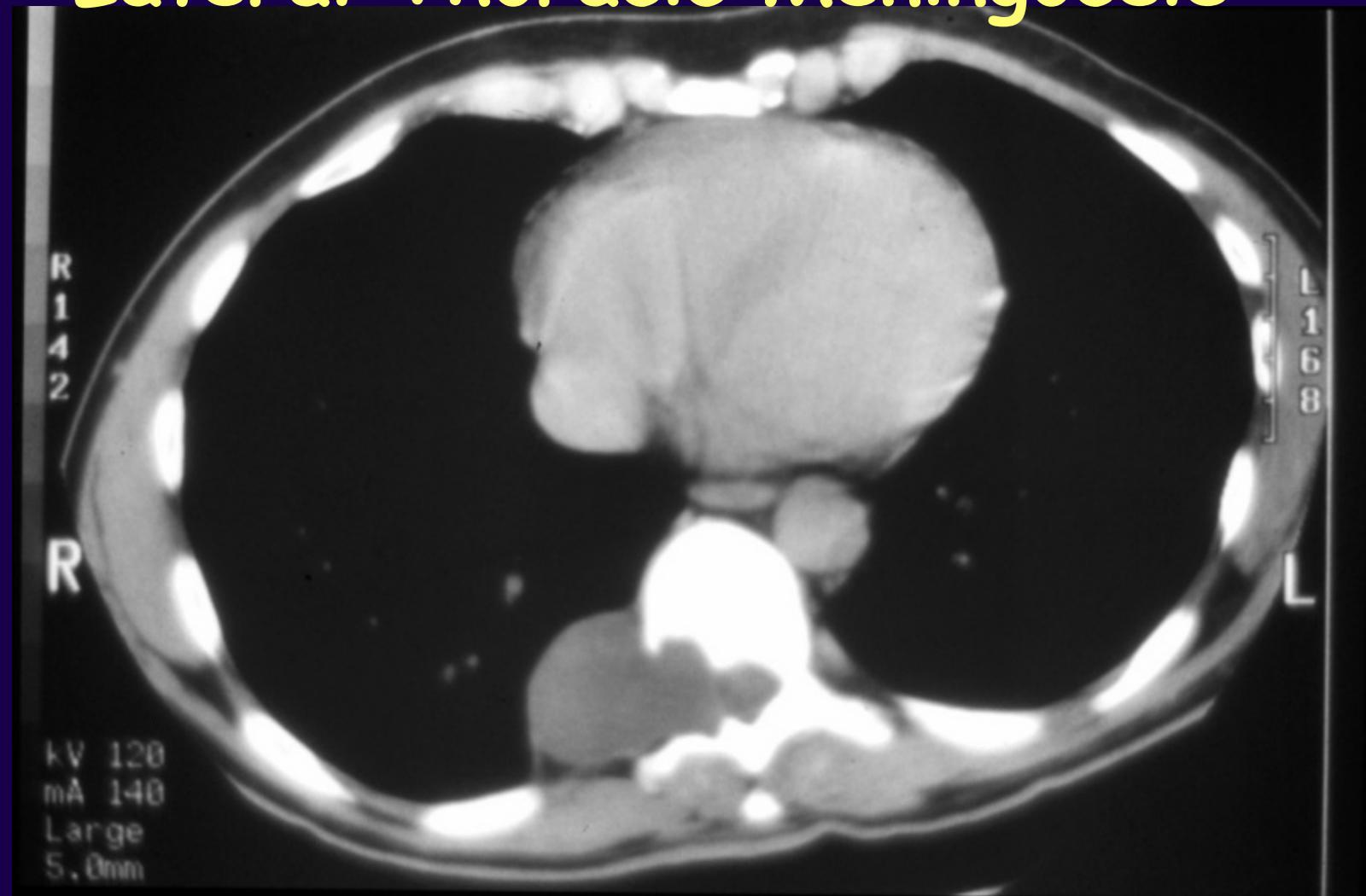
Arachnoid Cyst & Neurofibroma



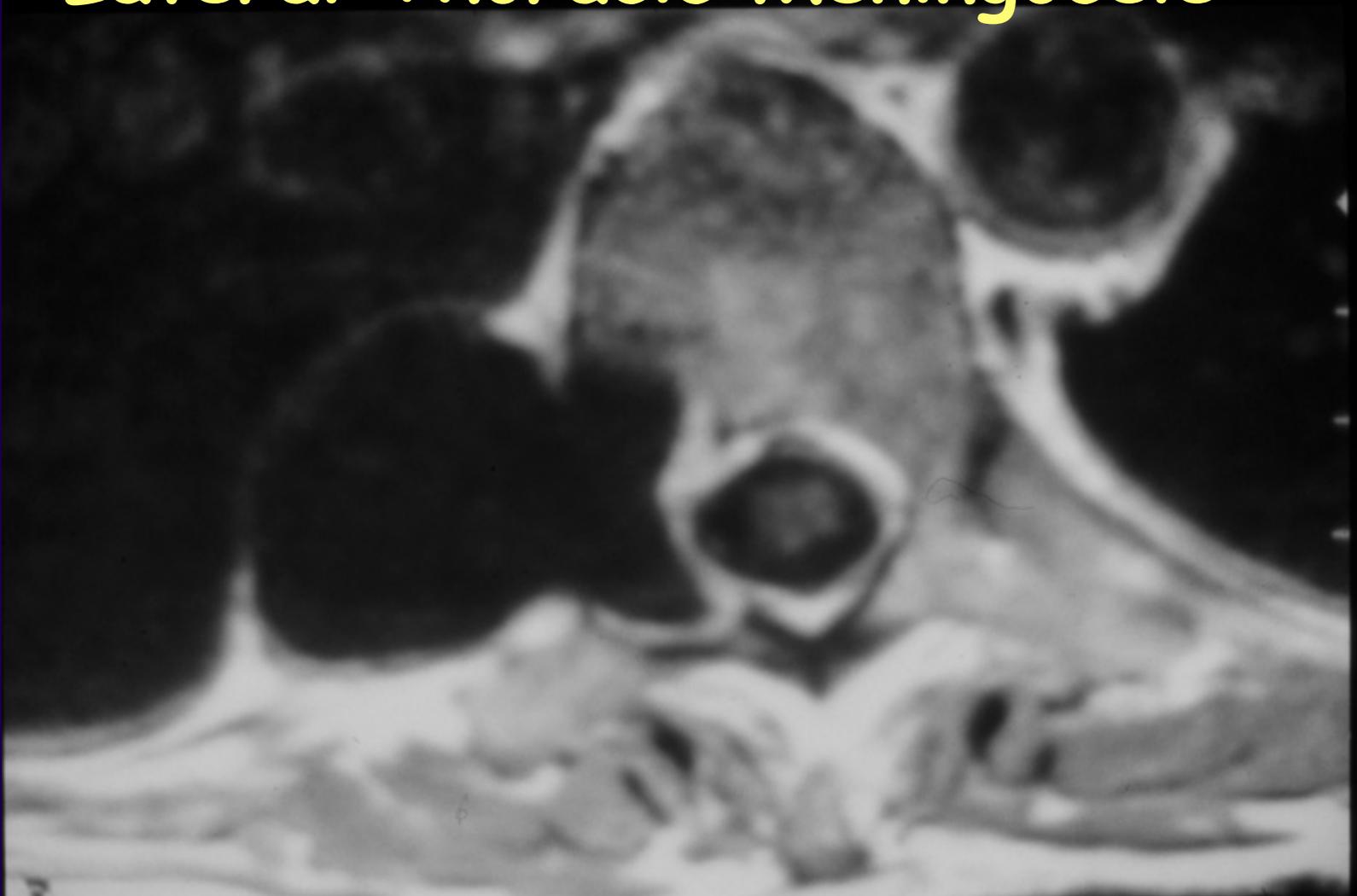
NEUROFIBROMATOSIS-1

- Posterior Meningocele (sporadic)
 - dorsal dysraphism, closure of tube
- Anterior Meningocele (sporadic)
 - neurenteric canal/cyst
 - anterior vertebral cleft
- Lateral Thoracic Meningocele (NF-1)
 - "pulsion diverticulum" of SAS
 - negative intrathoracic pressure
 - no overlying paravertebral MM.

Lateral Thoracic Meningocele



Lateral Thoracic Meningocele



Lateral Thoracic Meningocele



Lateral Thoracic Meningocele

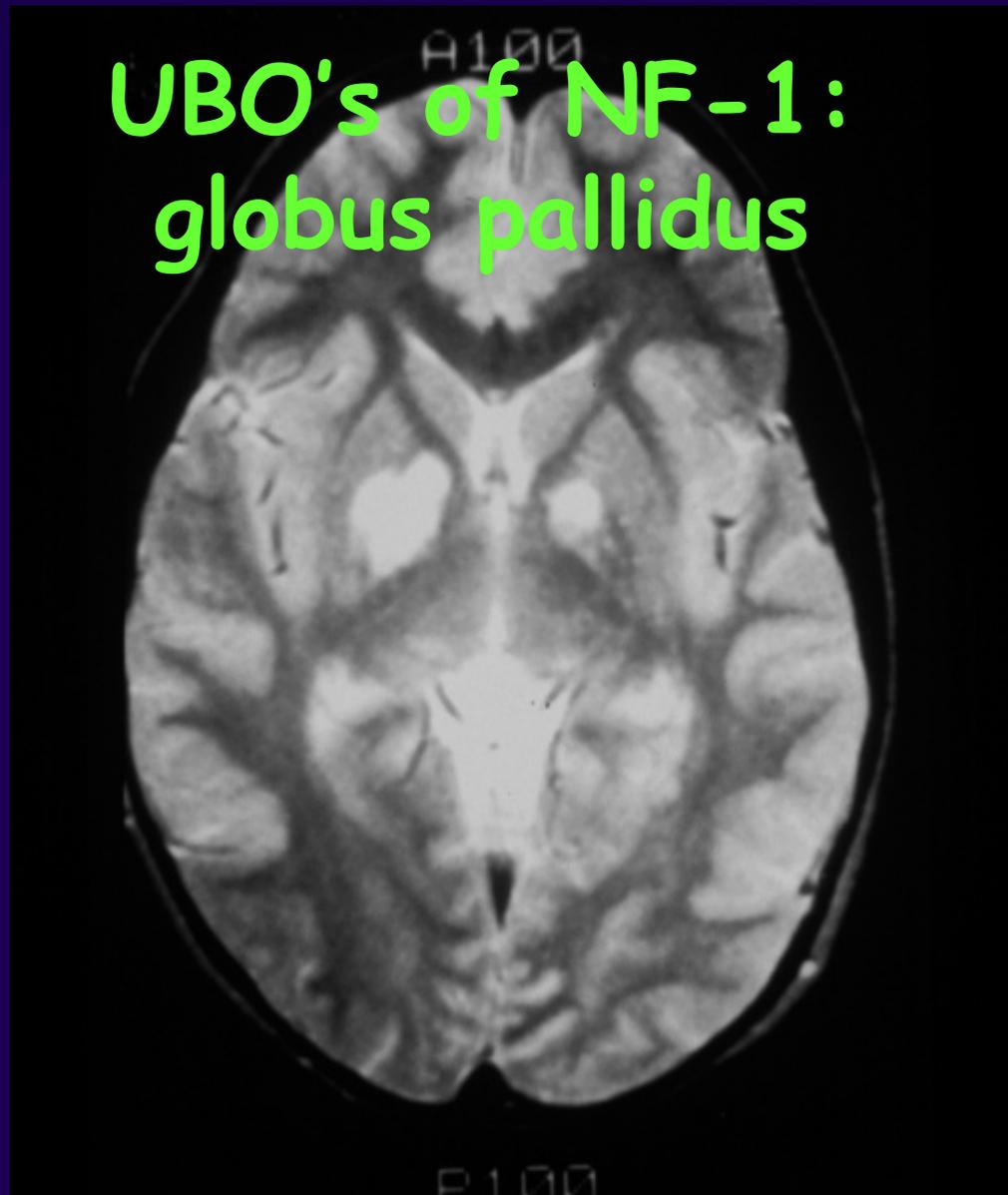


NEUROFIBROMATOSIS - 1: MR

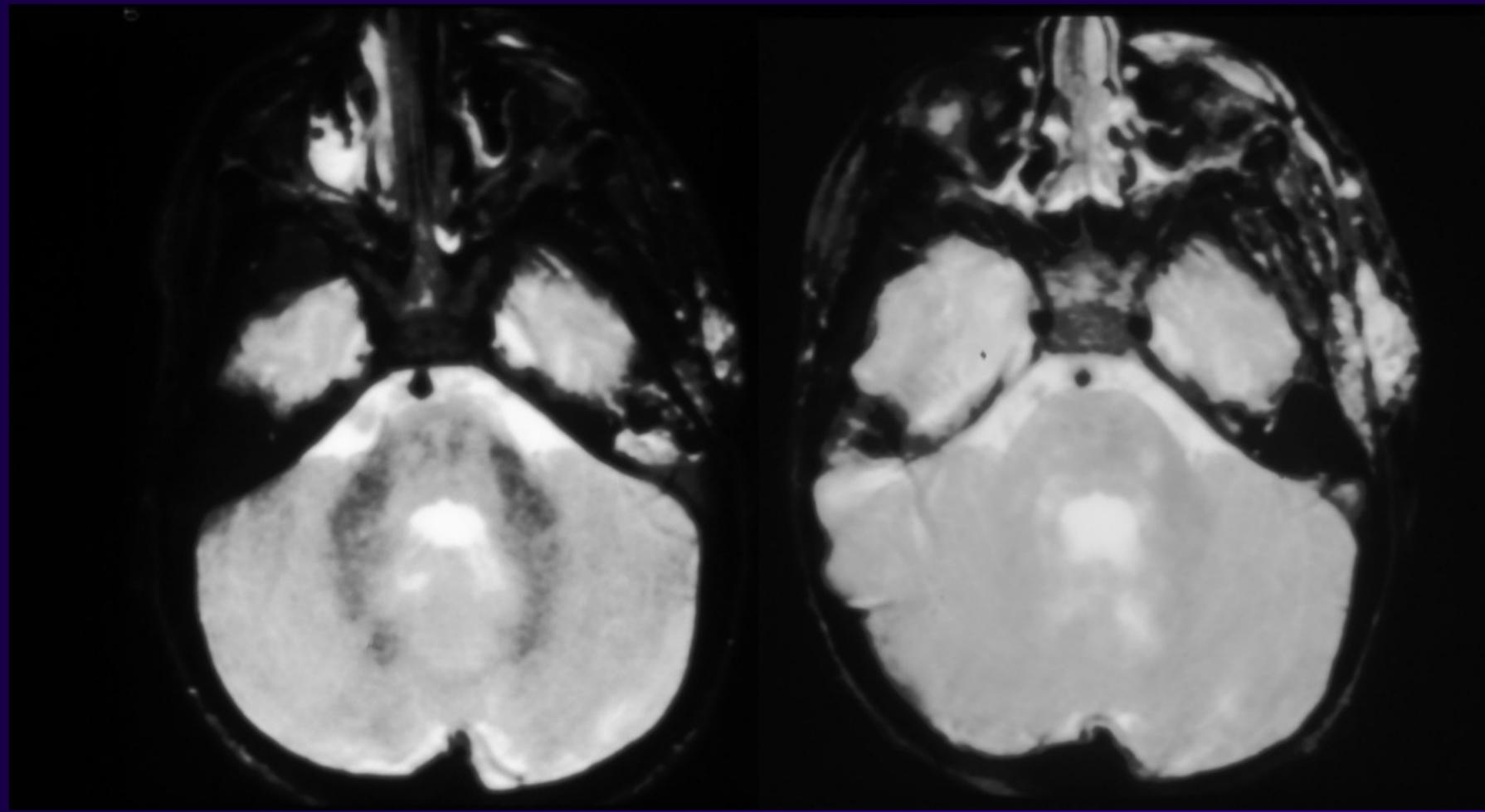
Signal Abnormalities

- T1W Bright Foci
 - globus pallidus
- T2W Bright Foci w/o mass, don't enhance
 - Cerebellar peduncles, Pons, midbrain
 - globus pallidus, thalamus, optic radiations
- What in the heck are they??
 - intracellular proteinaceous fluid?
 - dysmyelination??

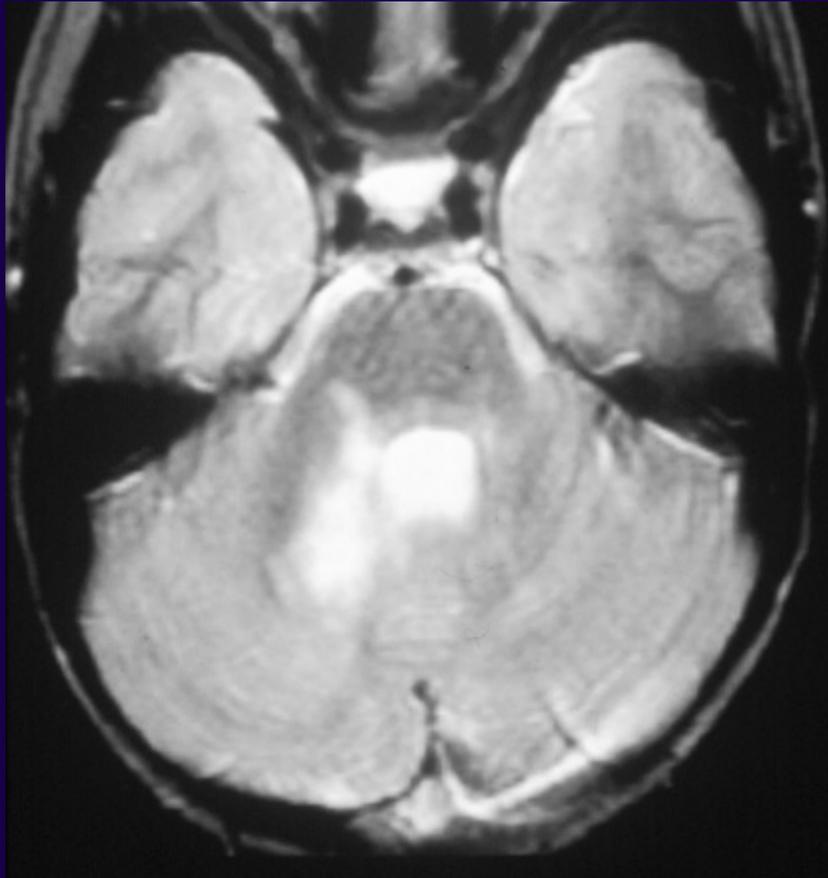
UBO's of NF-1:
globus pallidus



UBO's of NF-1



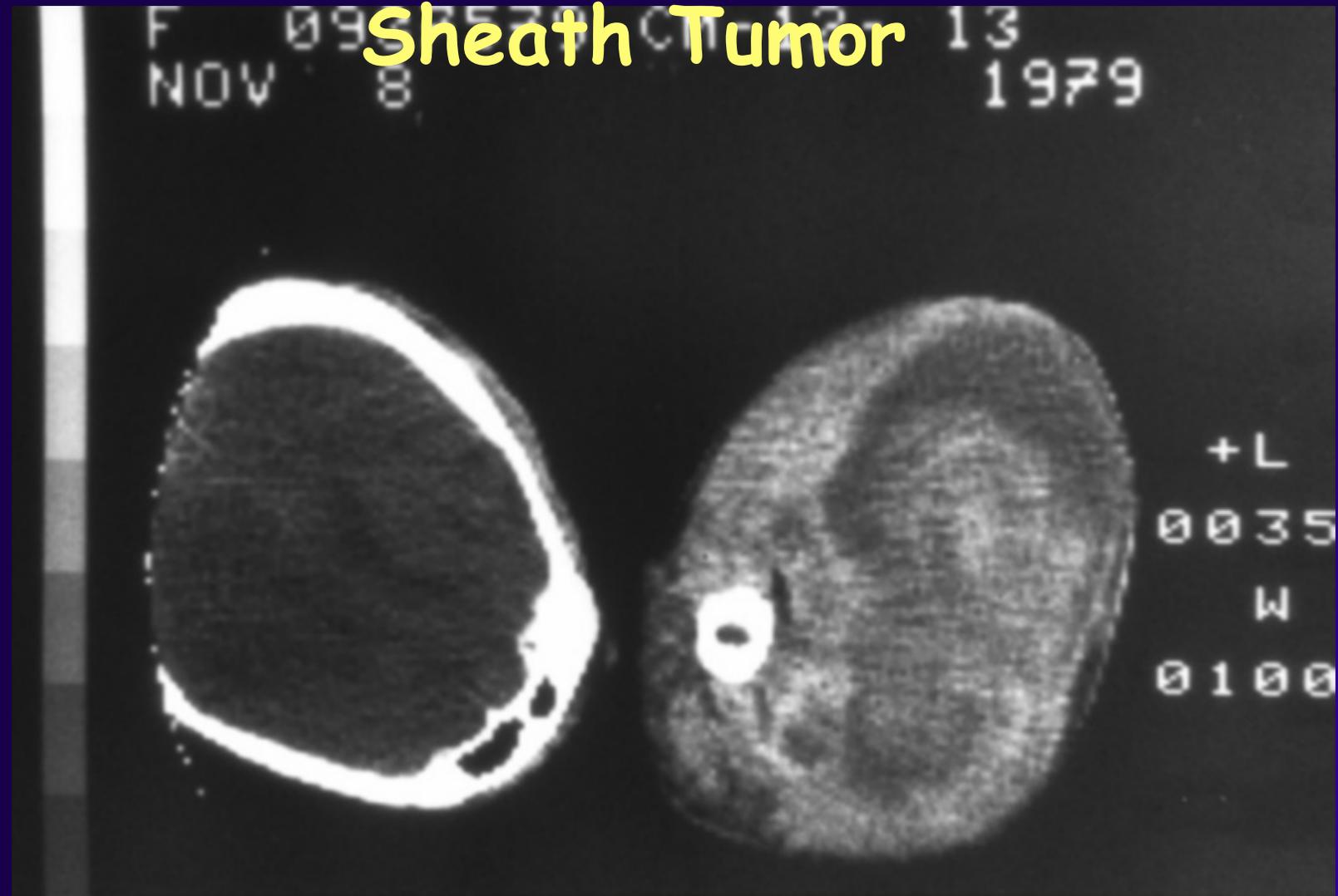
UBO's of NF-1: Cerebellar peduncle



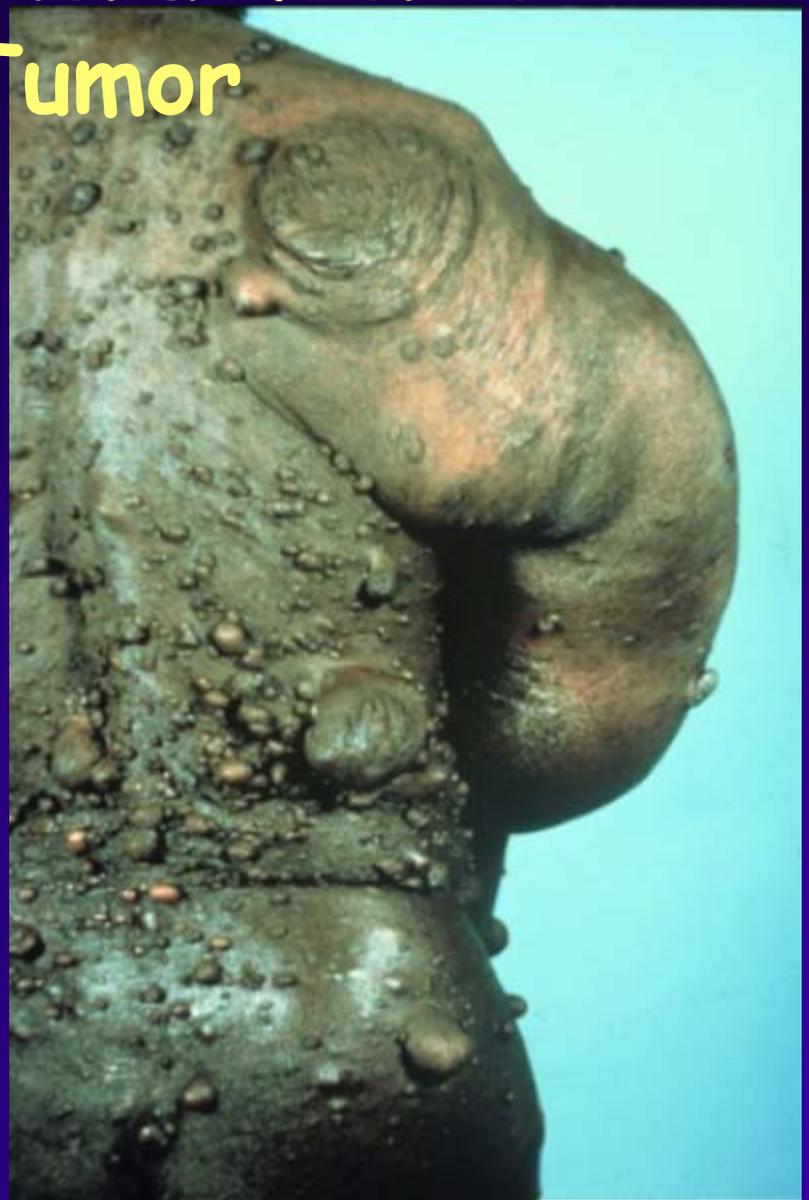
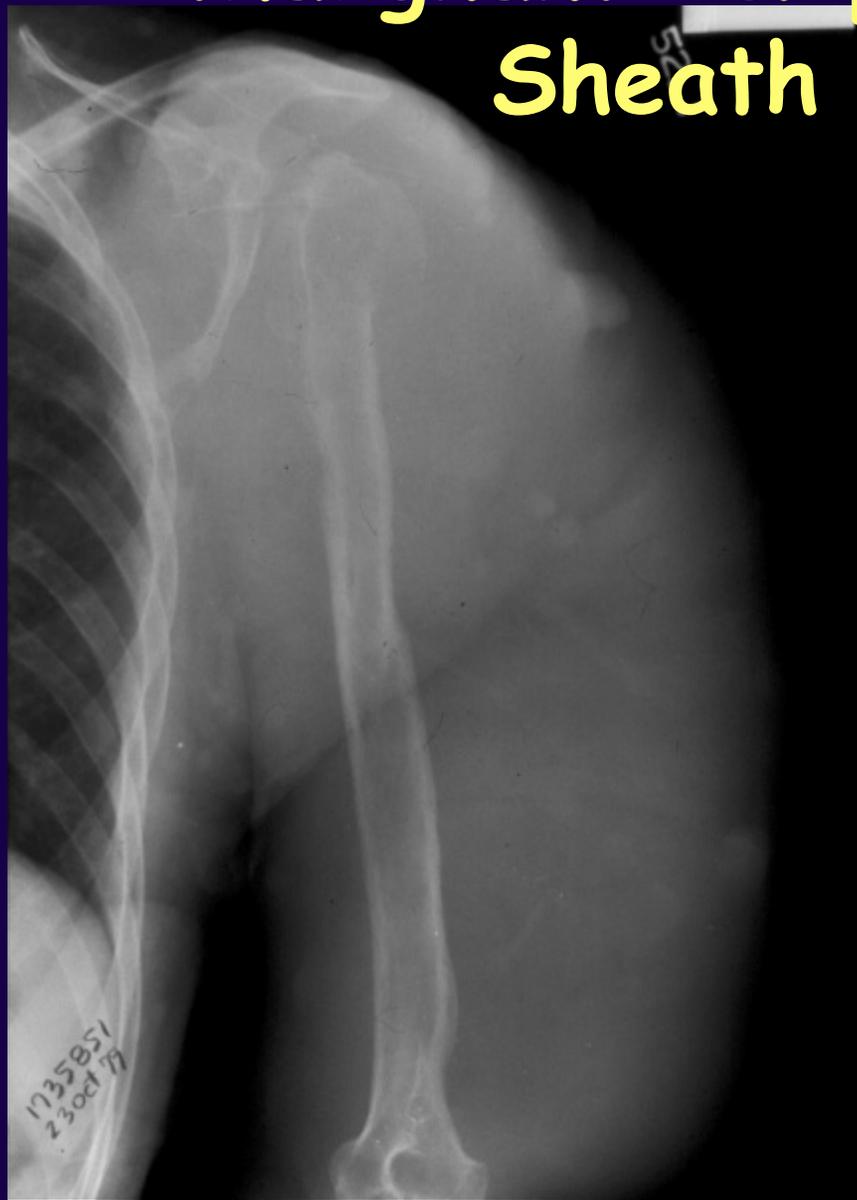
NEUROFIBROMATOSIS

- Malignant Nerve Sheath
 - Tumor(malignant PNST, neurofibrosarcoma,...)
- Embryonal Malignancies:Wilms, Rhabdomyosarcoma
- Leukemia (CML)
- Melanoma, Medullary Thyroid Ca.
- Low Incidence of Lung Cancer

Malignant Peripheral Nerve Sheath Tumor



Malignant Peripheral Nerve Sheath Tumor



NEUROFIBROMATOSIS - Type 2

- Incidence: 1/50,000
- Inheritance: Autosomal Dominant
- Age at Presentation: Birth to 40's (peak in 20's)
- Sx at Presentation: Hearing loss from VS
- Diagnostic Criteria: VIII masses
- Chromosome Abnl.: 22
- Cutaneous Findings: minimal (skin tags)
- CNS Findings: Schwannoma, Meningioma, Ependymoma (spinal cord)

CNS NEOPLASMS - Chromosome Loss of Heterozygosity

- MENINGIOMA - 22q (long arm)
- SCHWANNOMA - 22q
- EPENDYMOMA - 22
- MEDULLOBLASTOMA - 17p (short arm)
- NEUROFIBROSARCOMA - 17p
- RETINOBLASTOMA - 13q

NF-2 ("CENTRAL"), 1 OR MORE

- Bilateral VIIIth Masses
- Relative with NF-2 and either:
 - Unilateral VIIIth Mass
 - Any Two:
 - "Neurofibroma", Meningioma, Glioma, Schwannoma, (Congenital) Lens Opacity

NEUROFIBROMATOSIS - Type 2

- NEJM 319:278-83, 1988 (Gulf of Mexico)
- 23 Pts. (15M/8F), Kindred of 137
- 0.95 Penetrance
- 18 Acoustic Schwannoma (17 bil.)
- 8 Meningioma (3 mult.)
- 4 Ependymoma
- 2 Spinal "Neurofibroma"

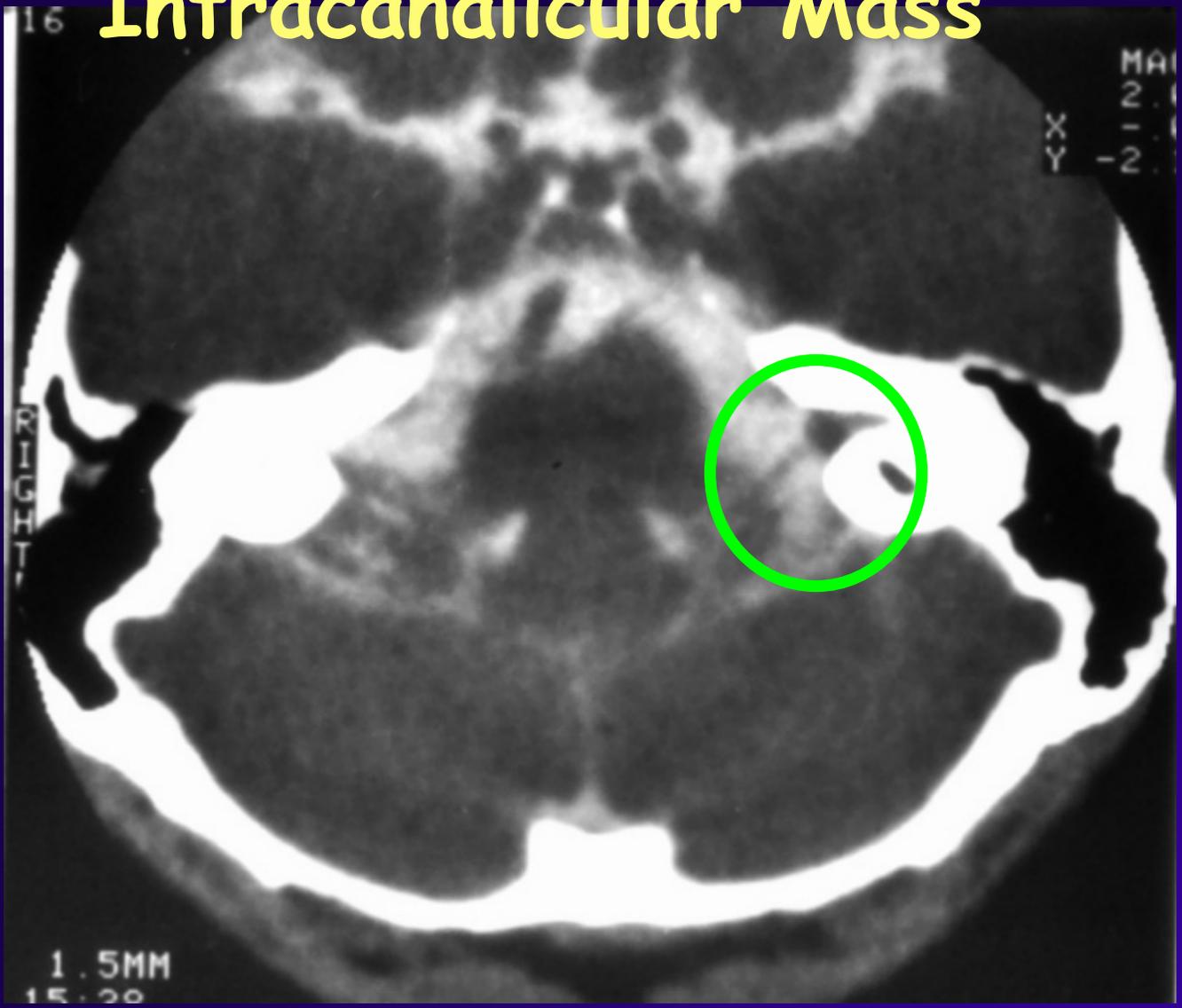
Bilateral CPA Masses



SCHWANNOMA

- 5-10% of All CNS Tumors
- Benign, Slowly growing
- F > M (Intracranial), M > F (Spinal)
- 30's - 60's, w/NF-2 10's - 30's
- Sensory Nerves (usually):
 - CNN VIII (Sup.Vestibular), V, X
 - Spine: Dorsal Roots
- Majority (>90%) are Sporadic
- Multiple in NF-2, Bilat.VIII Pathognomonic

Intracanalicular Mass

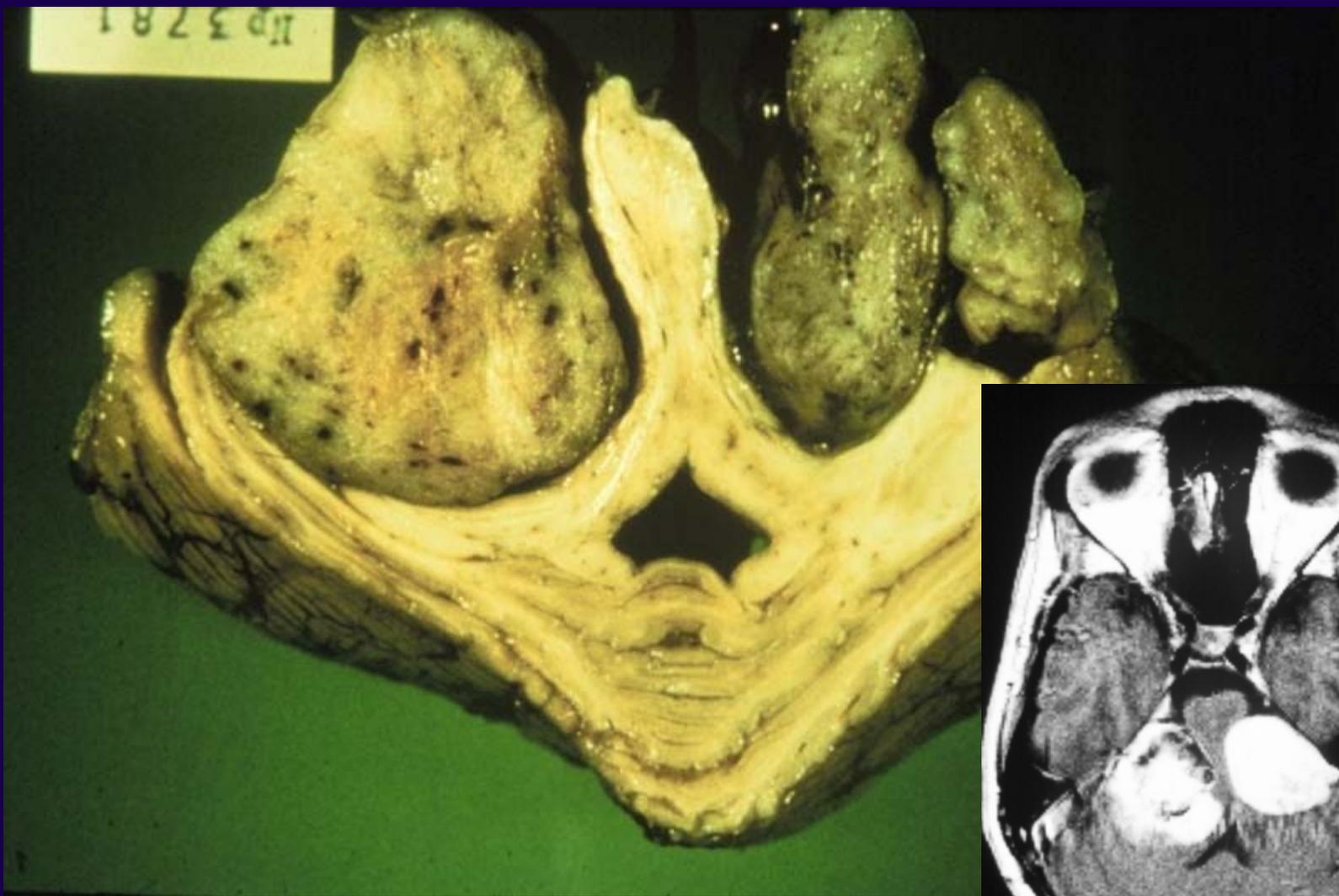


Bilateral Vestibular Schwannoma



Bilateral Vestibular Schwannoma

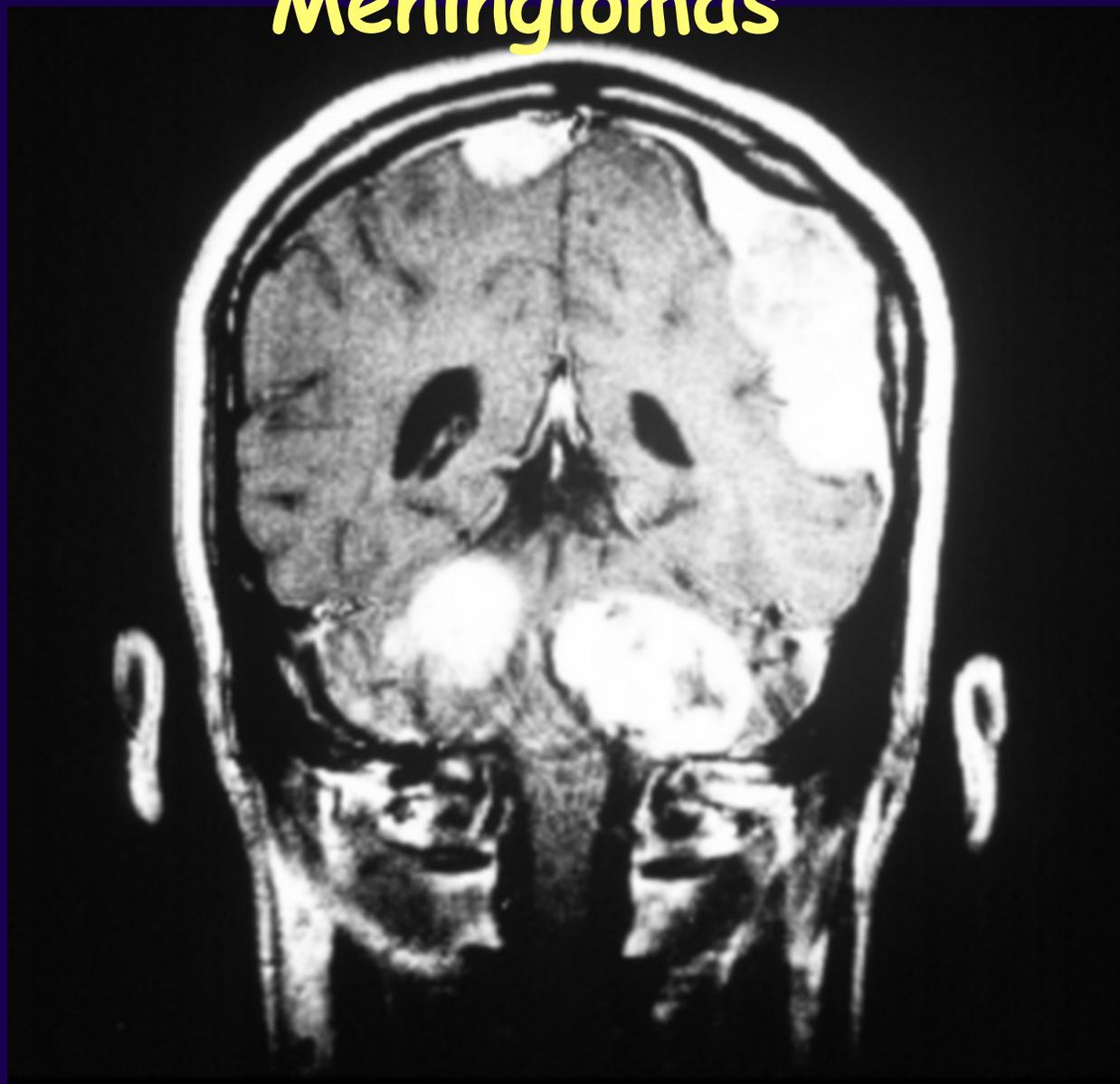
Radiology - <http://rad.medpix.net>

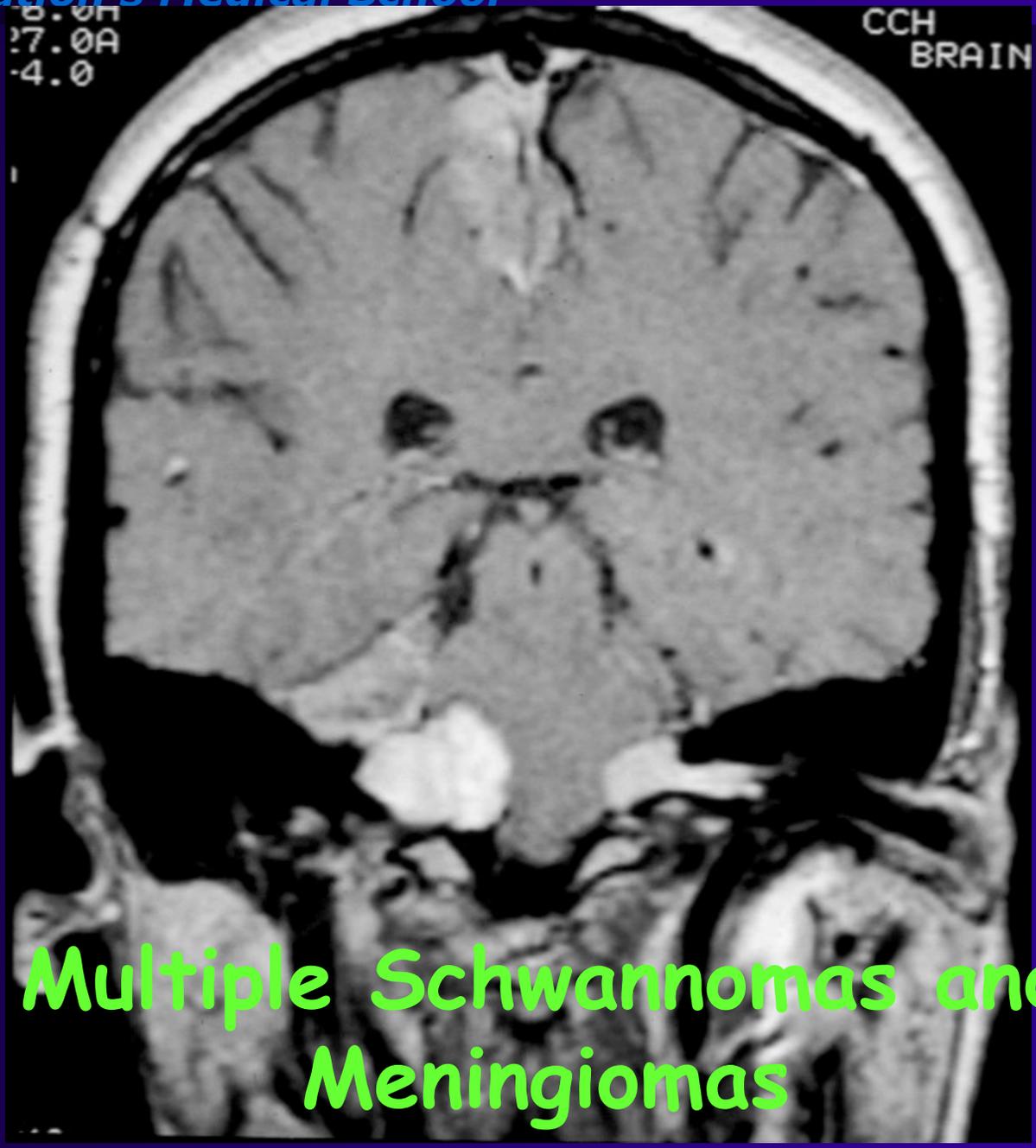


Neurofibromatosis - 2

- **Meningiomas:**
 - multiple transitional type meningioma
 - NOT meningothelial
- **Meningioangiomatosis:**
 - cortical (intracortical) vascular tissue
 - resembles a vascular malformation
 - meningothelial and fibroblast-like cells

Multiple Schwannomas and Meningiomas





Multiple Schwannomas and Meningiomas

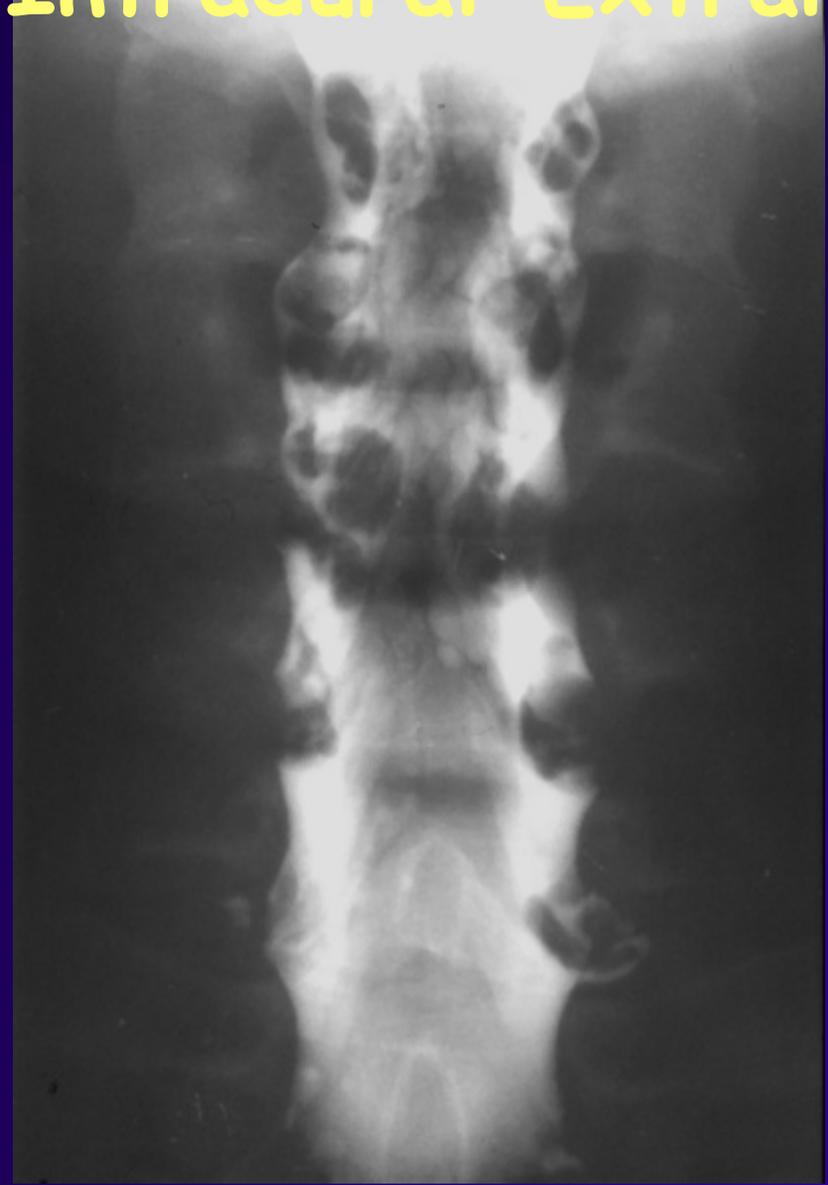


Multiple Schwannomas and Meningiomas and Ependymomas

NEUROFIBROMATOSIS-2

- Multiple Meningiomas (up to 45%)
 - Intraventricular Meningiomas
 - Childhood Meningiomas
- Multiple Meningiomas (1-10% of all MENIN.)
 - SPORADIC in 80-90%
- Intraventricular Meningiomas
 - SPORADIC in 90%
- Childhood Meningiomas
 - SPORADIC vs. Inherited (NF-2 or Not)

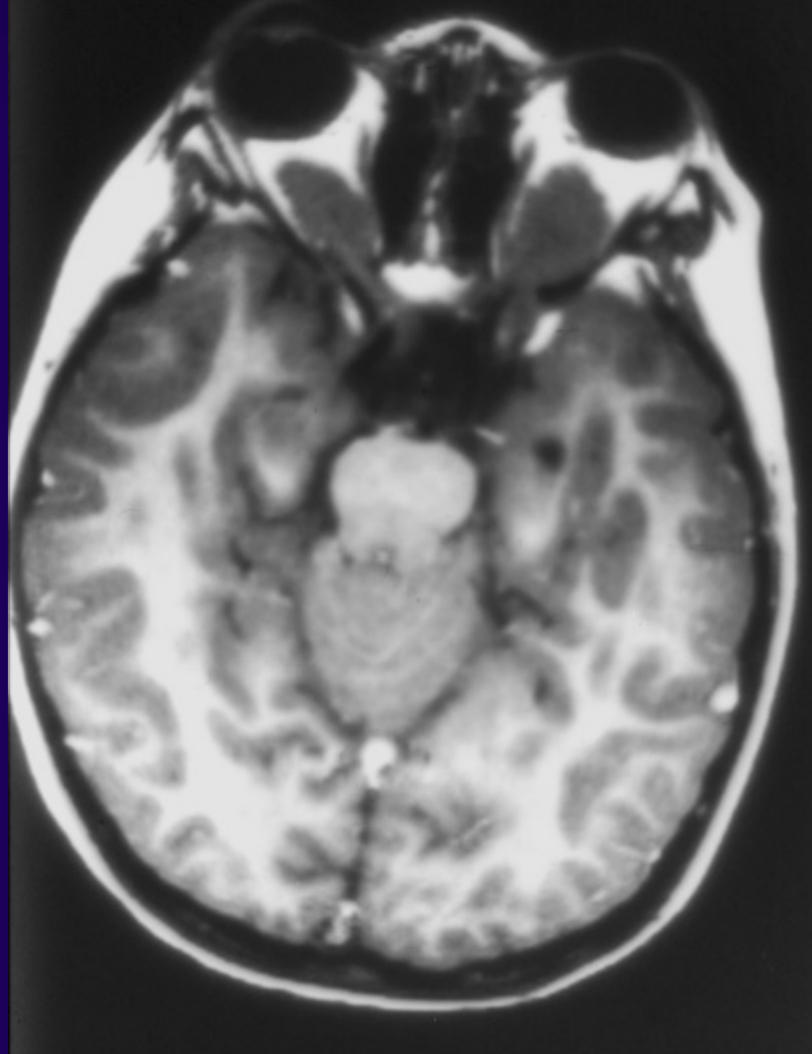
Multiple Intradural-Extramedullary



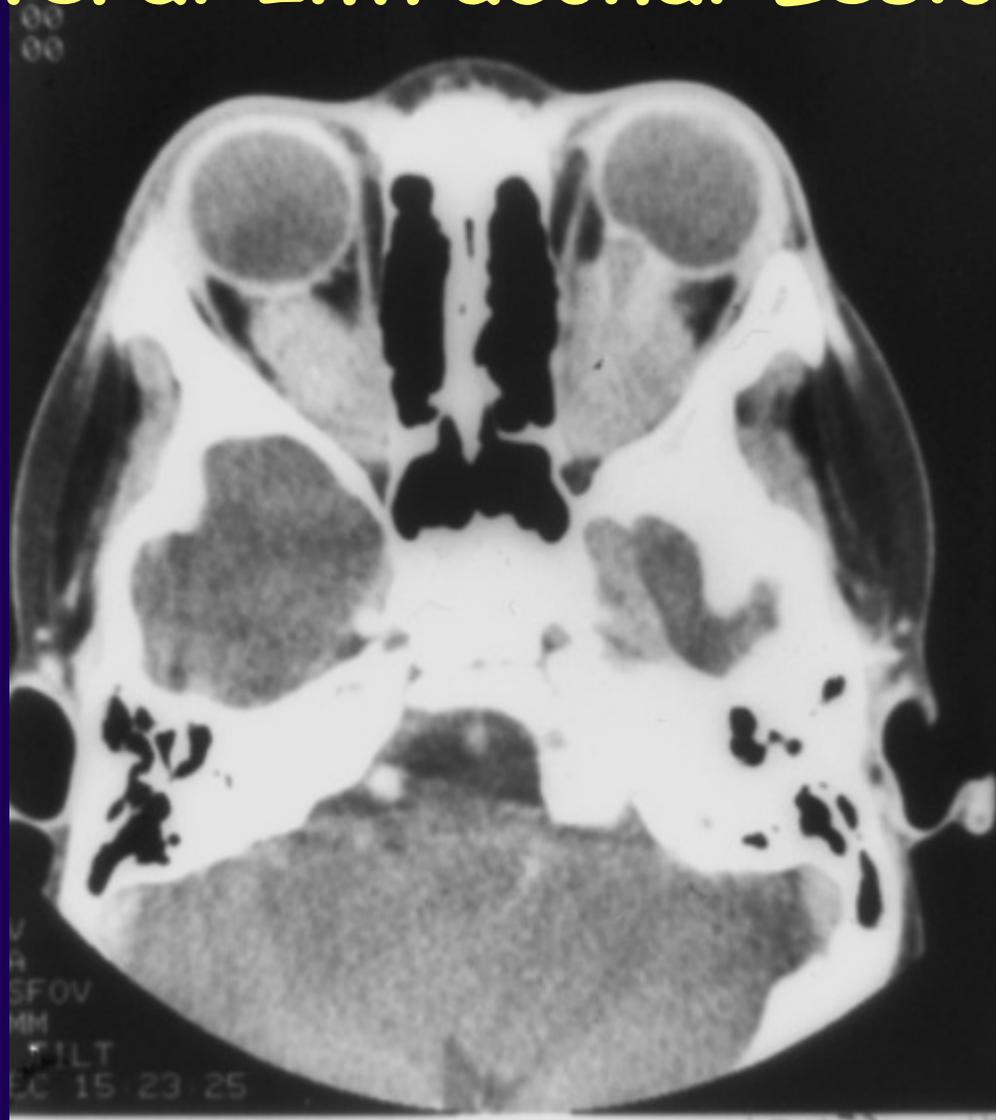
Multiple Nerve Root Lesions



Bilateral Intraconal Lesions



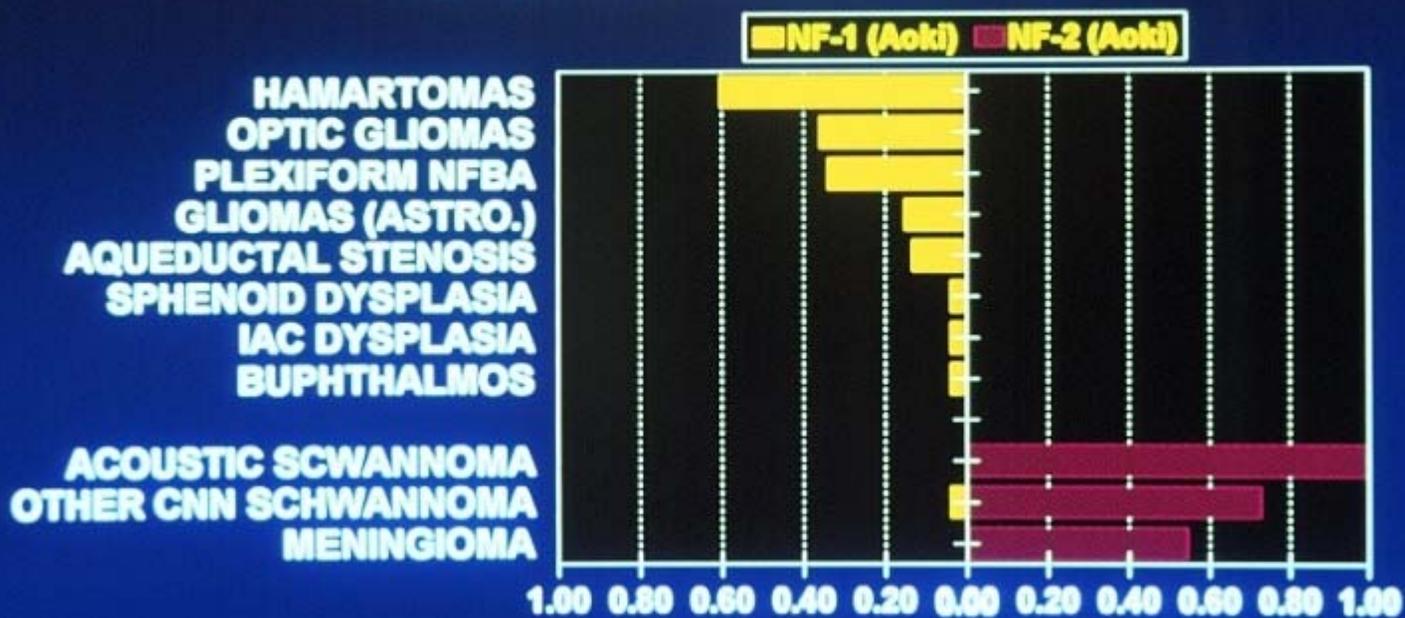
Bilateral Intraconal Lesions



NF-1 vs. NF-2

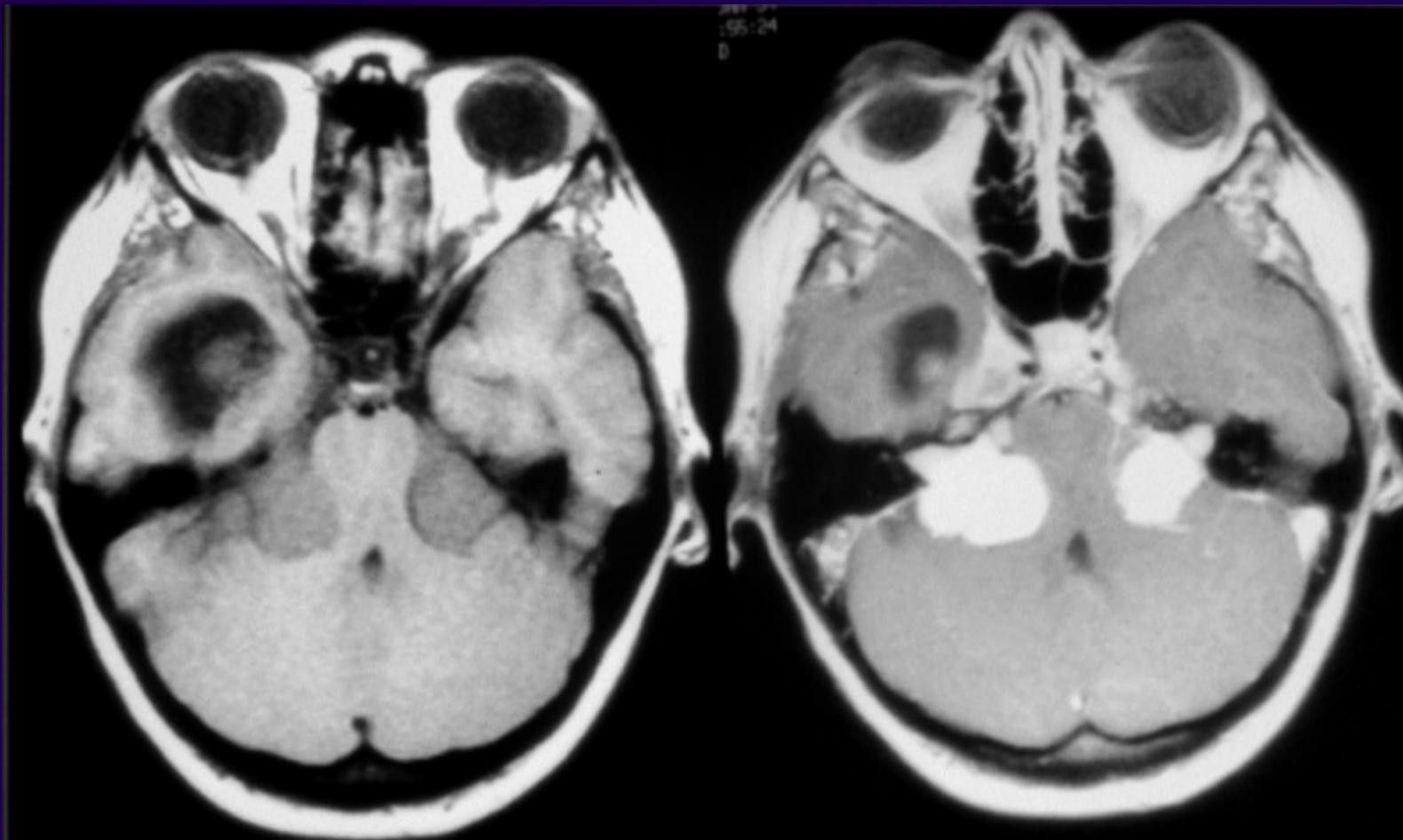
NEUROFIBROMATOSIS - 1&2

Imaging, Aoki et al AJNR 1989



James G. Smirniotopoulos, M.D. - Slide 48

Bilateral Vestibular Schwannoma



NEUROFIBROMATOSIS TYPE-2

=> MISME

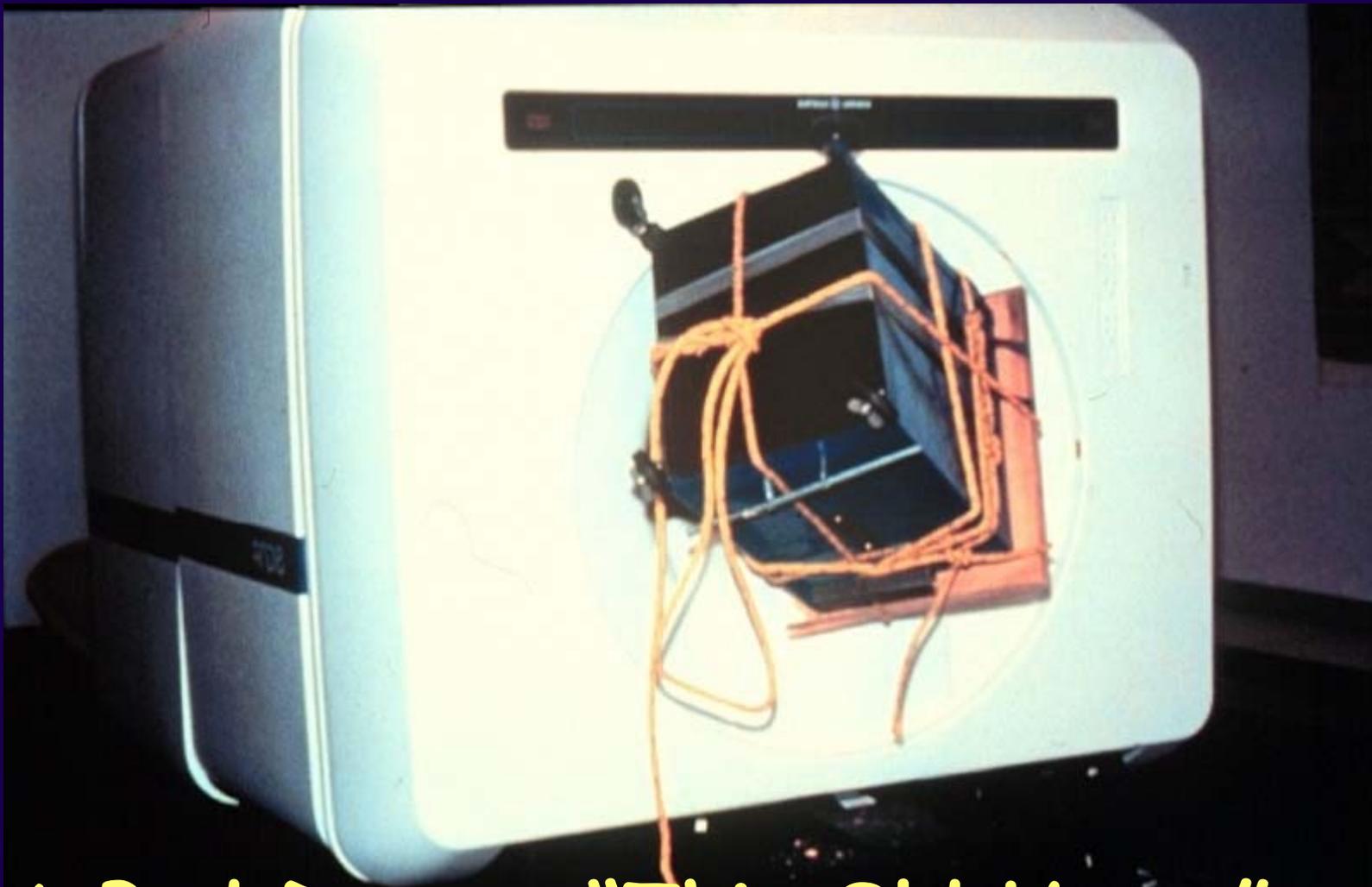
M ultiple

I nherited

S chwannomas

M eningiomas

E pendymomas



A Bad Day on "This Old House"

THE PHAKOMATOSES

- von Recklinghausen Disease
- MISME Syndrome
- **Sturge-Weber-Dimitri Syndrome**
- Bourneville Disease
- von Hippel-Lindau Syndrome

STURGE-WEBER: Definition:

A telangiectatic venous angioma of the leptomeninges, face, and choroid of the eye.

STURGE-WEBER: Manifestations

- Seizures, Mental Decline
- Facial Angioma
- Angiomatous Overgrowth
- Leptomeningeal Angioma
- Cortical Atrophy w/Ca++

Trigeminal Angiomatosis



STURGE-WEBER SYNDROME: Port Wine Stain (PWS)

- Facial Nevus Flammeus
- Blanches w/ pressure
- Trigeminal Dermatome
 - V1 - Ophthalmic
 - V2 - Maxillary
 - V3 - Mandibular

"Port-Wine Stain"



"Port-Wine Stain"



"Port-Wine Stain"



Association of PWS with SWS

- All 3 >> 1+2 >> 1 or 2 alone >> other
- medial aspect of eyelid (V1 or V2)

STURGE-WEBER: Orbit/Eye

- BUPHTHALMOS
 - congenital glaucoma
 - enlarged globe
- CHOROIDAL ANGIOMA
- EPISCLERAL TELANGIECTASIA
- ANGIOMATOUS OVERGROWTH EOM's

Choroidal Telangiectasia



STURGE-WEBER: Vascular

- Absence of cortical veins
- Poor filling of sagittal sinus
- Persistent Primitive Plexus (SAS)
- Recruitment of Medullary Veins
- Prominent Choroid Plexus

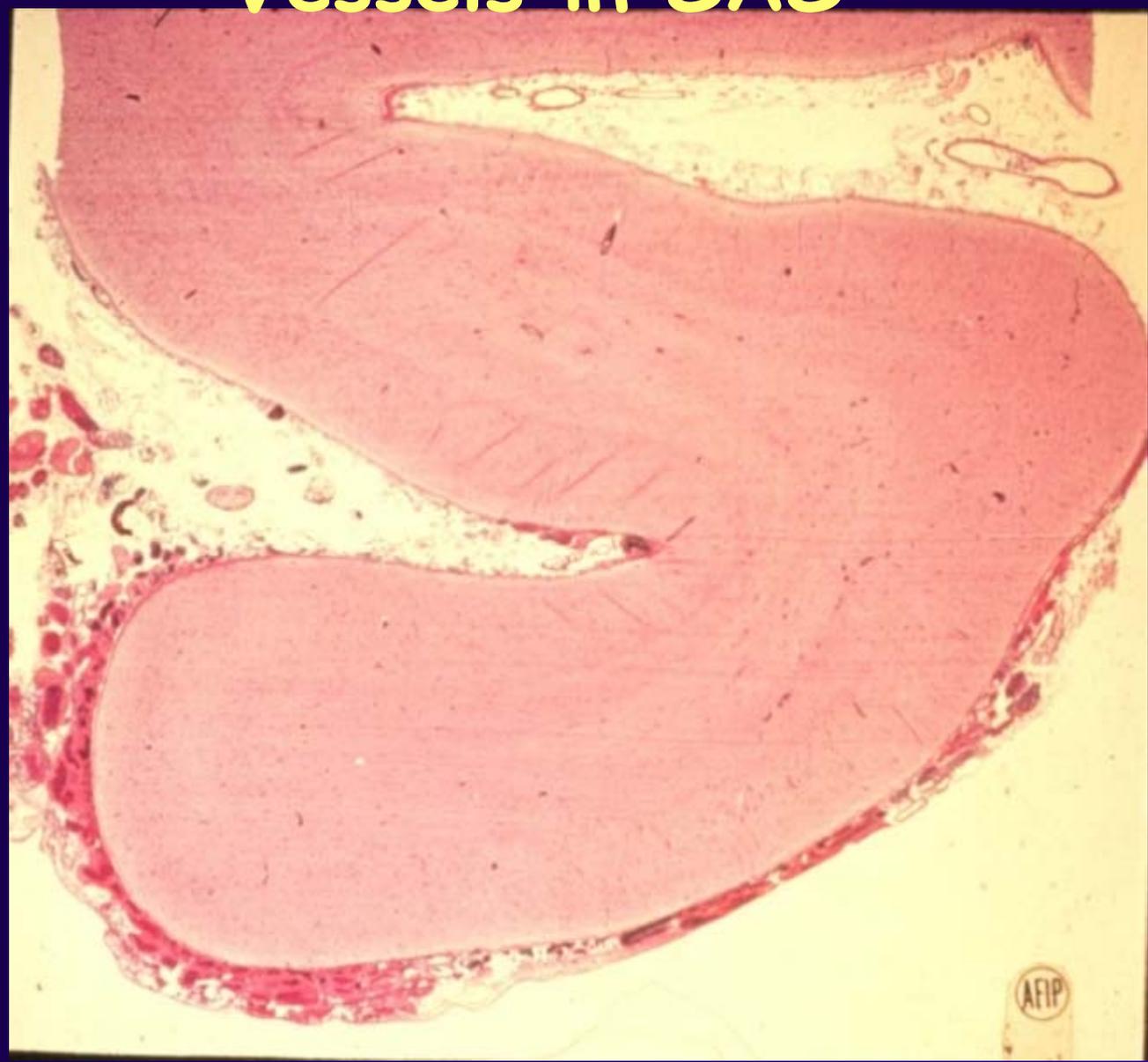
Medullary Veins



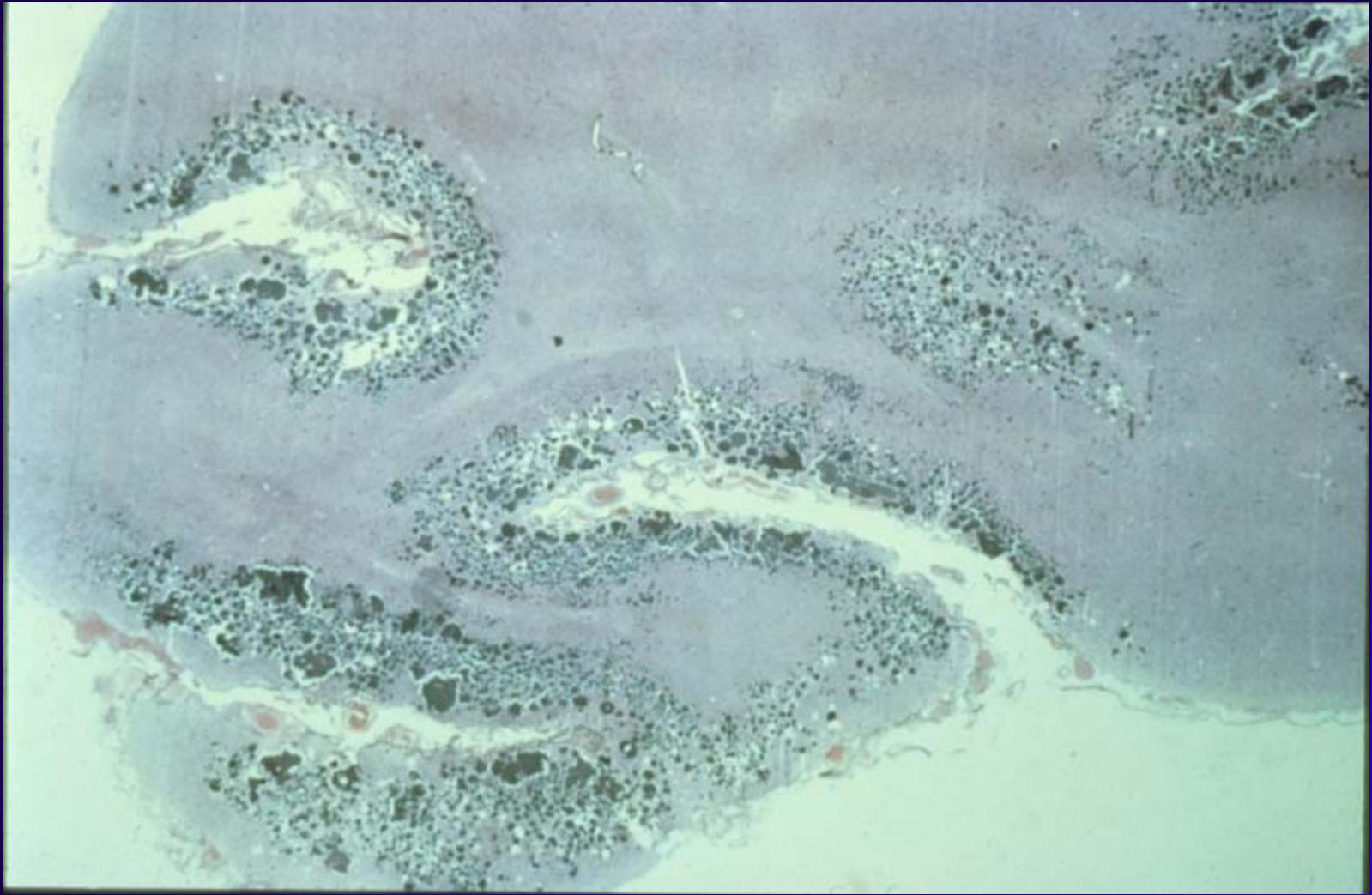
Persistence of Primitive Plexus



Vessels in SAS

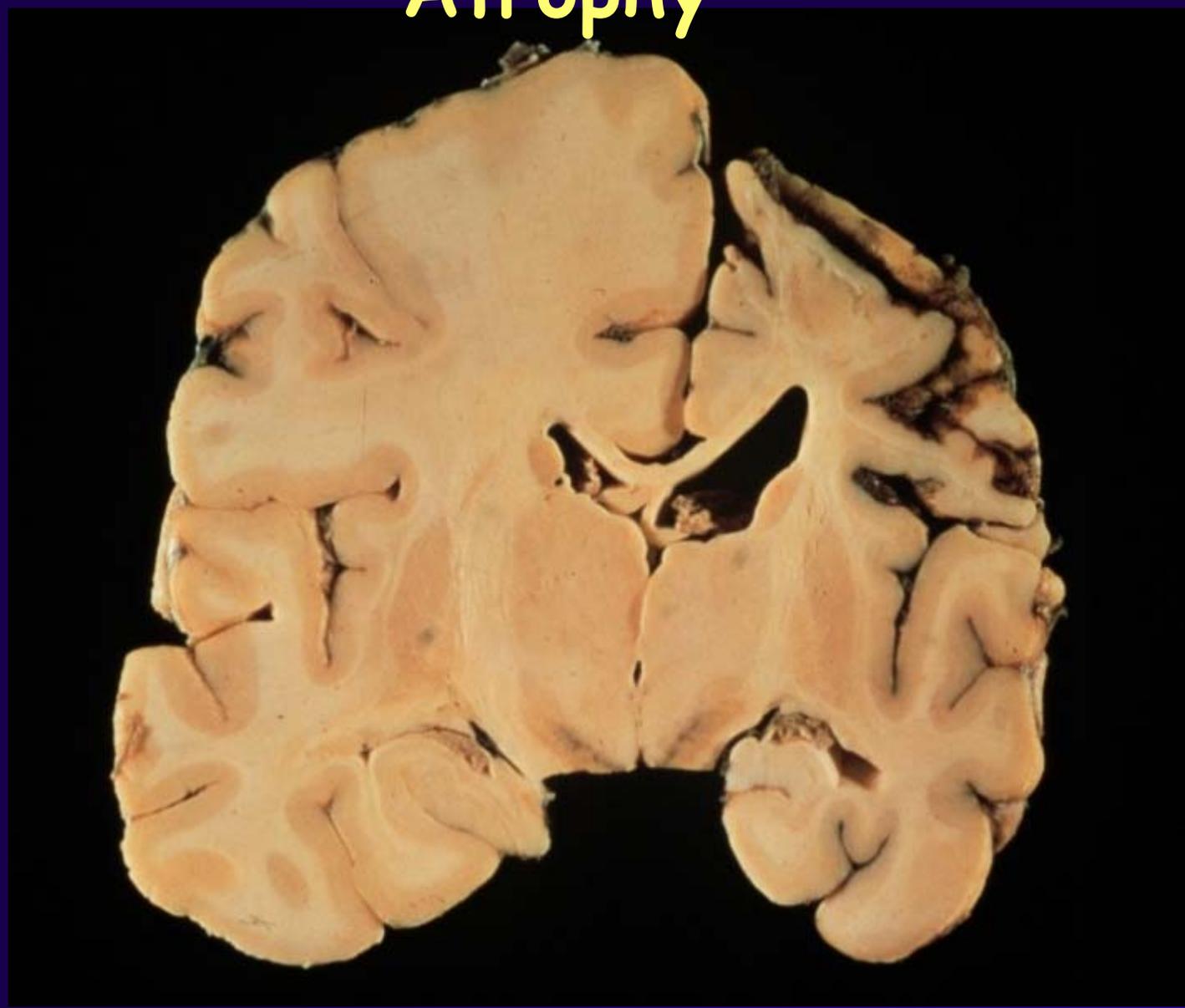


Atrophy and Calcification



Radiology - <http://rad.medpix.net>

Atrophy



Atrophy and Calcification



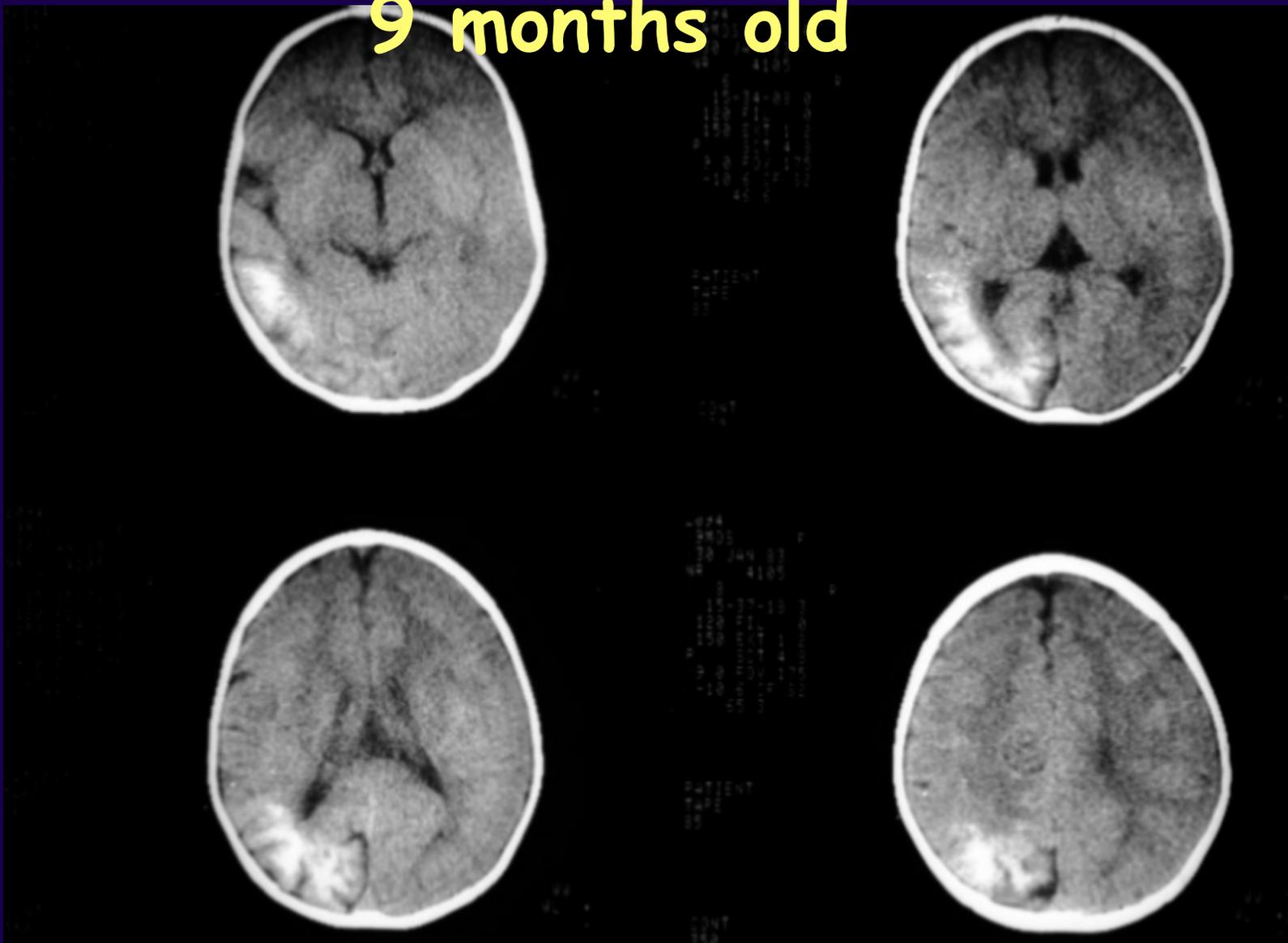
STURGE-WEBER: Calcification

- Abnormal (sluggish) circulation
- Chronic Cerebral Ischemia
- Progressive Cell Loss (Atrophy)
- Progressive Cerebral calcification
 - early - subcortical WM (?)
 - Later - middle layers of cortex

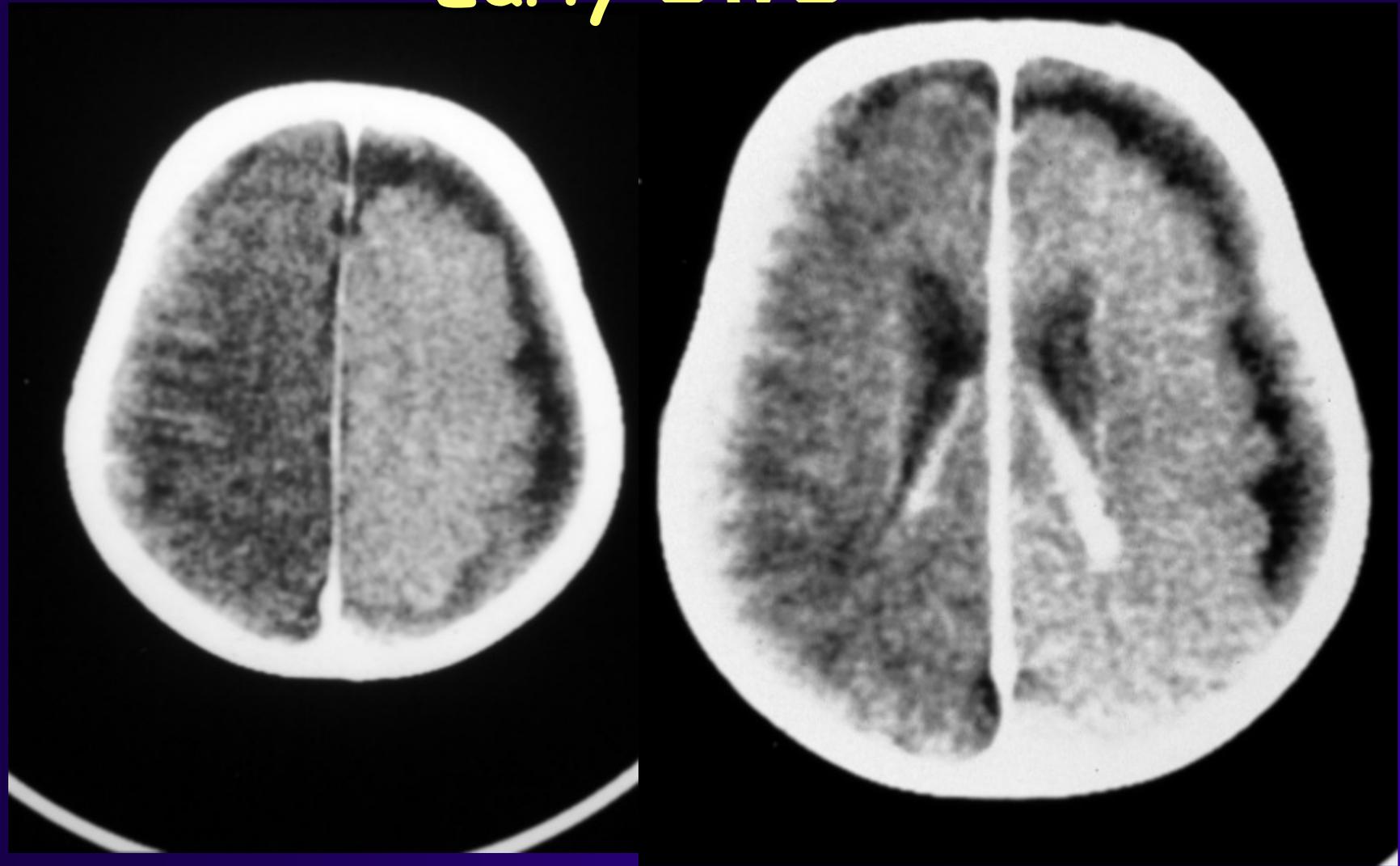
Atrophy and Calcification



9 months old

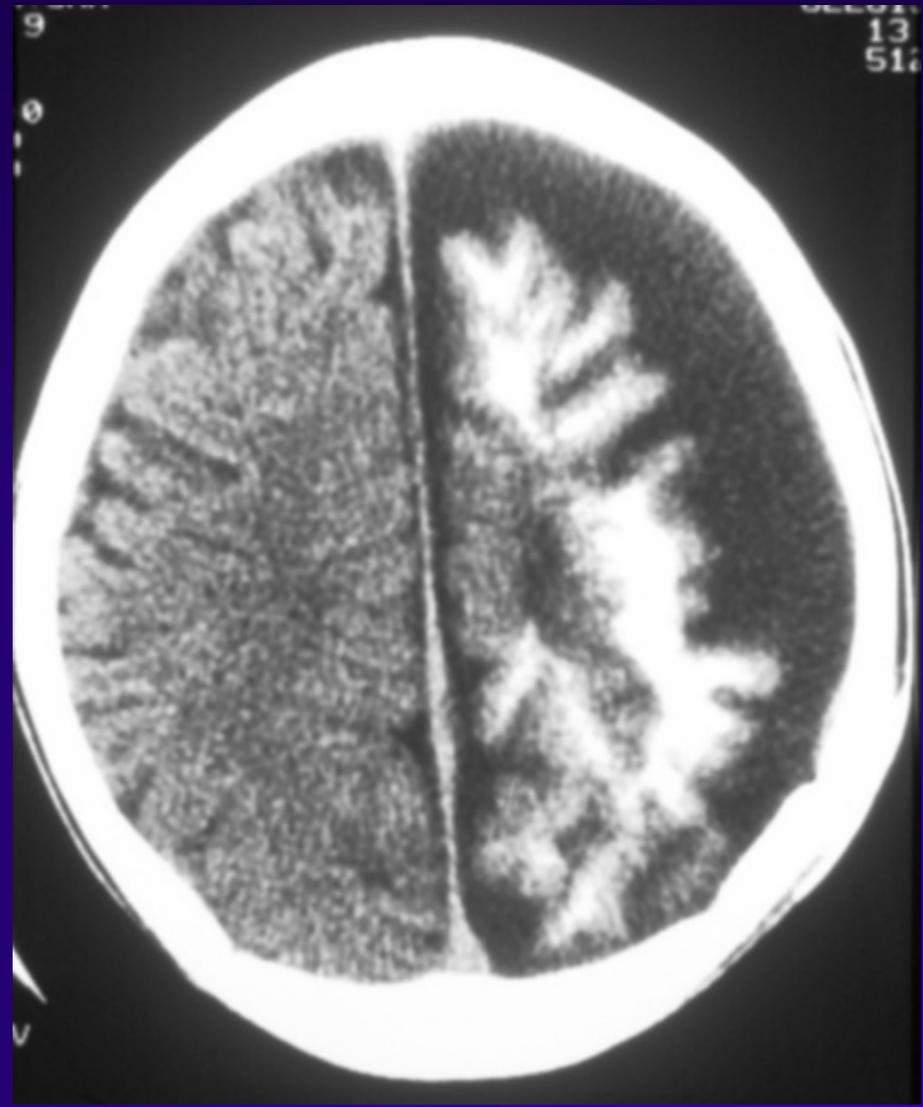
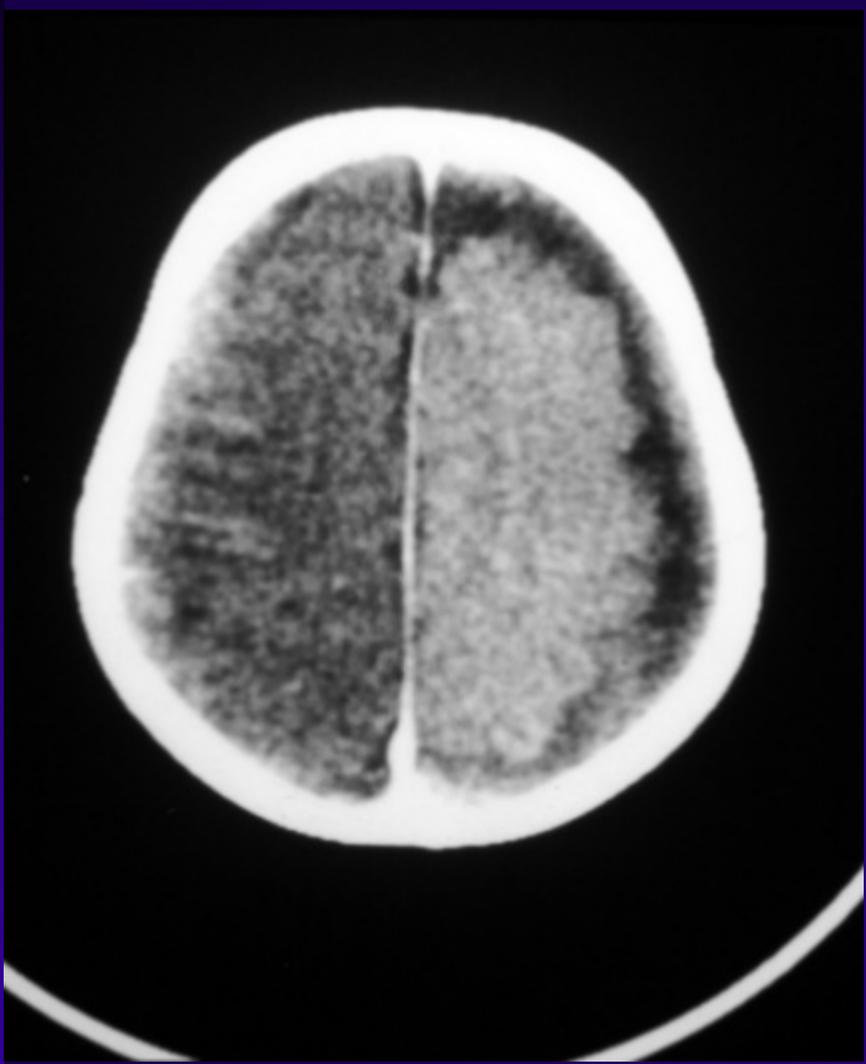


Early SWS



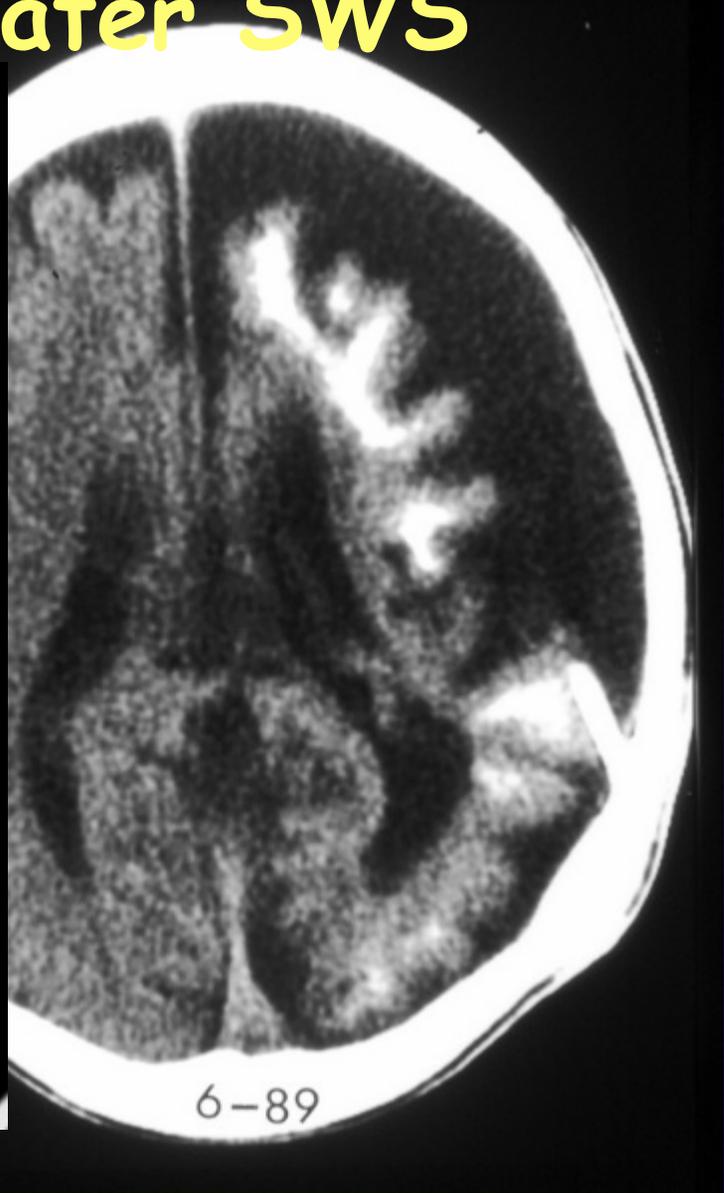
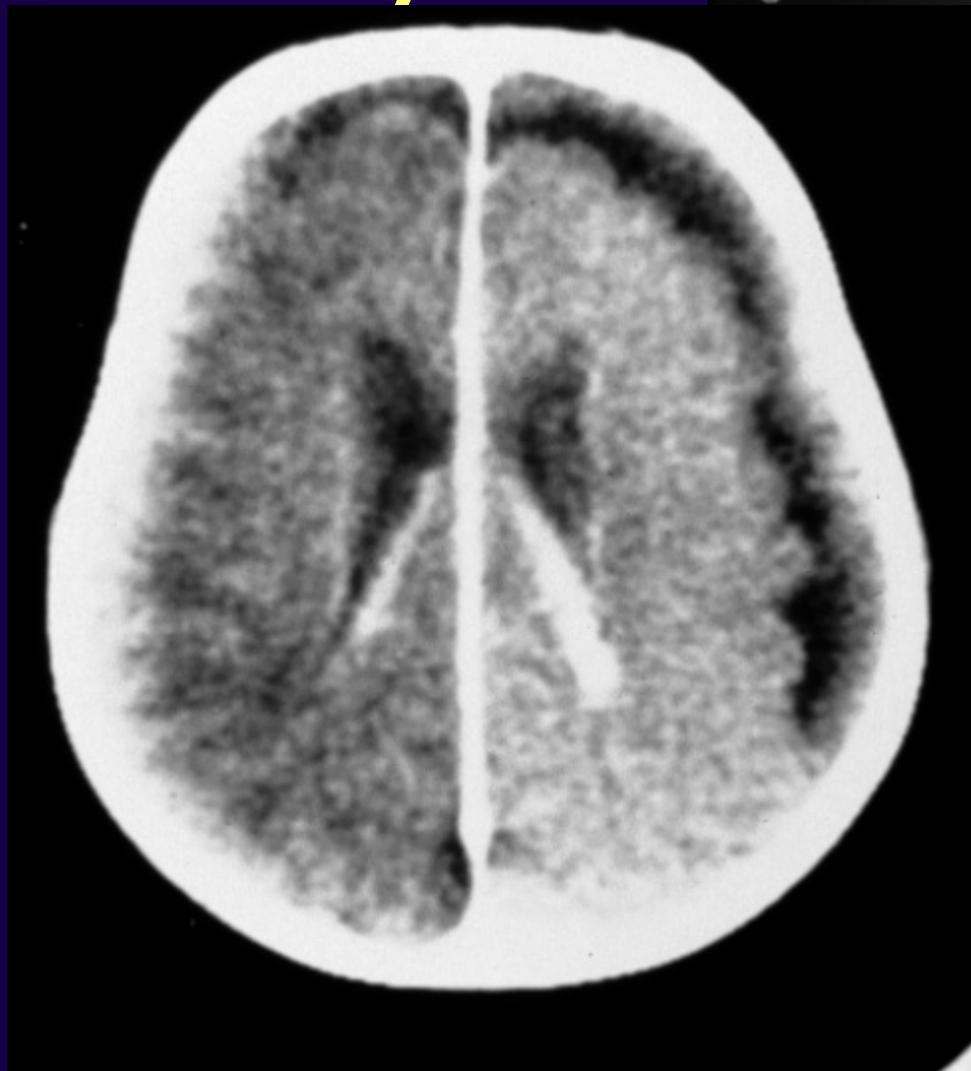
Early - - - -

Later SWS



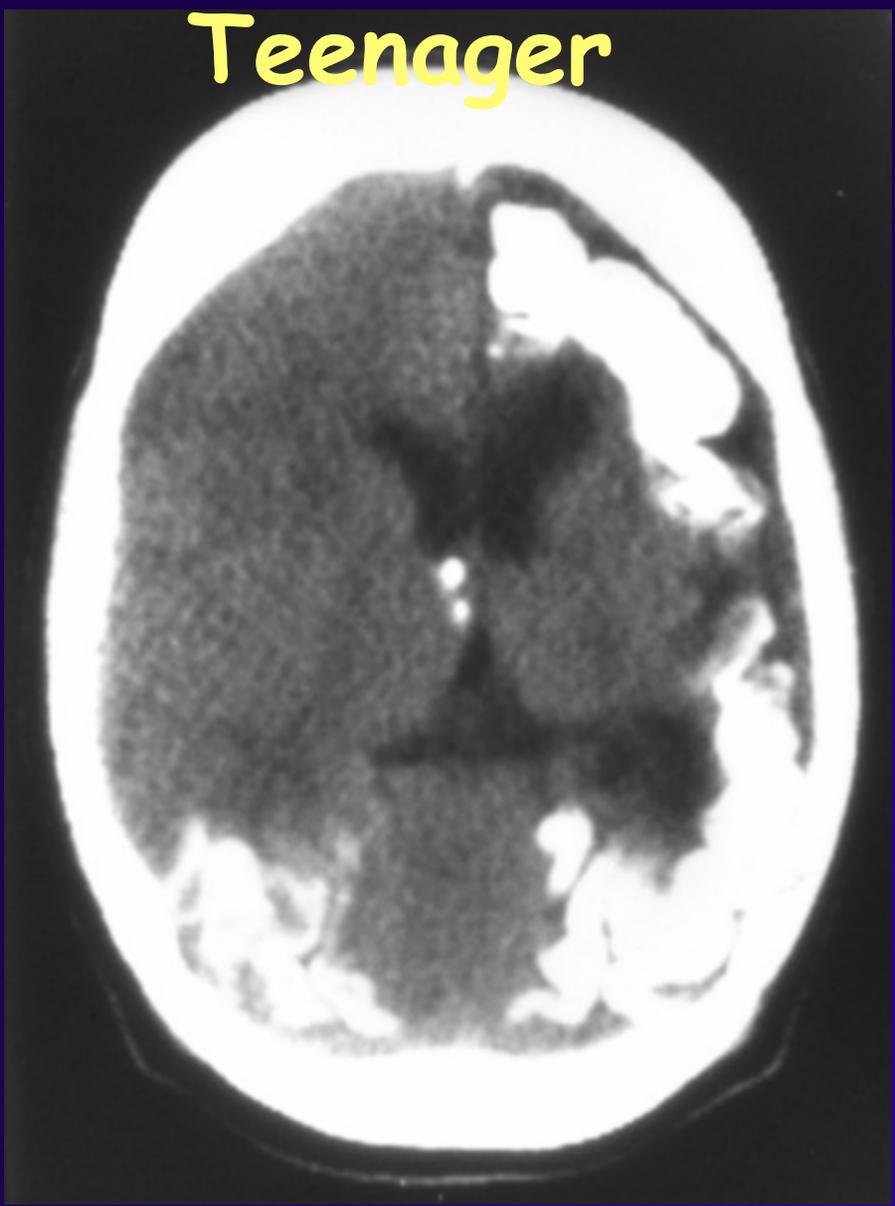
Early ----- Later SWS

85 5MM
8

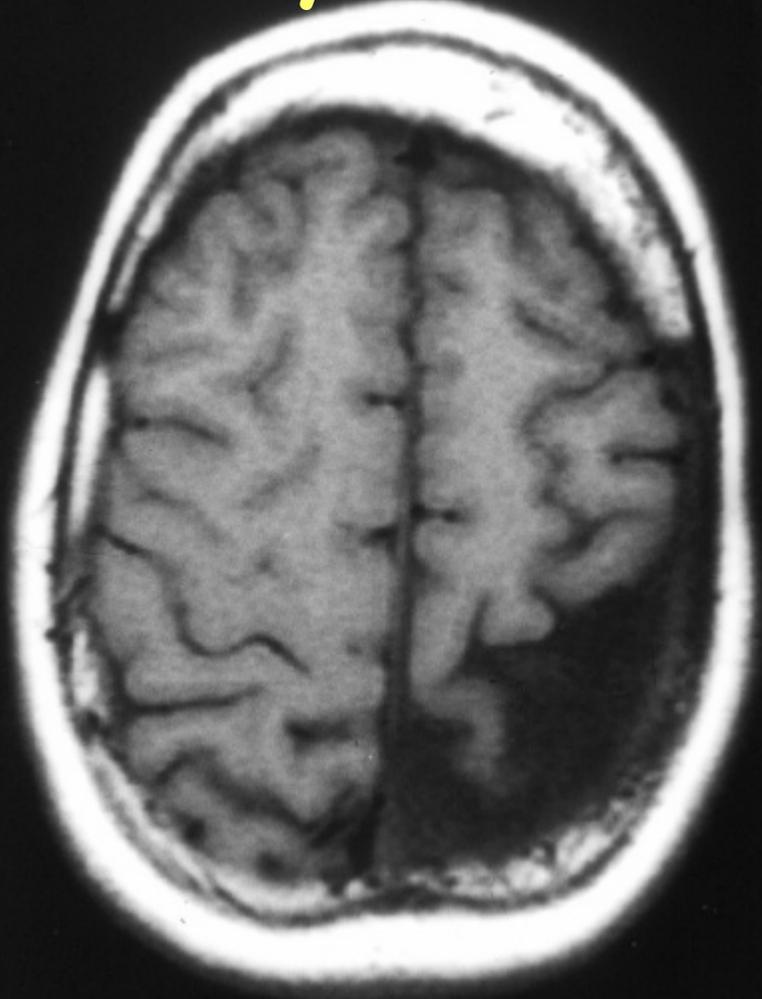


ILT
14-45-12

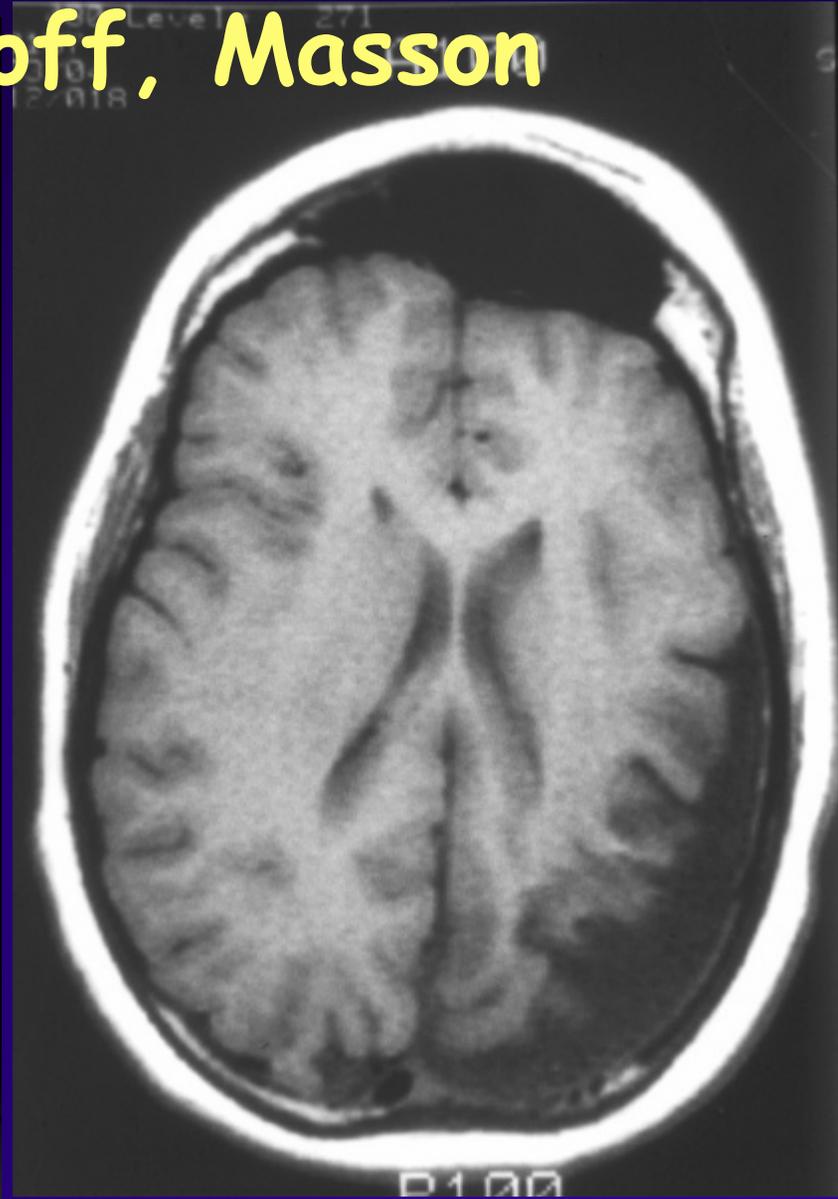
Teenager



Dyke, Davidoff, Masson

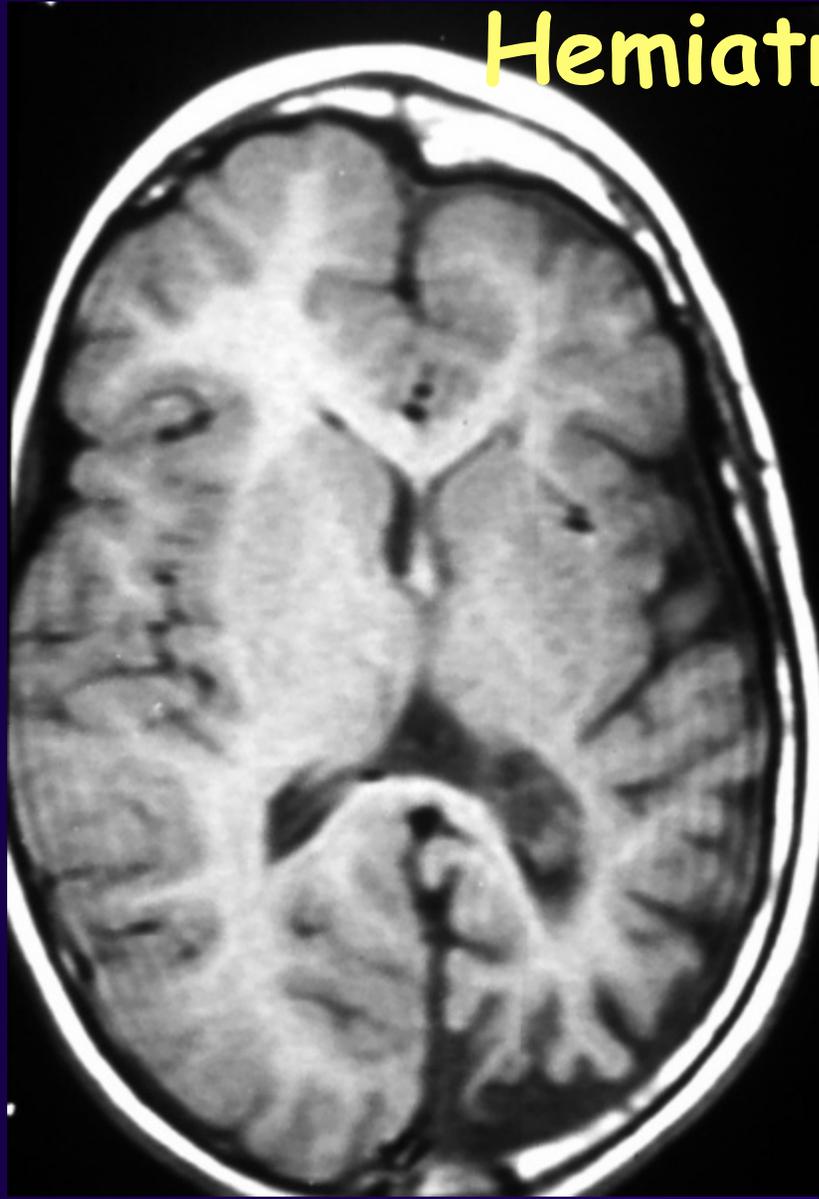


P100

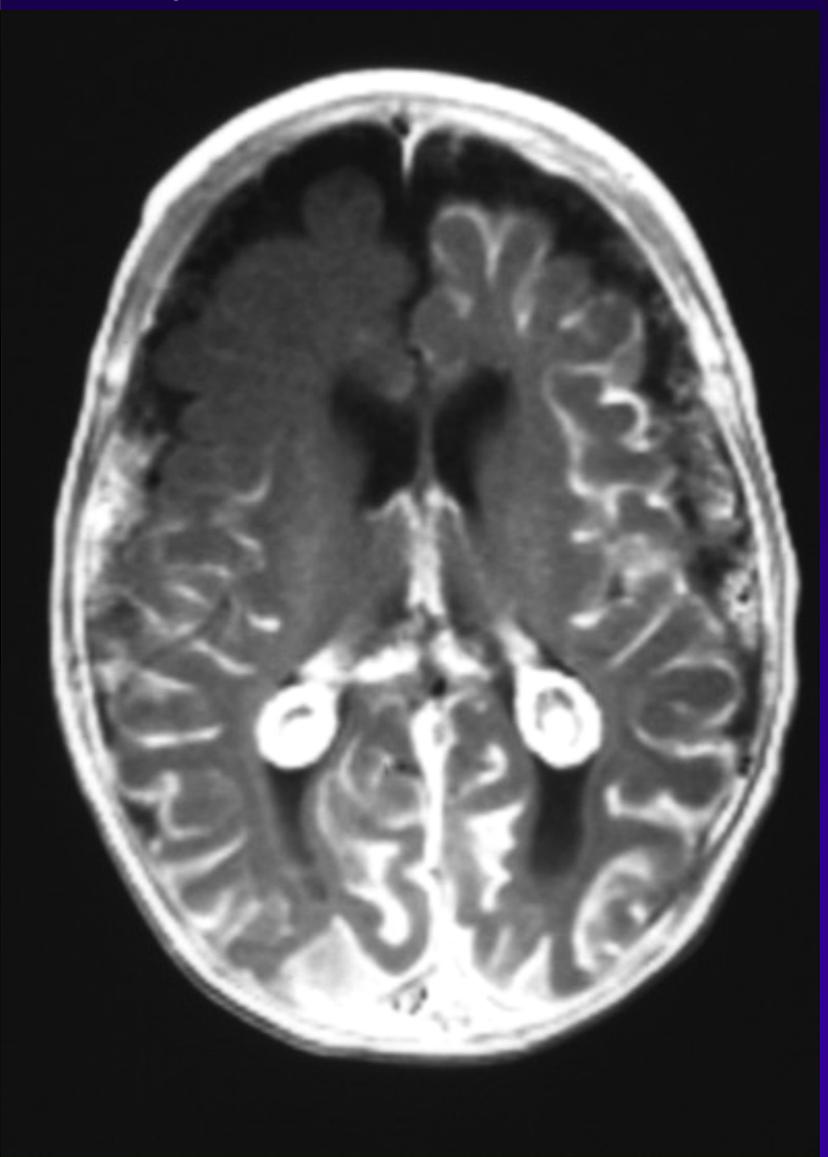
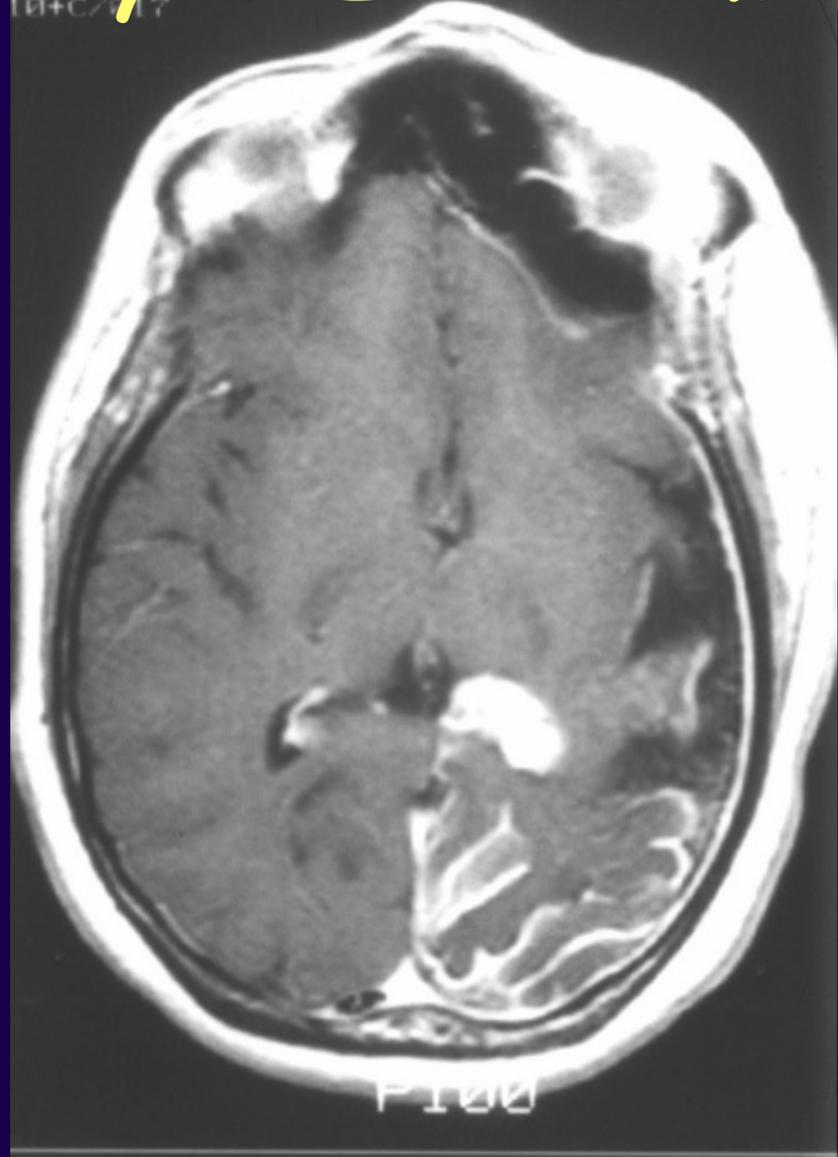


P100

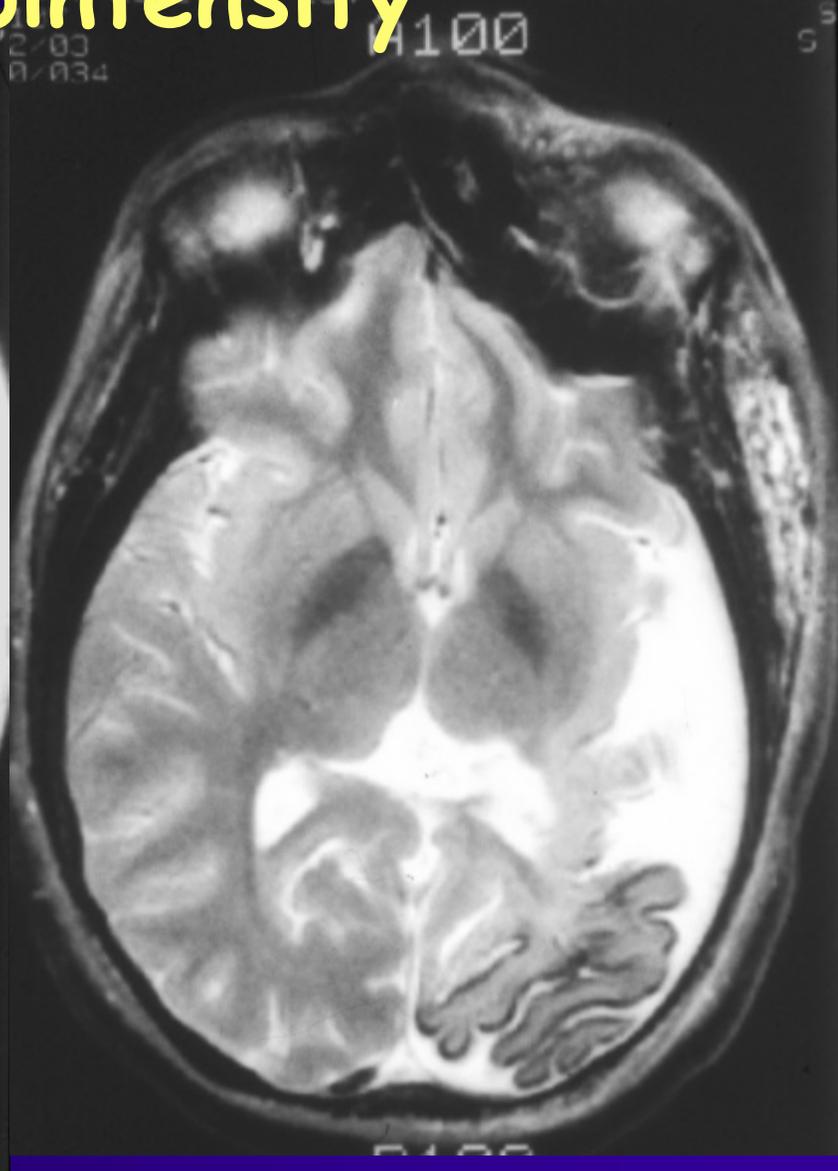
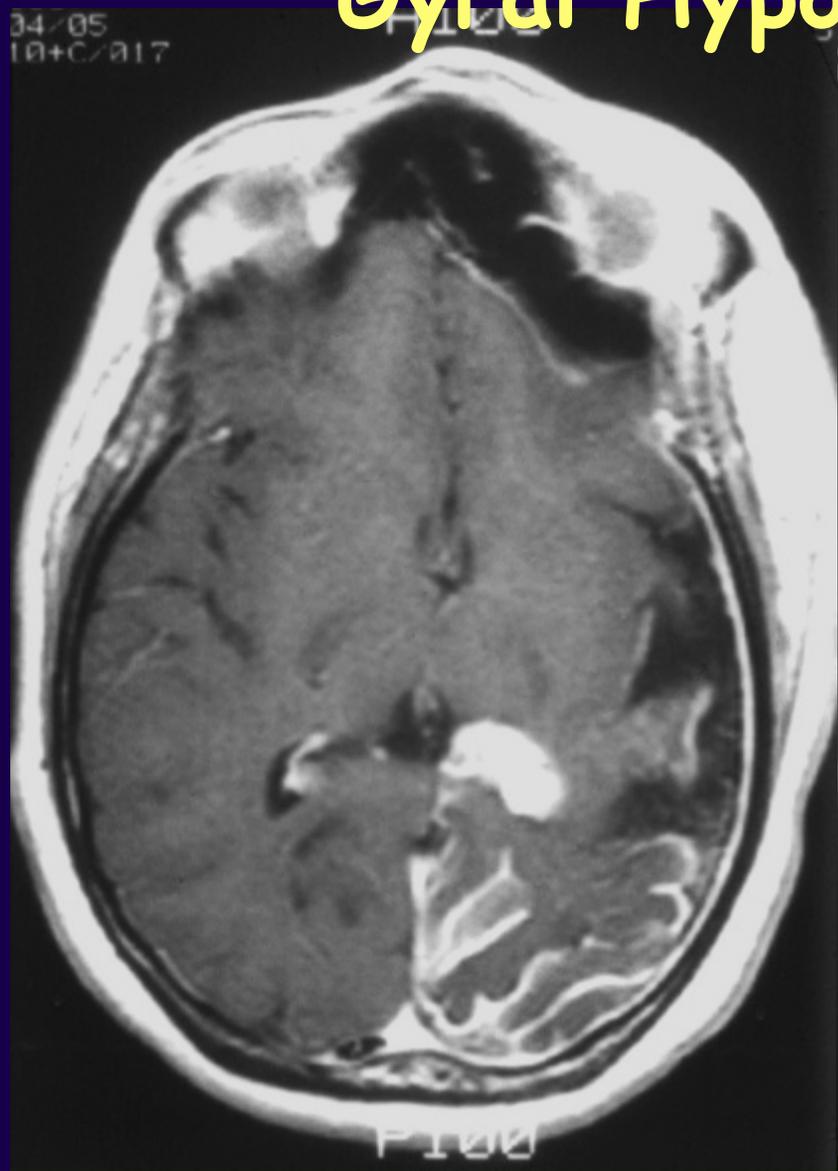
Hemiatrophy



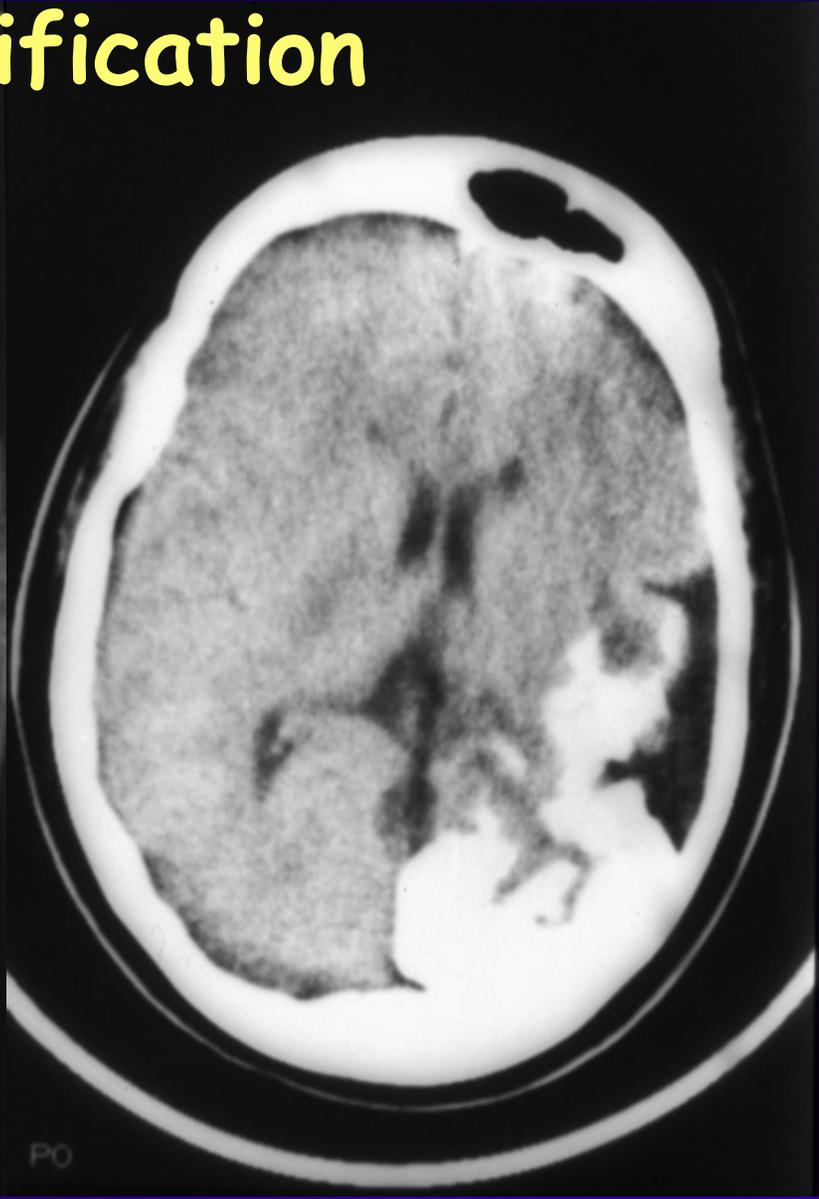
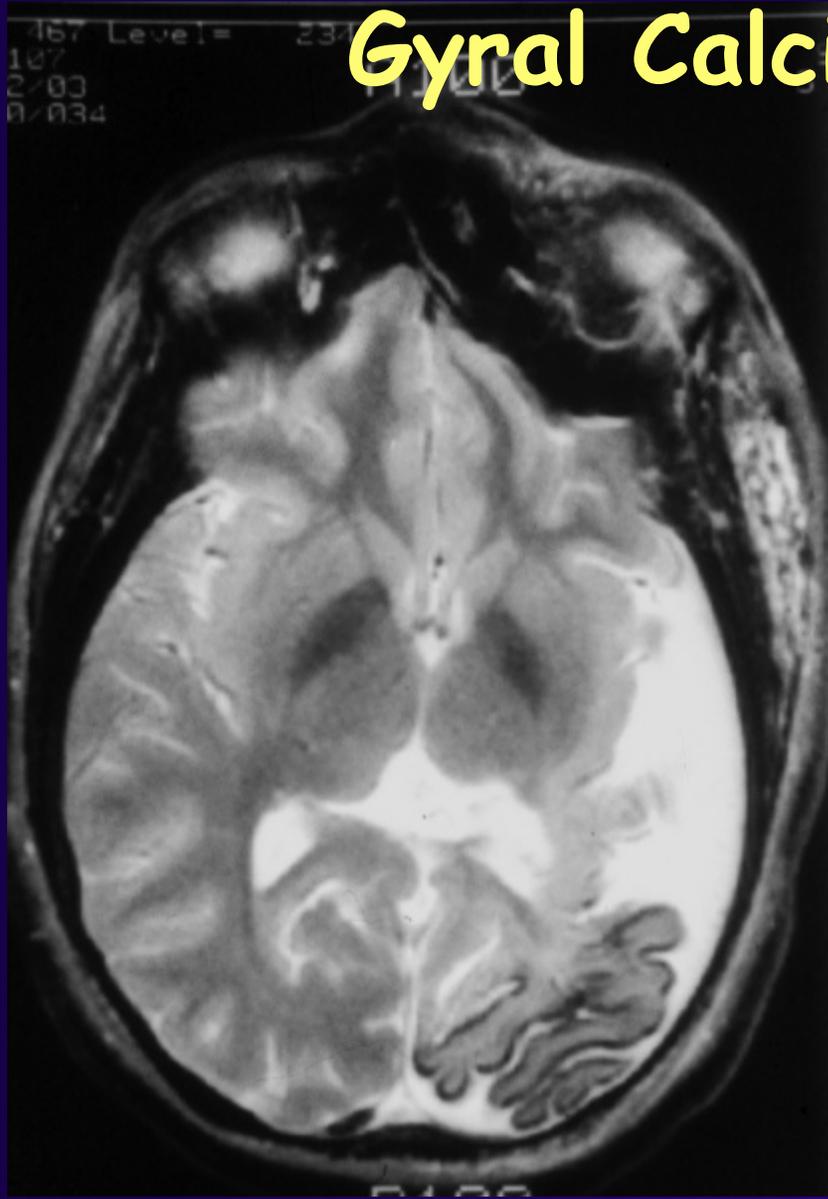
Gyral Enhancement & Choroid Plexus



Gyral Hypointensity



Gyral Calcification



STURGE-WEBER: Treatment

- Symptomatic (anticonvulsants)
- Cosmetic Tattooing
- Laser Treatment of Skin Lesions
- Hemispherectomy
- Aspirin (mild antiplatelet)?

TUBEROUS SCLEROSIS

Original "VOGT TRIAD"

- FACIAL NEVUS (ADENOMA SEBACEUM)
- SEIZURES
- MENTAL DEFICIENCY

TUBEROUS SCLEROSIS

- AUTOSOMAL DOMINANT
- No Racial/Sexual
- High Spontaneous Mutation
- High Penetrance
 - "SPORADIC" over-reported
- Multiple Genes
 - TSC1 - 9q
 - TSC2 - 16p

TUBEROUS SCLEROSIS

- Definitive (need 1)
 - (1) facial angiofibroma
 - (2) unguis fibroma
 - (3) retinal hamartoma
 - (4) cortical tubers
 - (5) subependymal nodules
 - (6) multiple renal AML

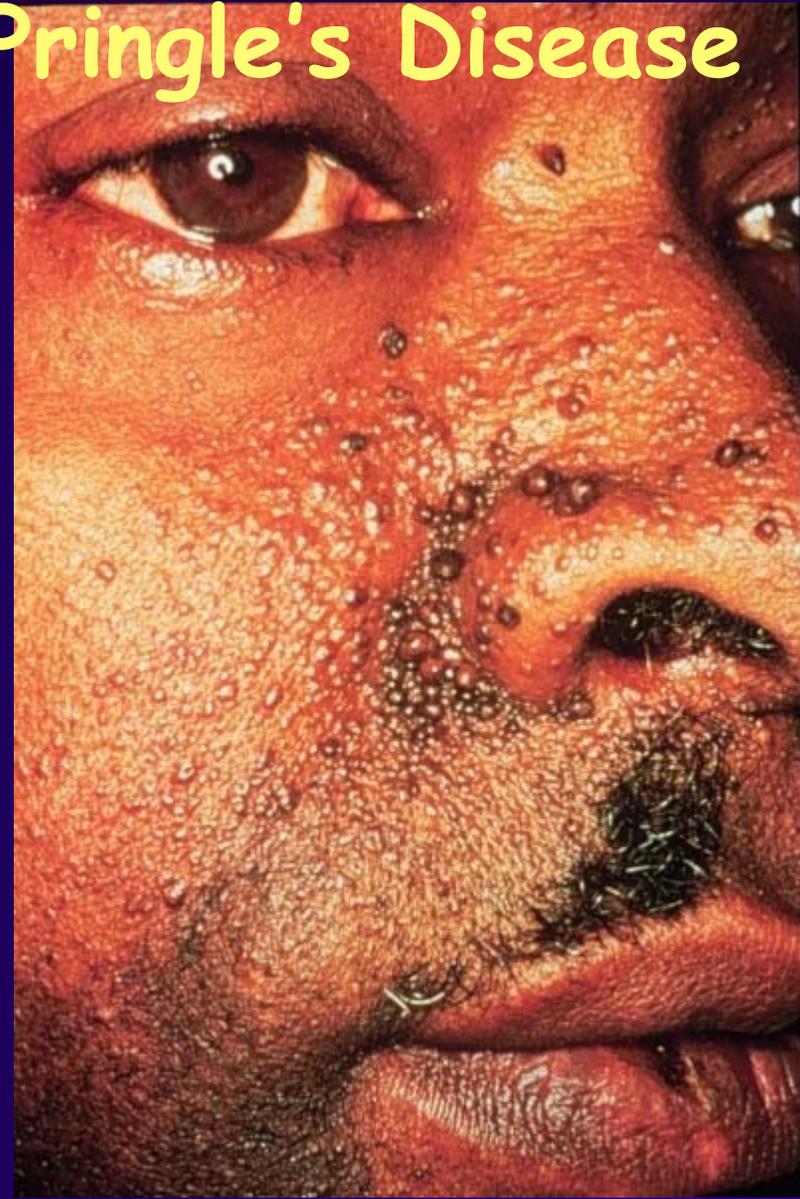
TUBEROUS SCLEROSIS

- Presumptive (need 2)
 - (1) hypomelanotic nodules
 - (2) shagreen patch
 - (3) single renal AML
 - (4) multicystic kidney
 - (5) cardiac rhabdomyoma
 - (6) pulmonary lymphangiomyomatosis
 - (7) radiographic "honeycomb" lung
 - (8) first degree relative with TS

Tuberous Sclerosis: Cutaneous

- "Adenoma Sebaceum"
- Peau D'orange
- Ash-Leaf Macule
- Ungual Angiofibromas

Pringle's Disease



Adenoma Sebaceum

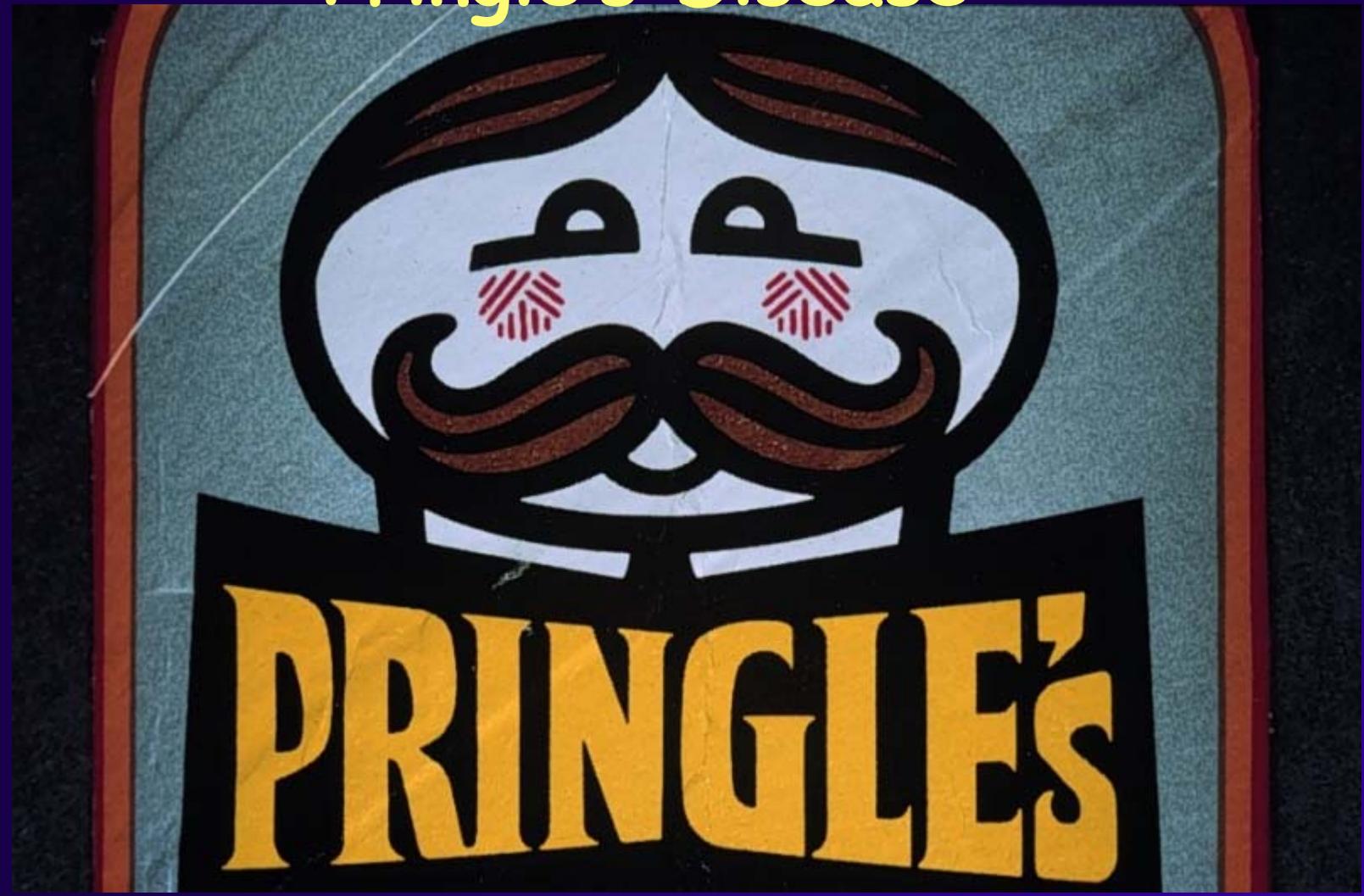
- AKA PRINGLE'S DISEASE
- NOT present at birth
- develop before puberty
- nasolabial fold ->bi-malar
- papules of angiofibroma

Pringle's Disease



Radiology - <http://rad.medpix.net>

Pringle's Disease





Subungual Fibroma



Periungual Fibroma



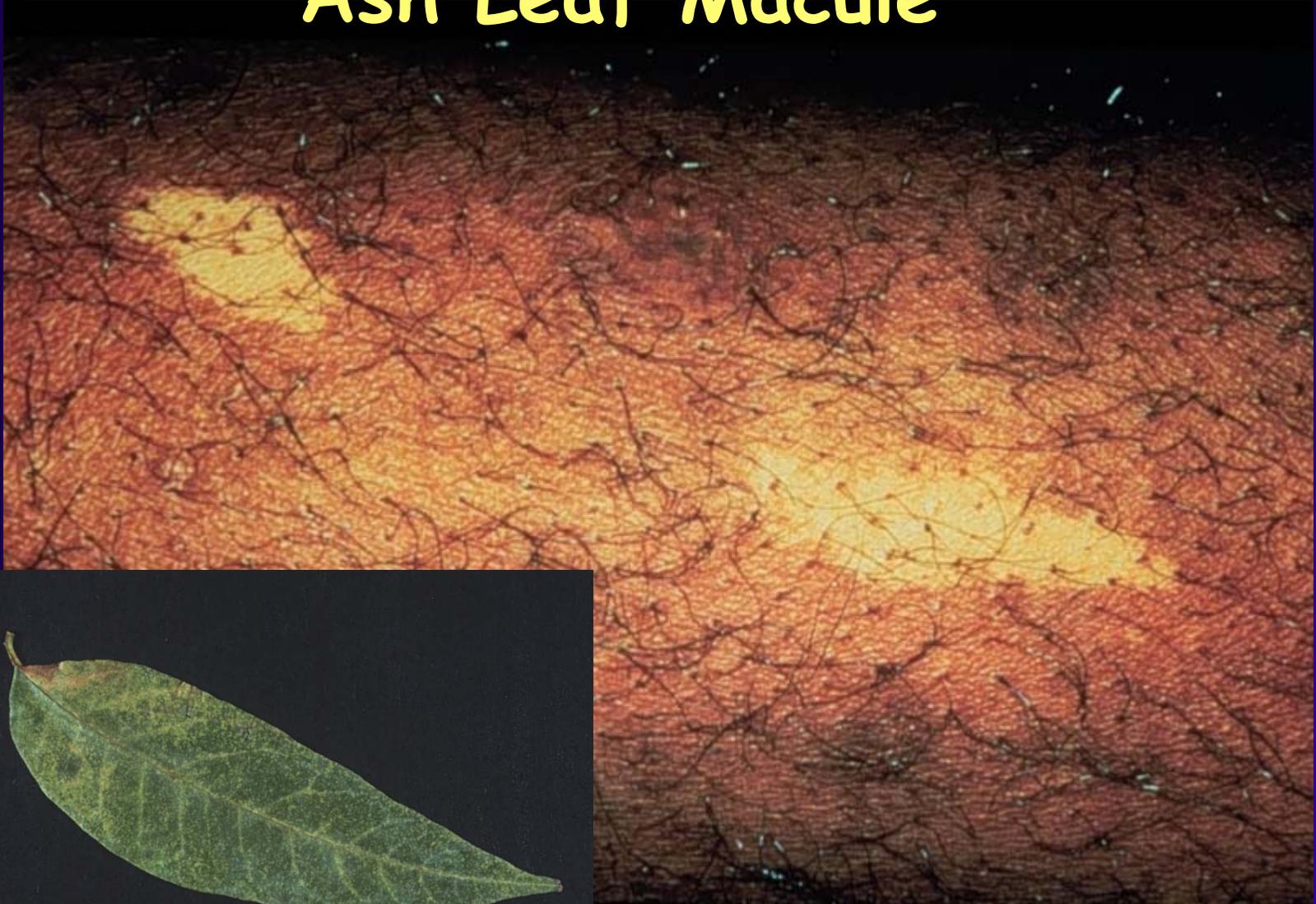
Confetti Hypopigmentation



Depigmentation:

- Ash-Leaf Spots
 - (Lance- Ovate Shape)
- Confetti- Like Hypopigmentation
 - (Inverse Freckle)

Ash Leaf Macule



Other Cutaneous Manifestations

- Subepidermal Fibrosis:
 - Dorsal Surfaces
 - "Shagreen Patch"
 - "Peau D'orange"
 - "Pigskin"
 - "Elephant Hide"

Peau D'orange



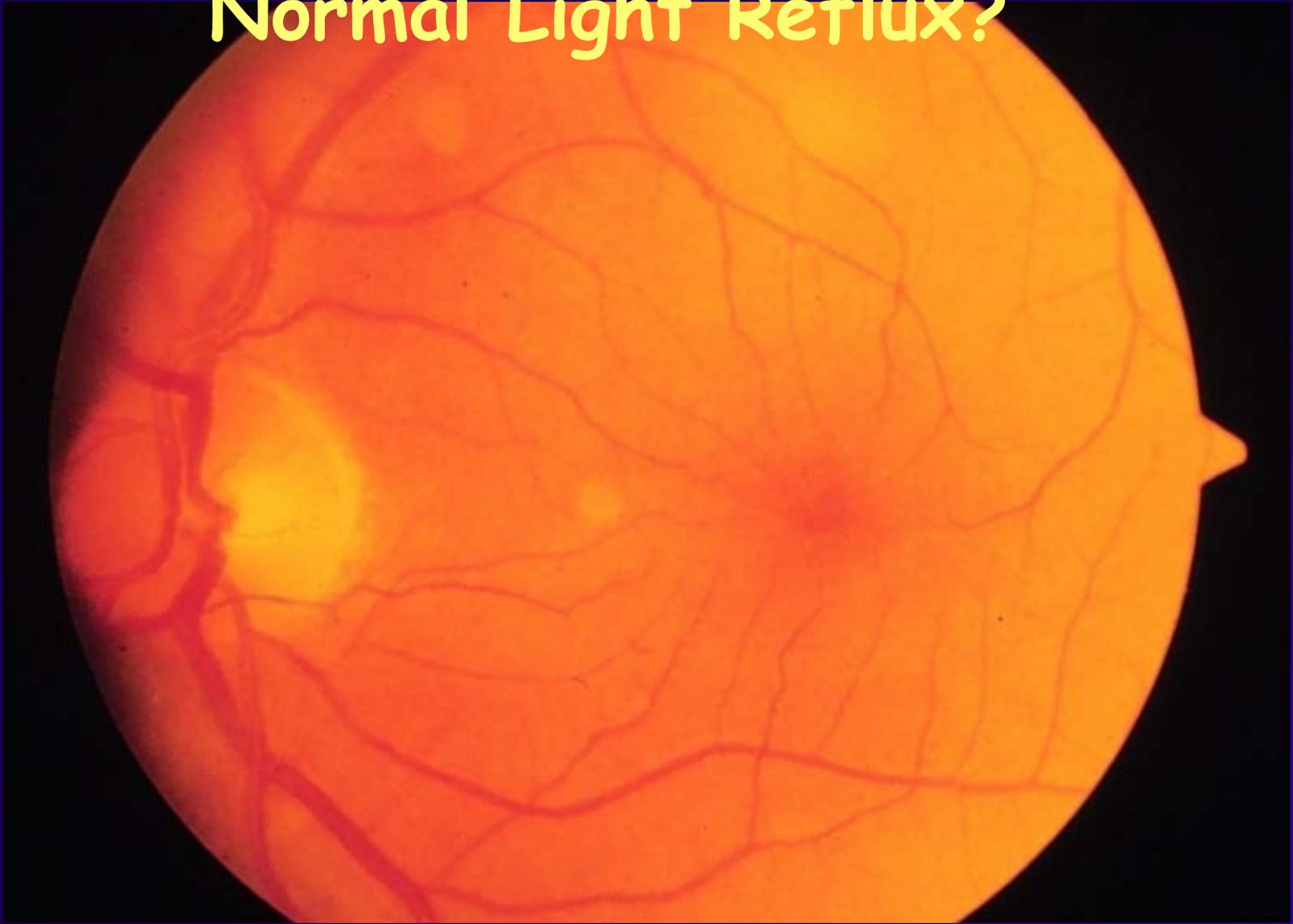
TUBEROUS SCLEROSIS: Ocular

- PHAKOMA
 - benign astrocytic hamartoma
 - LEUKOKORIA
 - White light reflex
 - Calcification Common
 - Especially over Optic Nerve

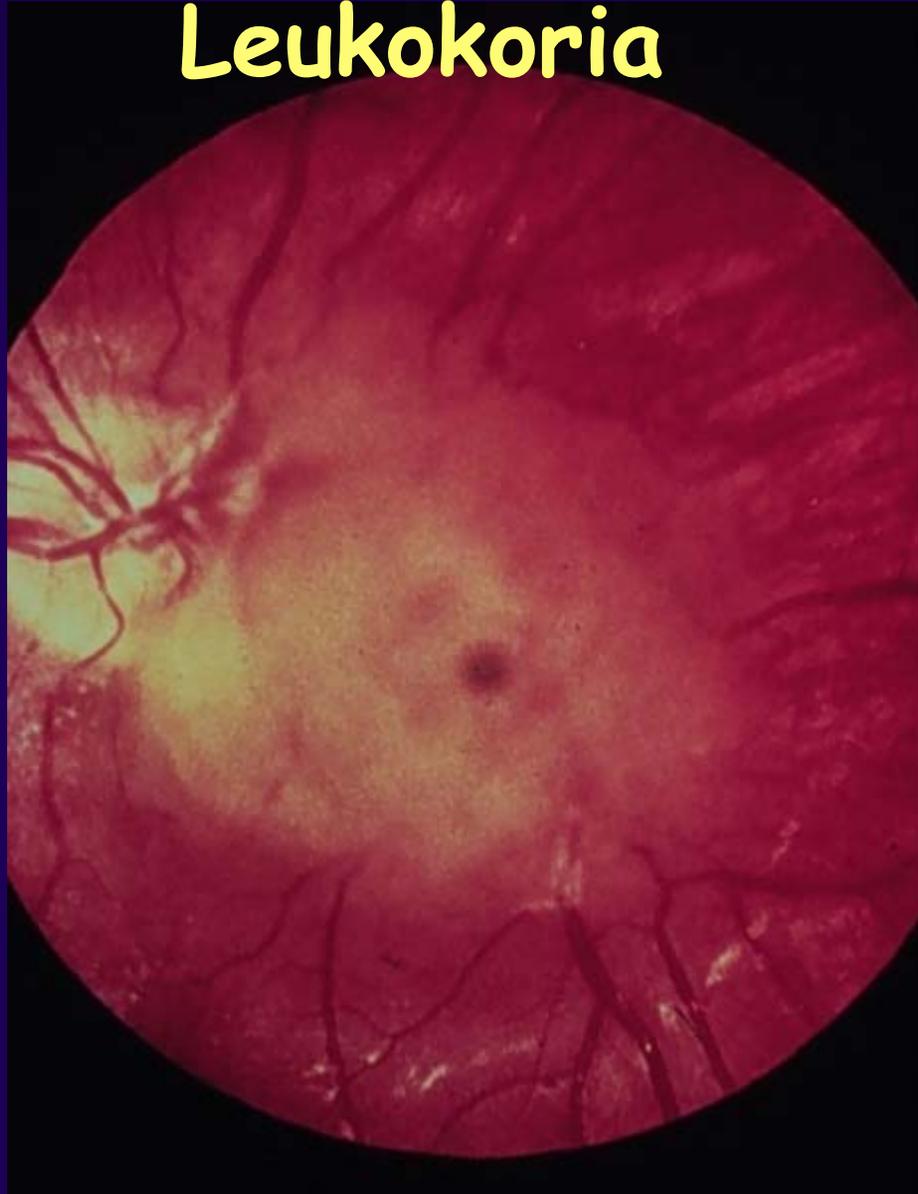
Normal Light Reflex



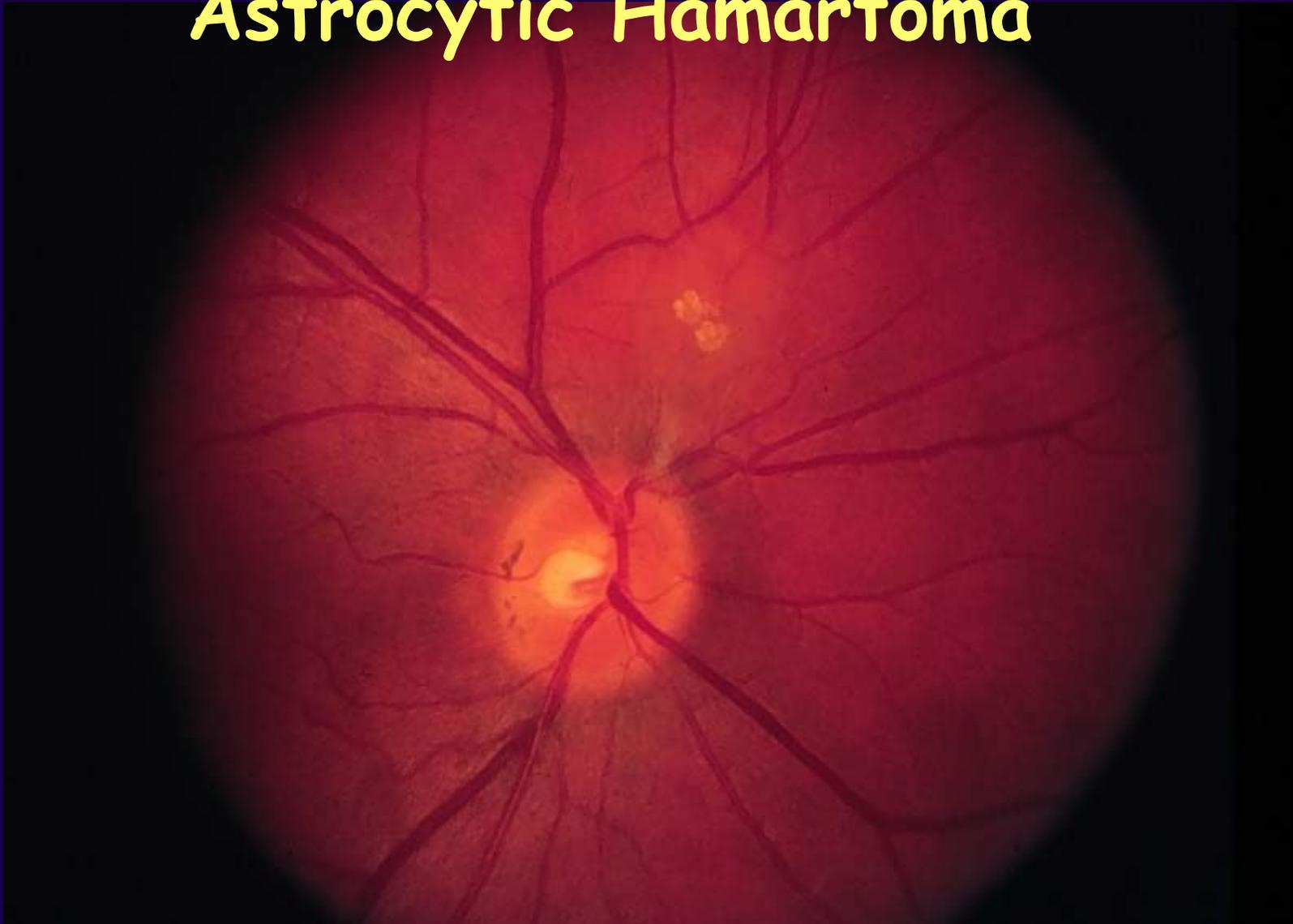
Normal Light Reflex?



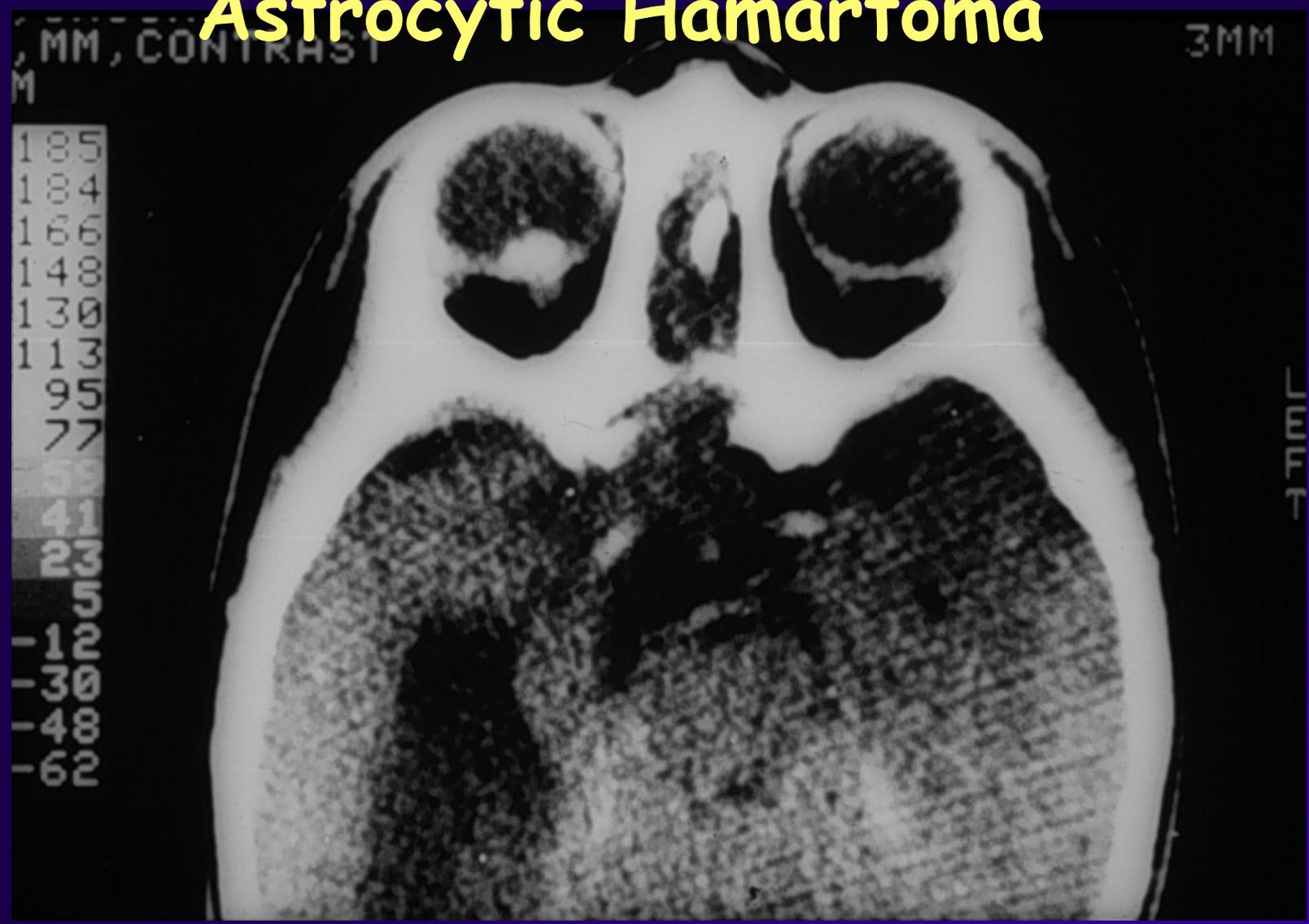
Leukokoria



Astrocytic Hamartoma



Astrocytic Hamartoma



Astrocytic Hamartoma



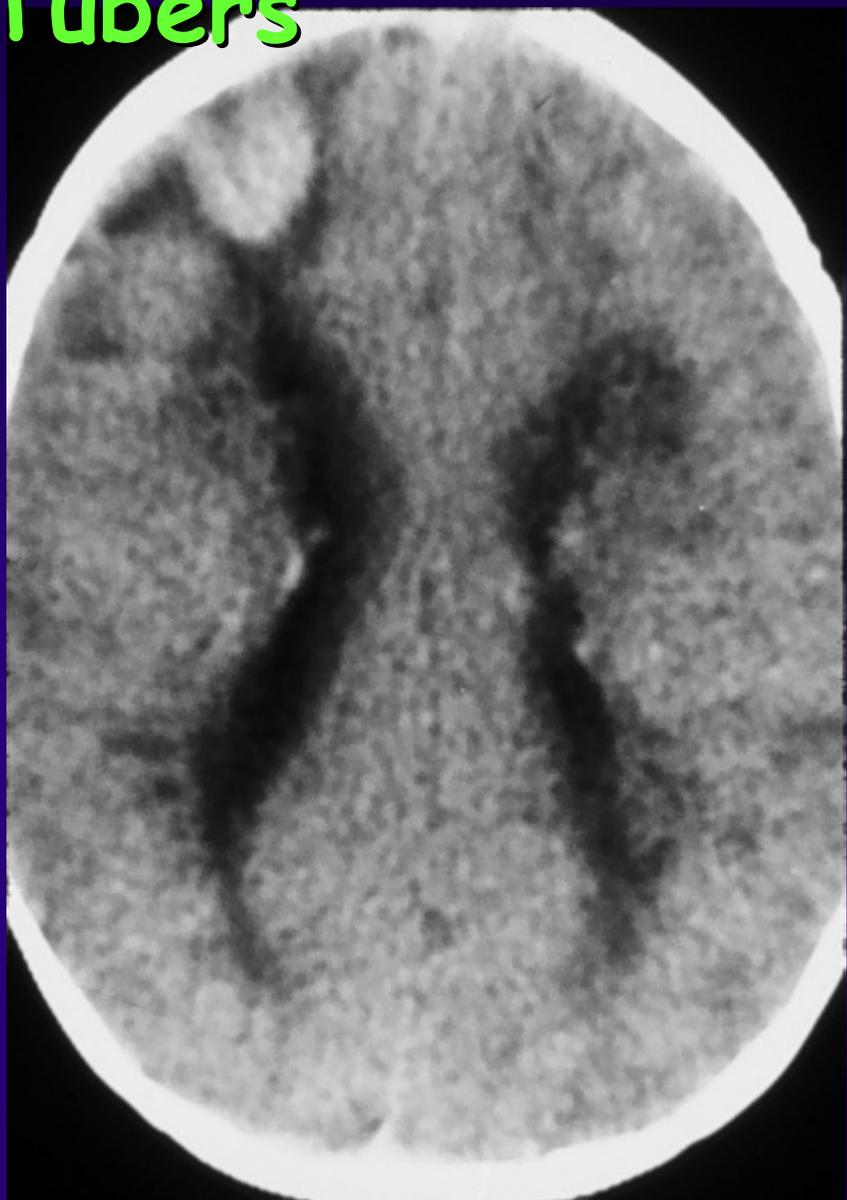
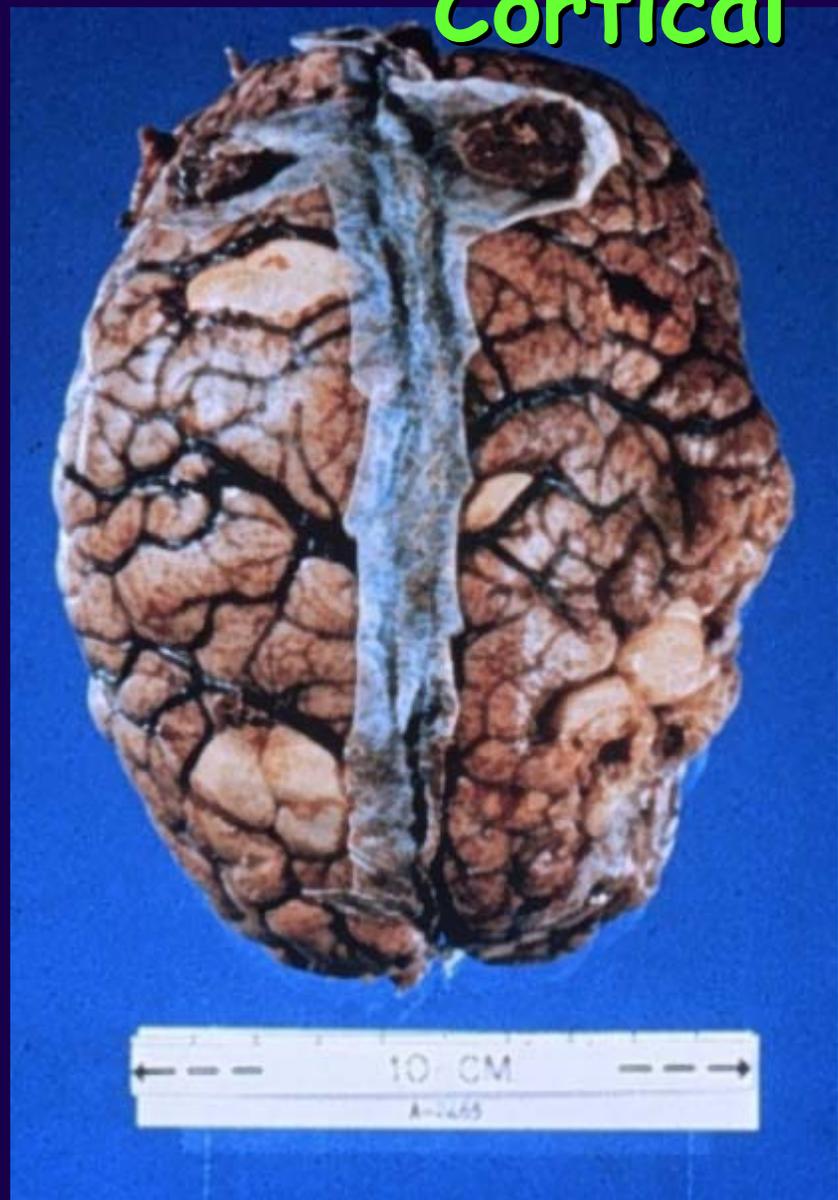
TUBEROUS SCLEROSIS - BRAIN:

- HETEROTOPIAS AND HAMARTOMAS
 - in white and gray matter
- CORTICAL TUBERS
 - "HAMARTOMAS"
 - but with abnormal "N" cells
 - neither Astrocyte nor Neuron
 - Decreased Myelination
 - No laminar architecture

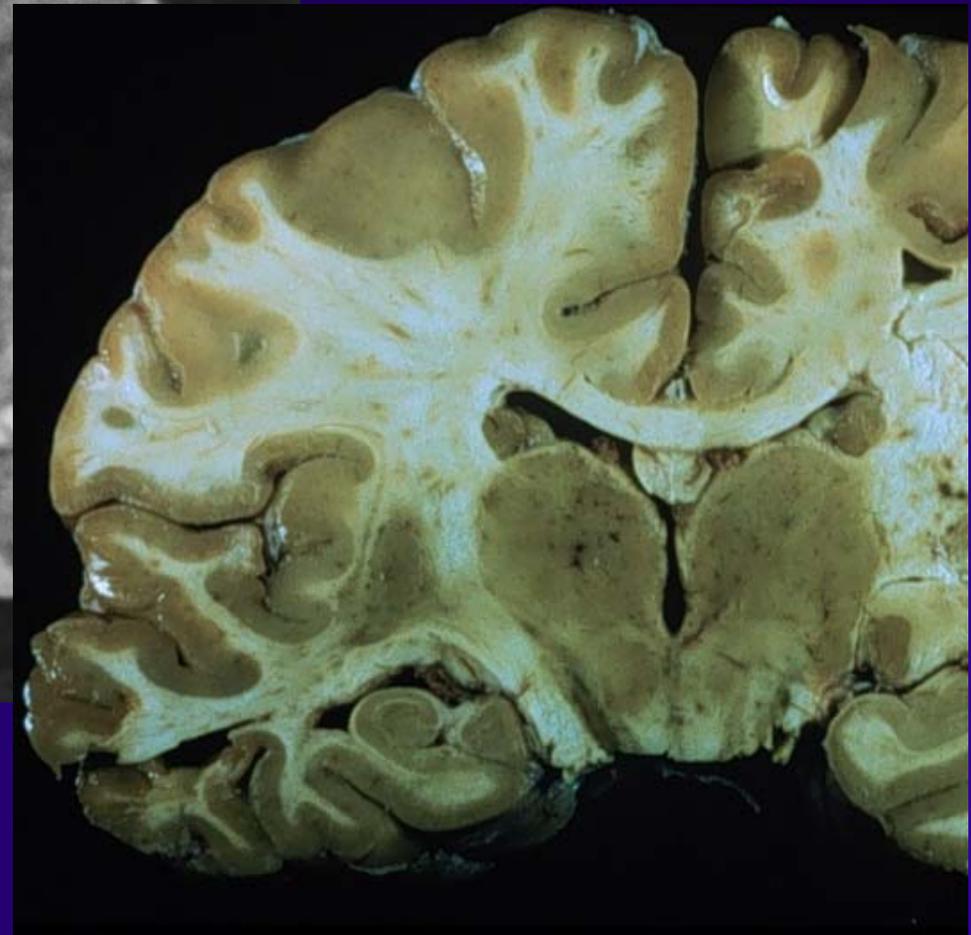
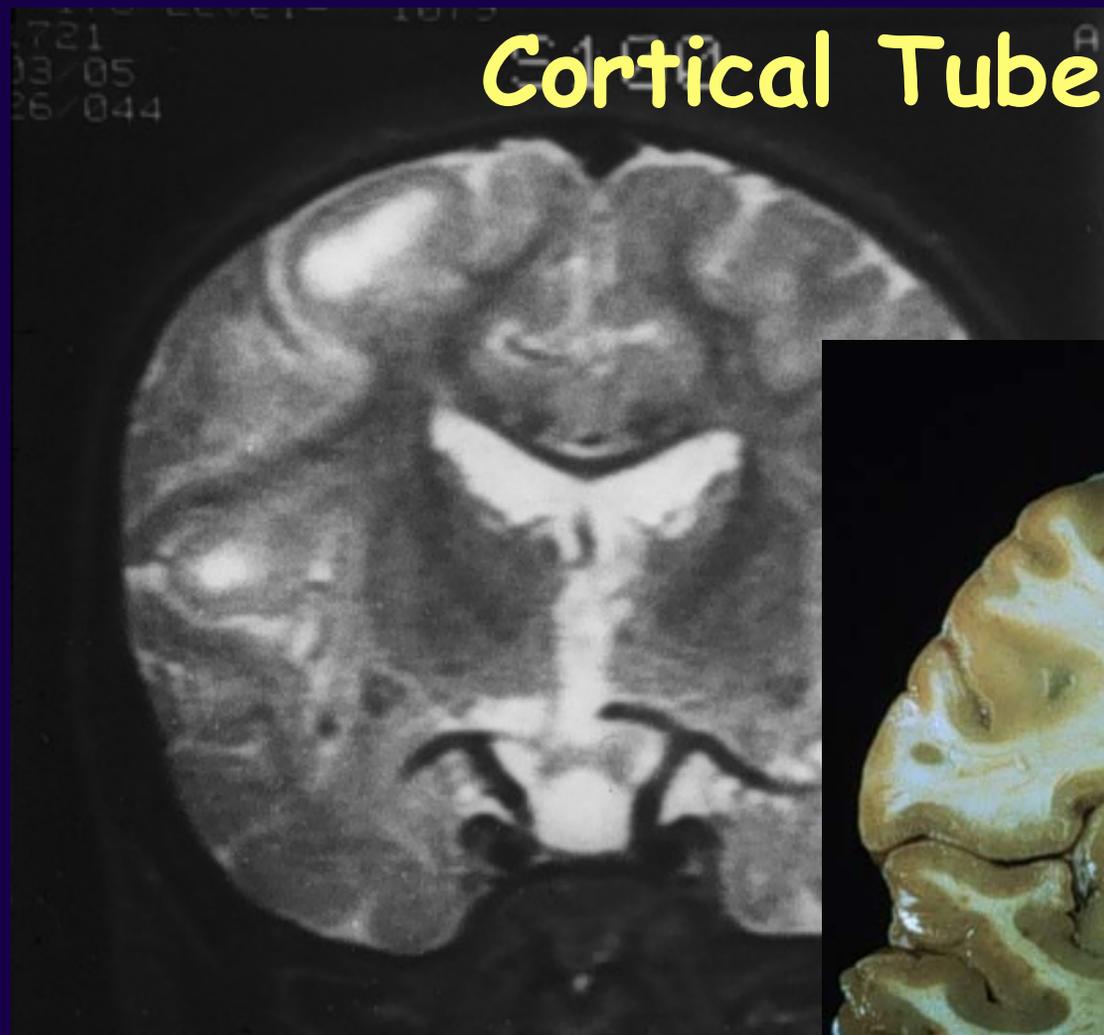
TUBEROUS SCLEROSIS - BRAIN:

- SUBEPENDYMAL NODULES (almost 100%)
 - "hamartomas" vs. neoplasia
 - Caudothalamic groove
 - Polypoid "Candle Gutterings"
- DILATED VENTRICLES
 - variable
 - obstructive, atrophic vs. "idiopathic"
- TUMORS 15%
- Sub-ependymal Giant Cell Astrocytoma
 - True neoplasm, Benign WHO Grade I

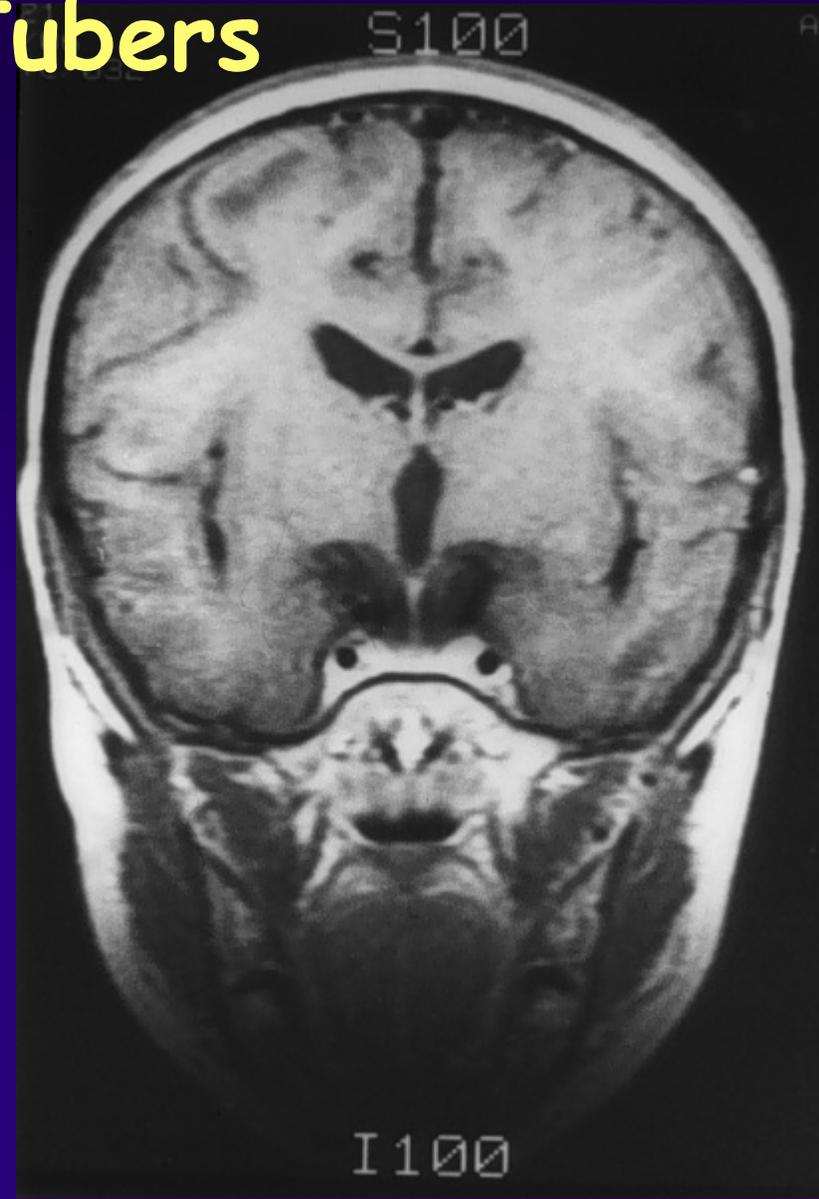
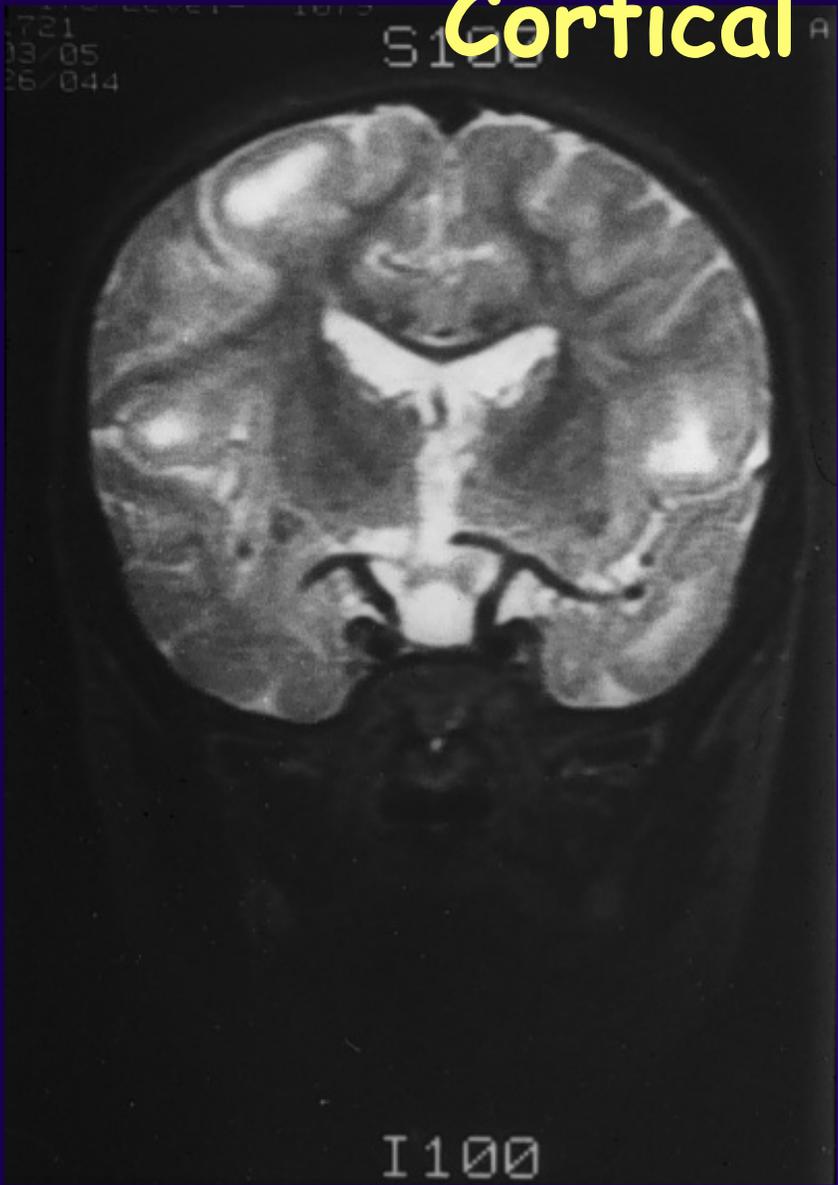
Cortical Tubers



Cortical Tubers

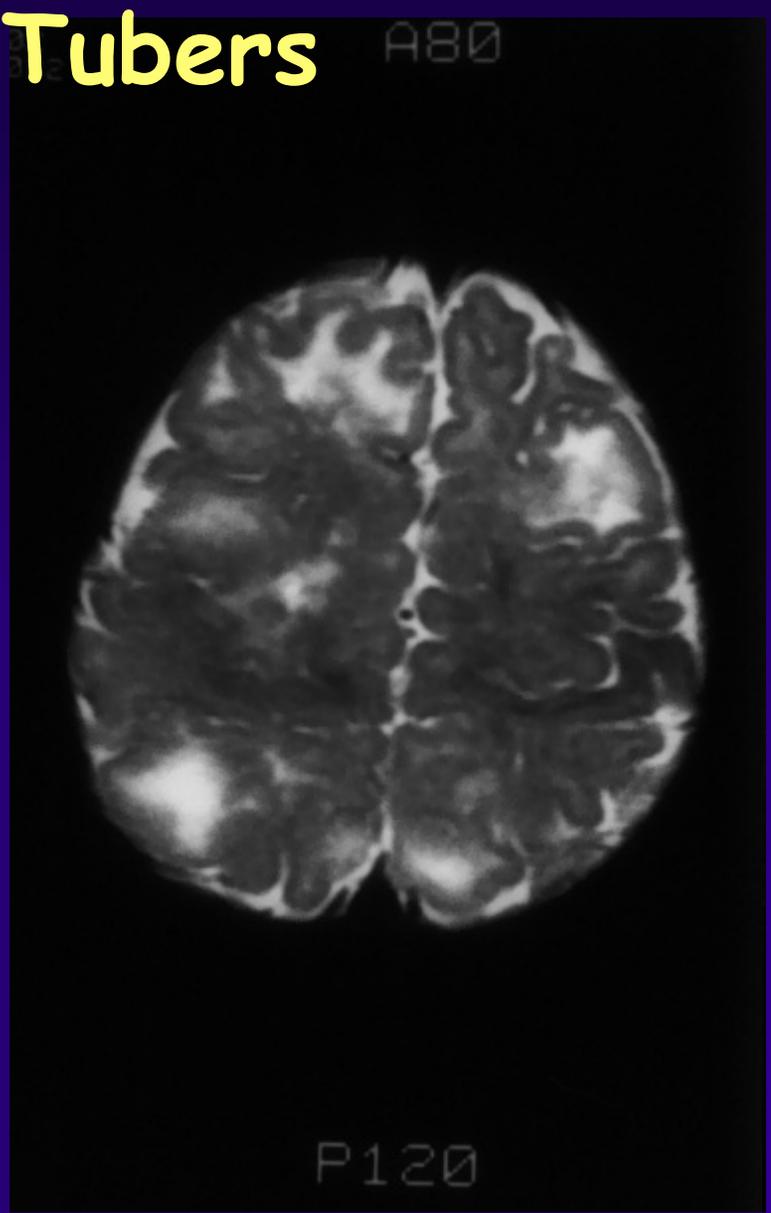
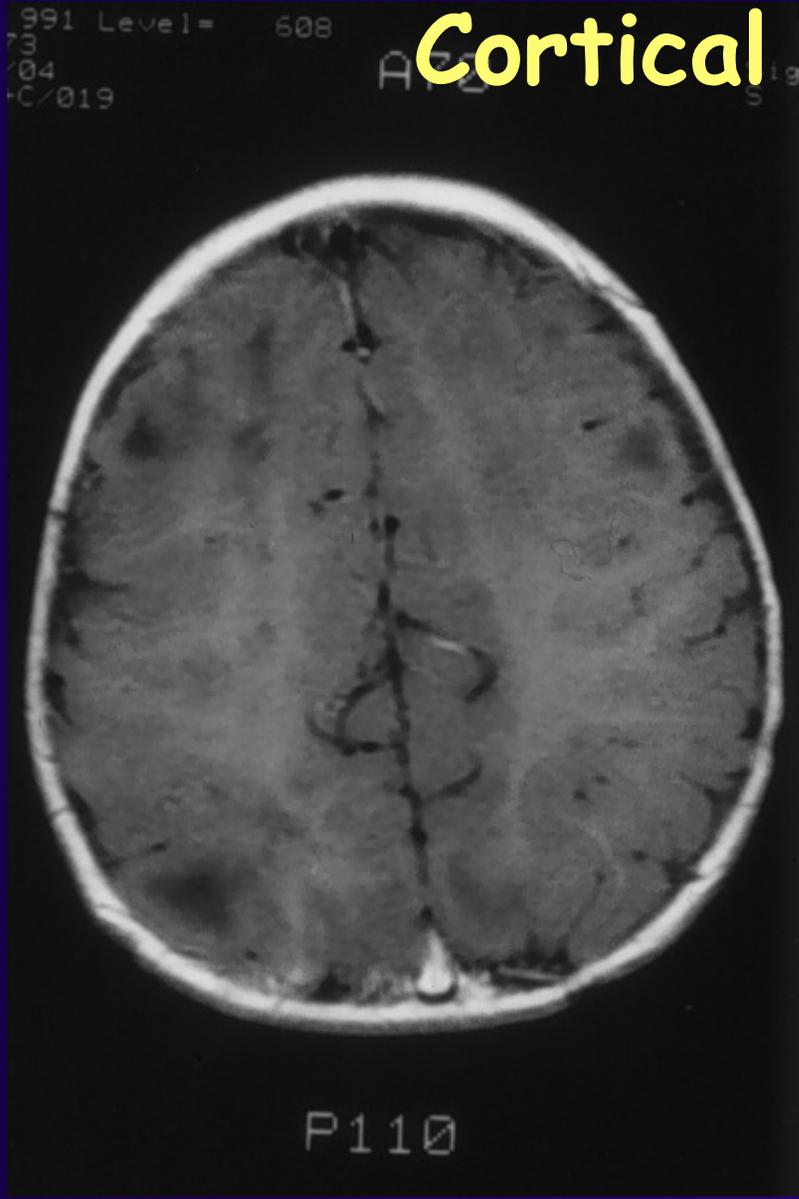


Cortical Tubers



Radiology - <http://rad.medpix.net>

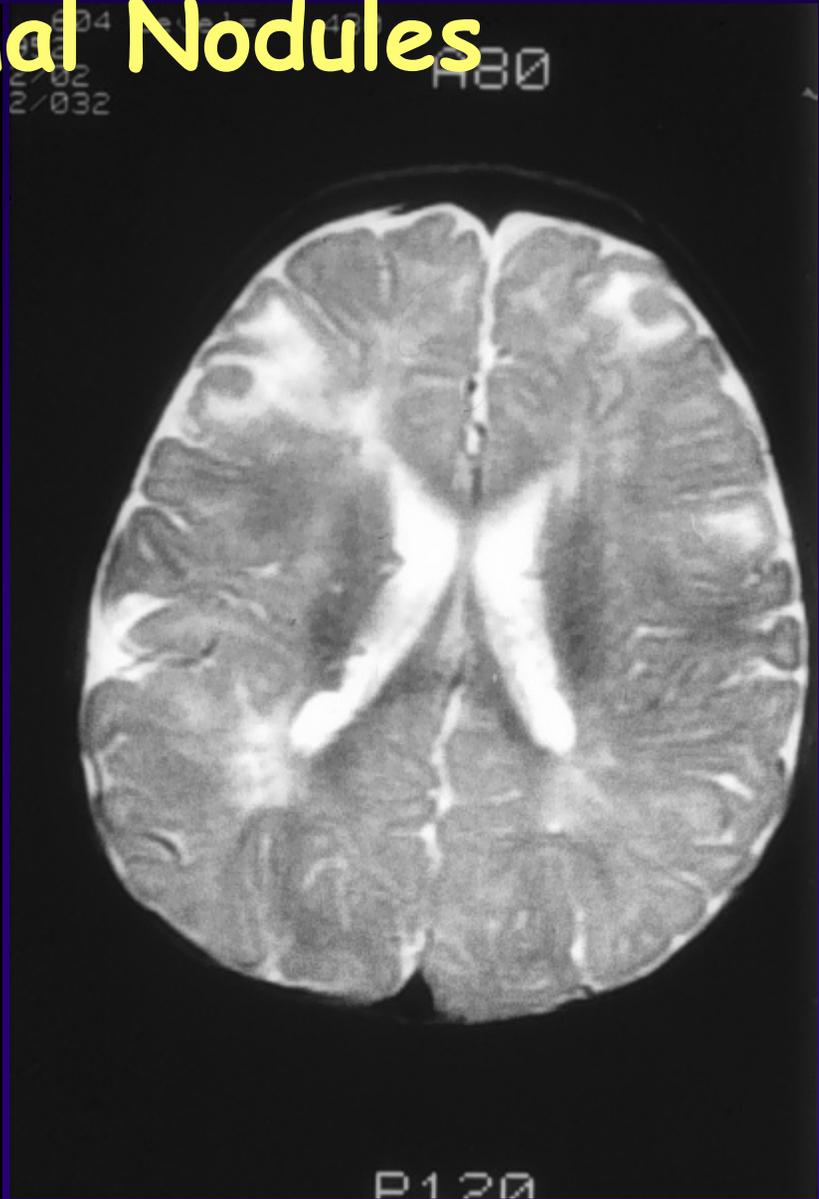
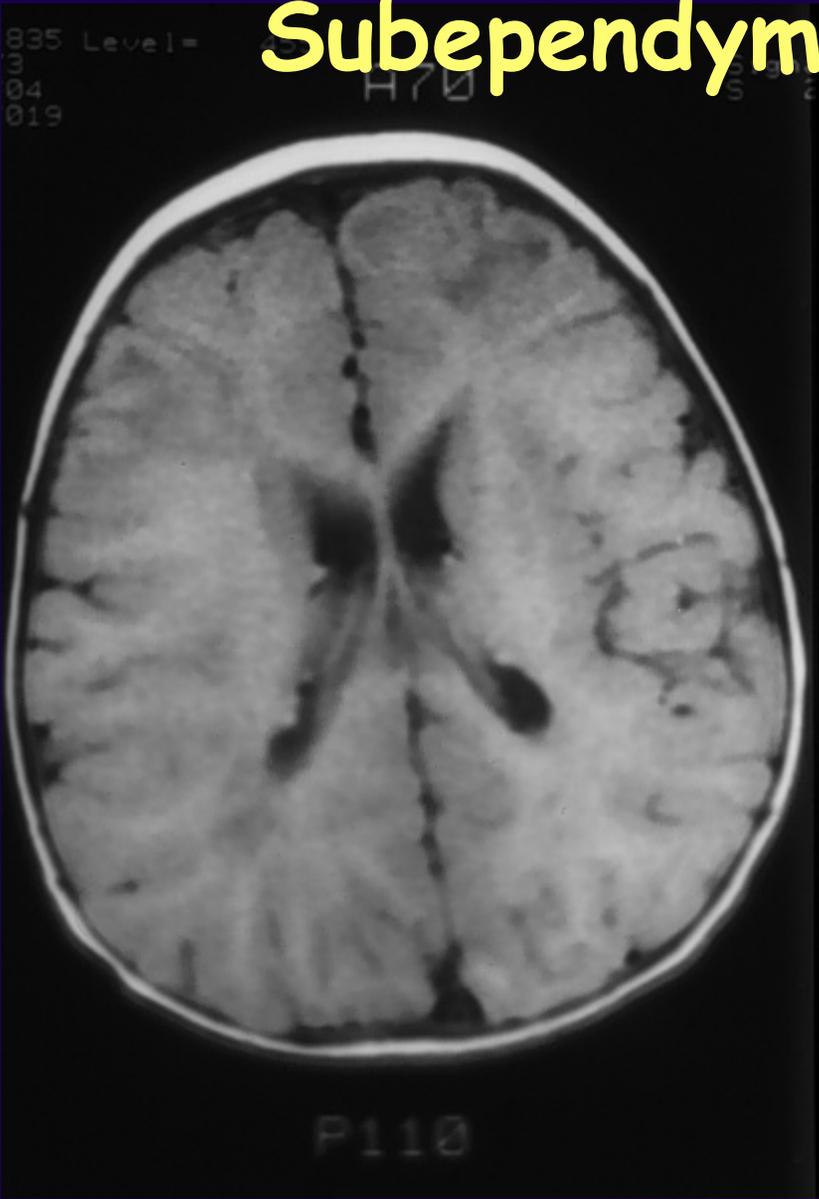
Cortical Tubers



Subependymal Nodules



Subependymal Nodules

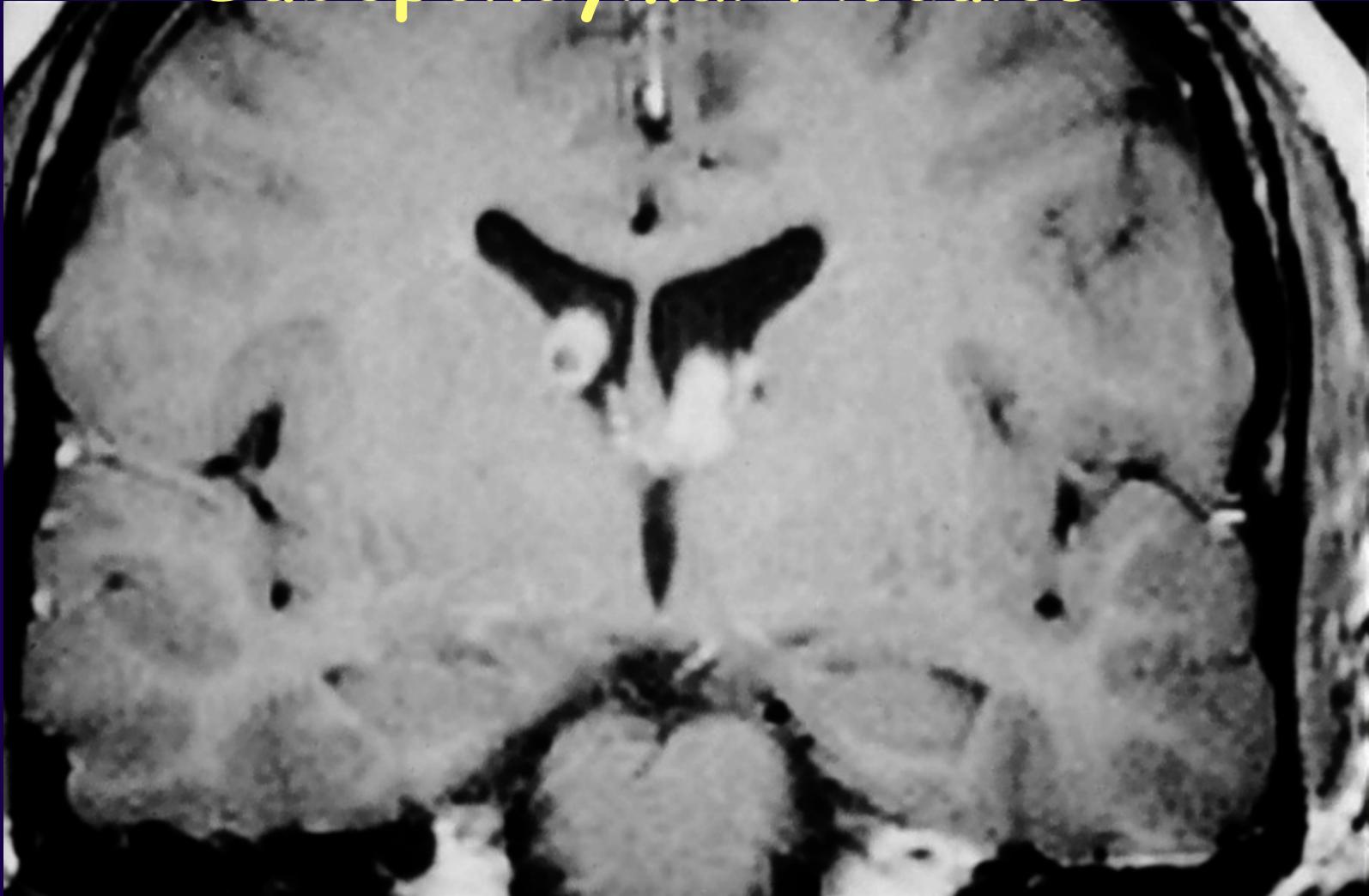


Subependymal Nodules

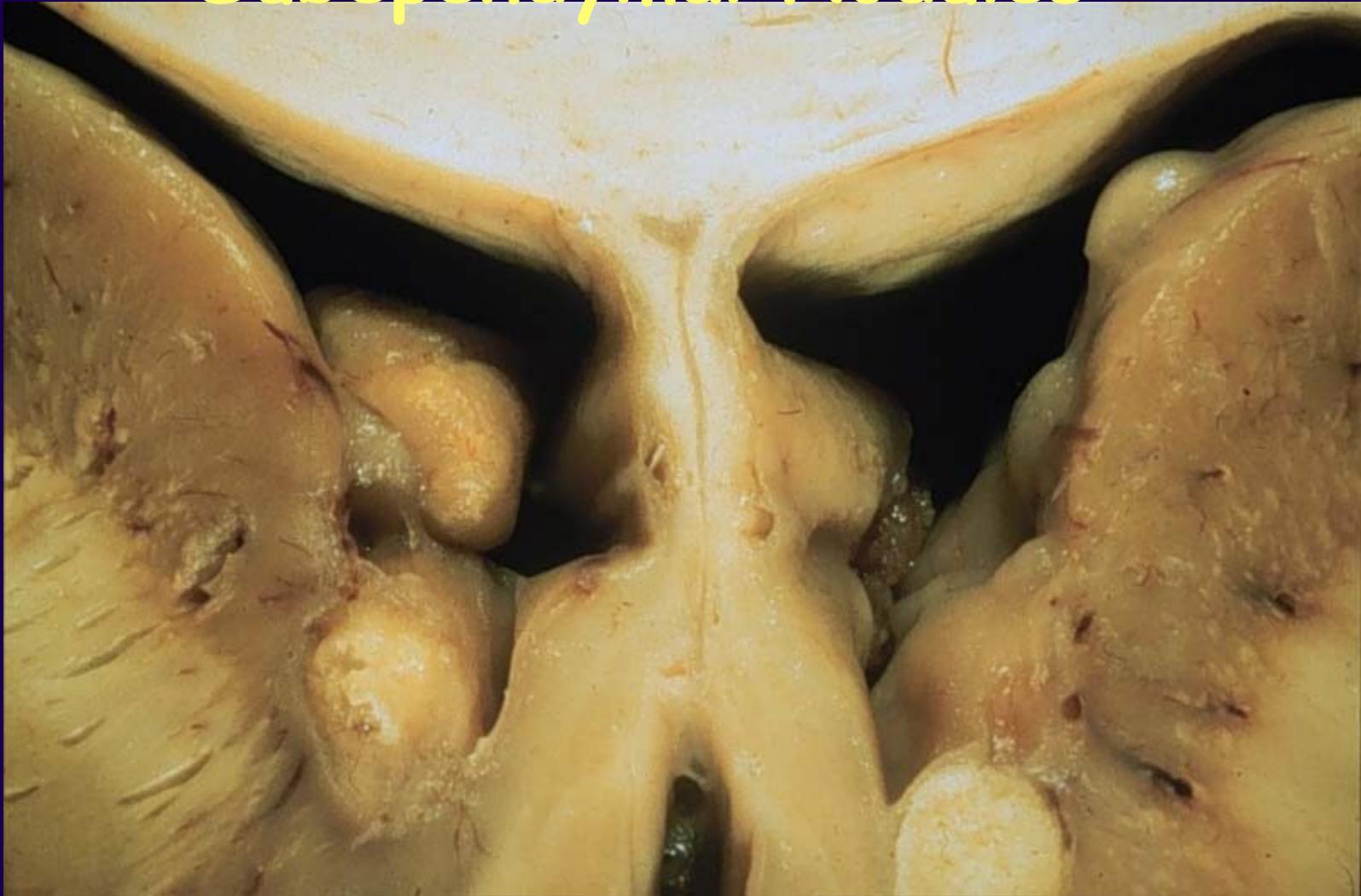


Radiology - <http://rad.medpix.net>

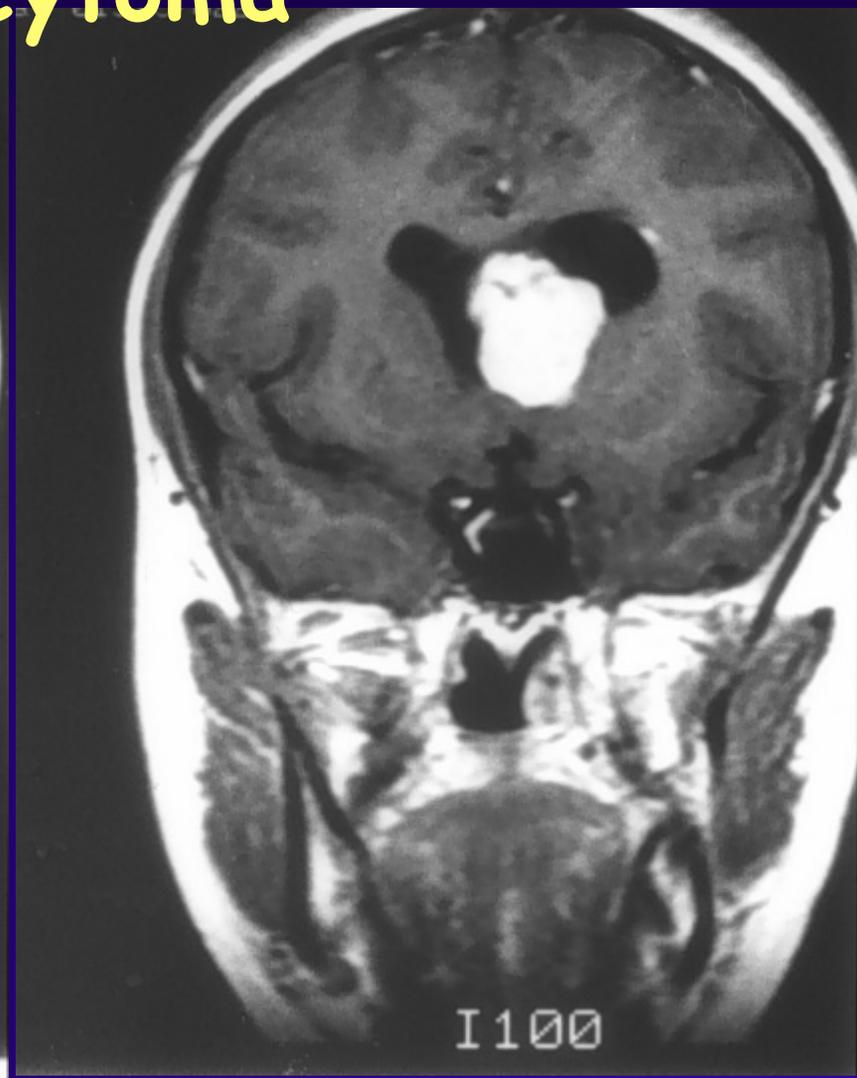
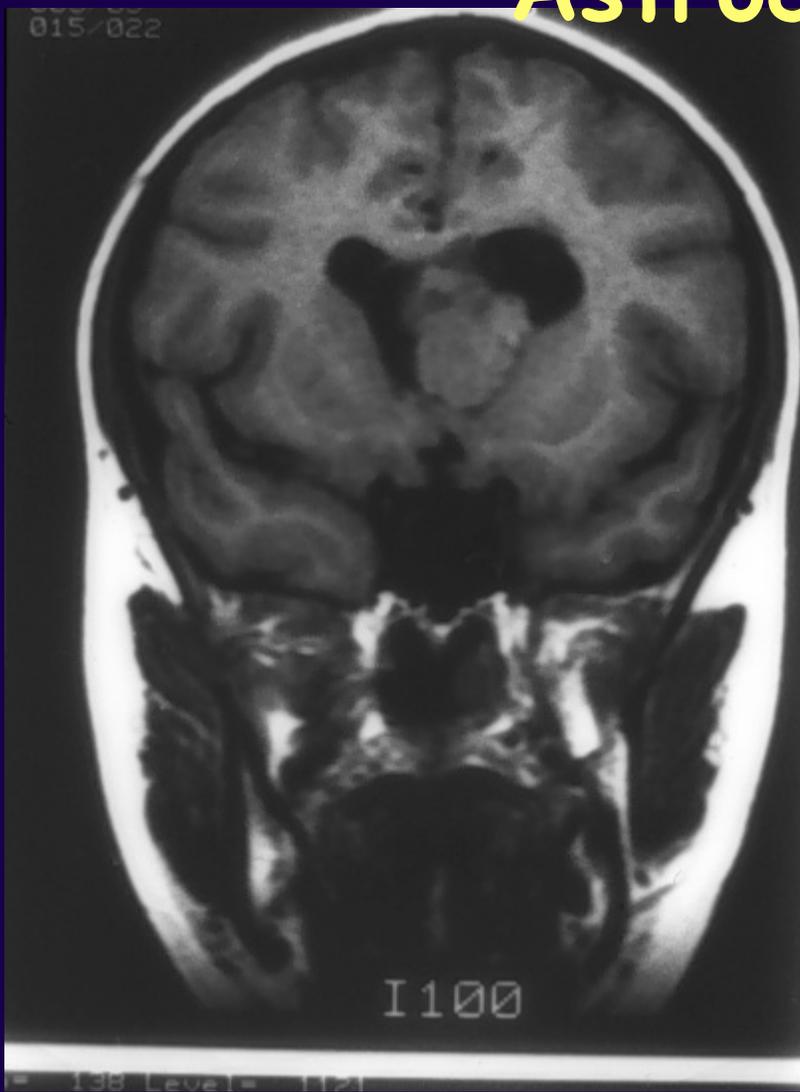
Subependymal Nodules



Subependymal Nodules



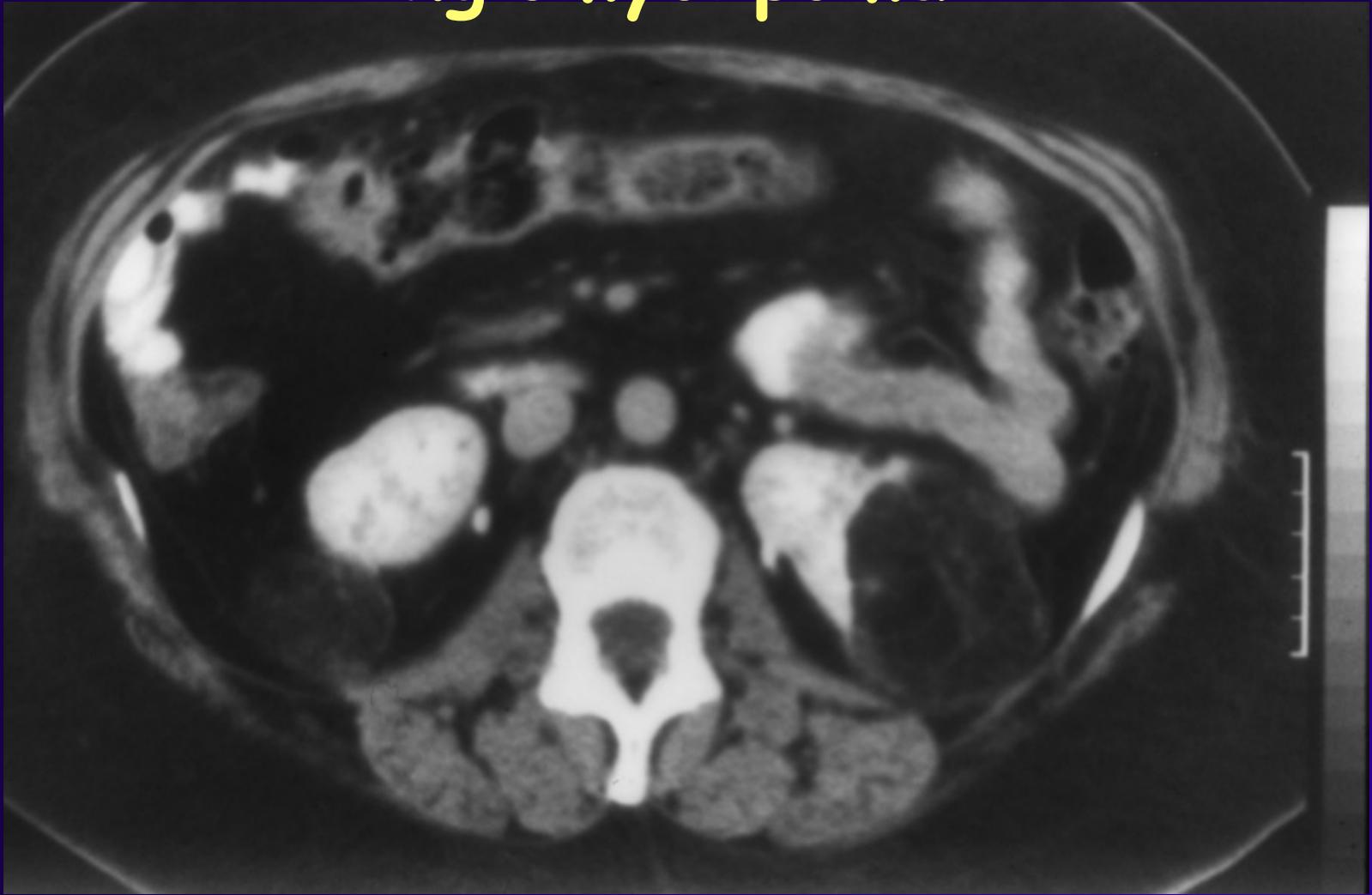
Subependymal Giant Cell Astrocytoma



TUBEROUS SCLEROSIS

- Renal
 - Angiomyolipoma
 - Multiple Simple Cysts
 - Another cause of PCKD
 - RCC Reported

Angiomyolipoma



Angiomyolipoma



Angiomyolipoma

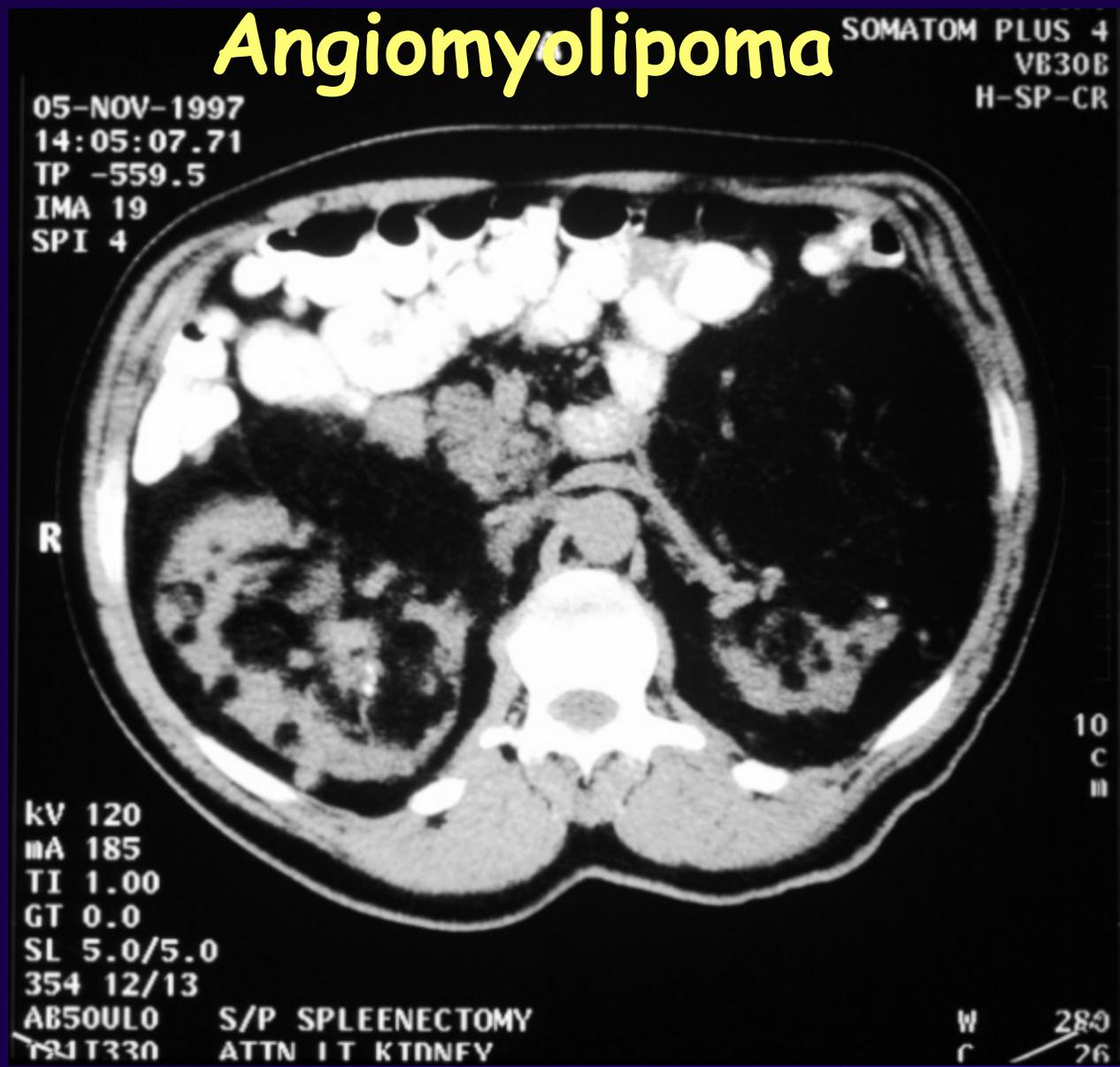


Radiology - <http://rad.medpix.net>

ANGIOMYOLIPOMA:

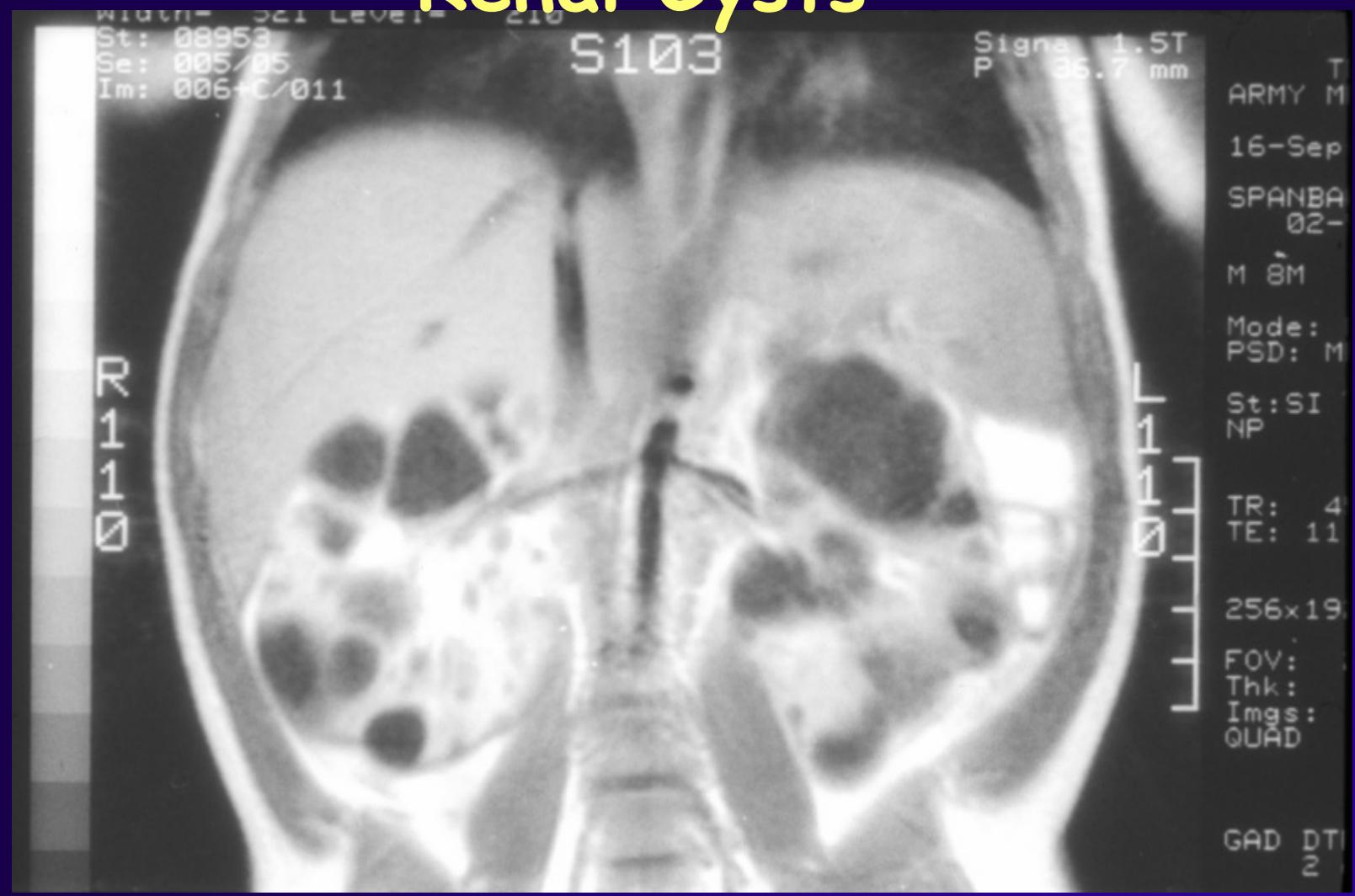
- 10% w/enough FAT for plain film
- 1/6 OF Solitary AML Pts. Have TS
- 1/3-12 OF solitary AML Pts. Have other stigmata of TS
- 50-80% OF Pts. W/TS will have AML
- 3/4 MULTIPLE
- 1/3 - 1/2 BILATERAL (probably more)
- variable amts. of FAT, Smooth mm., and vessels

Angiomyolipoma

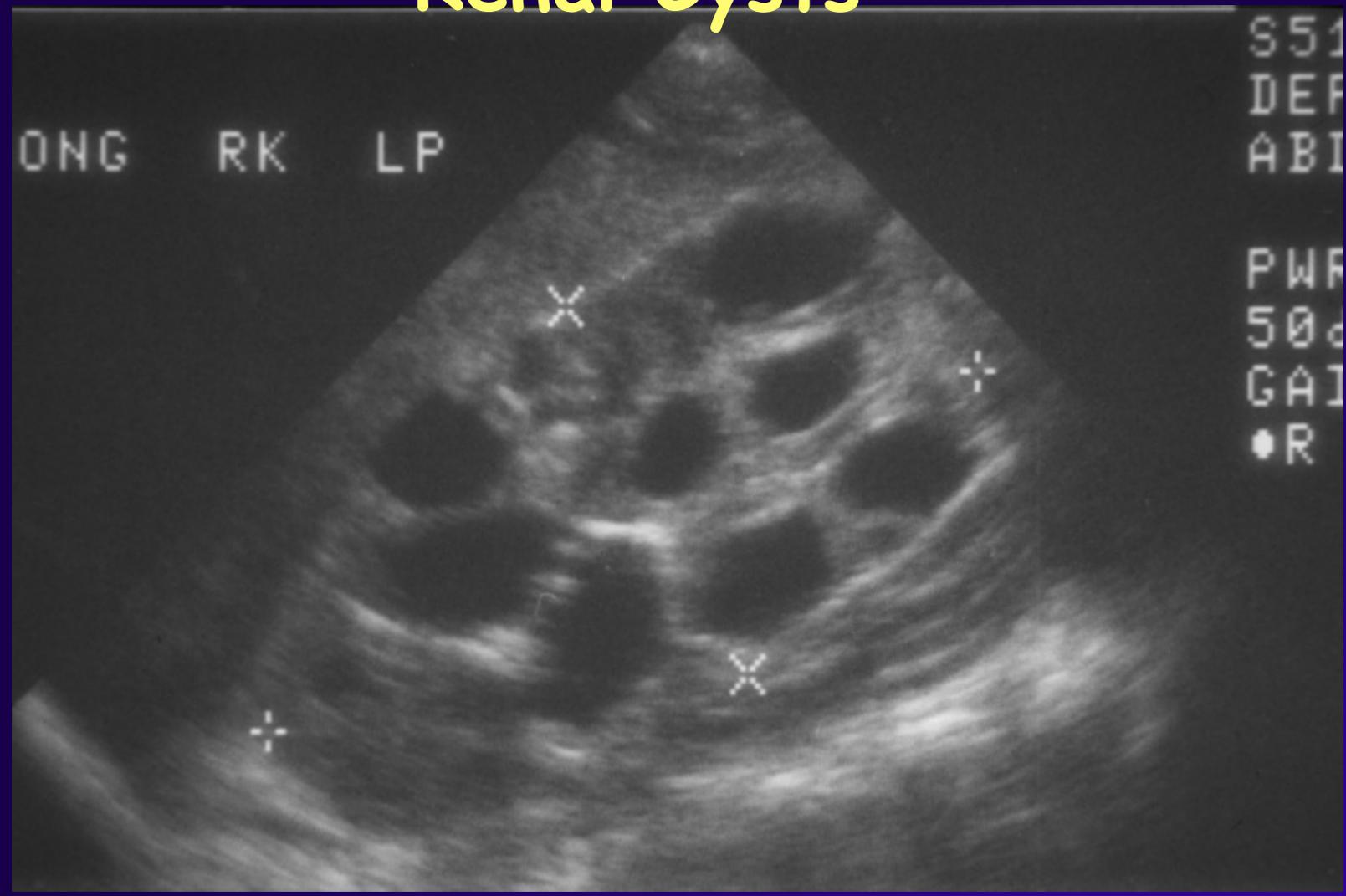


Renal Cysts

Radiology - <http://rad.medpix.net>



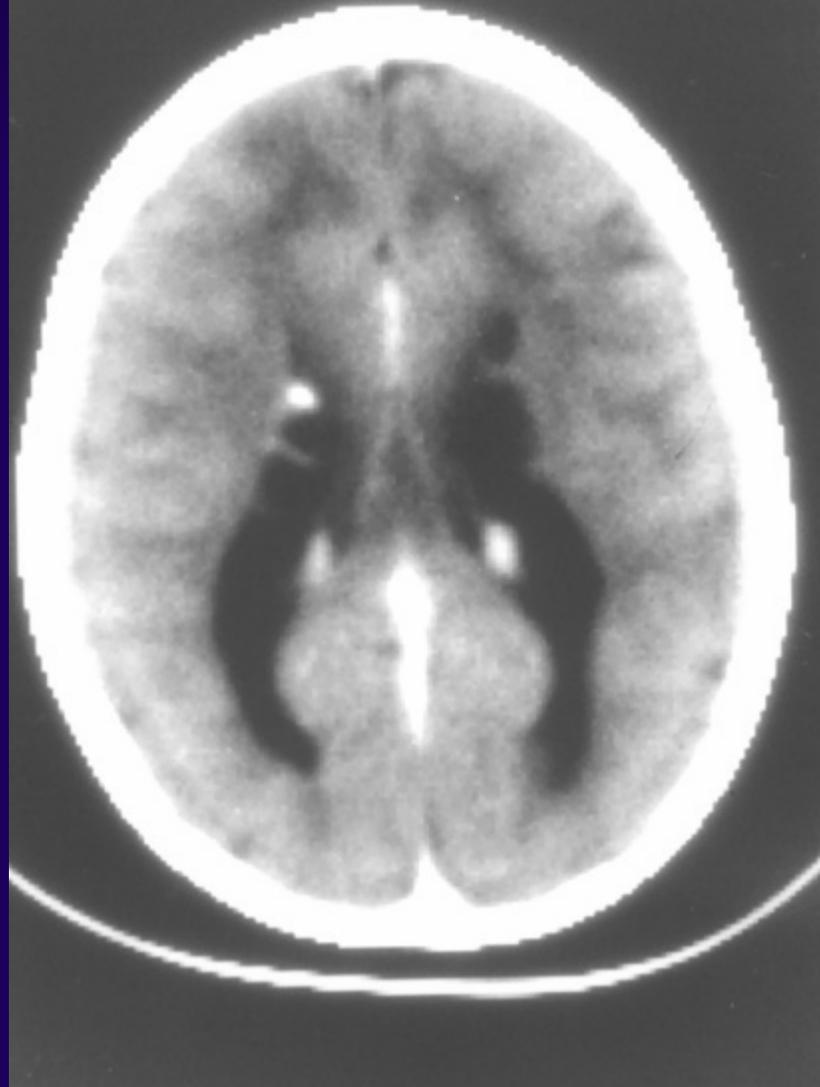
Renal Cysts



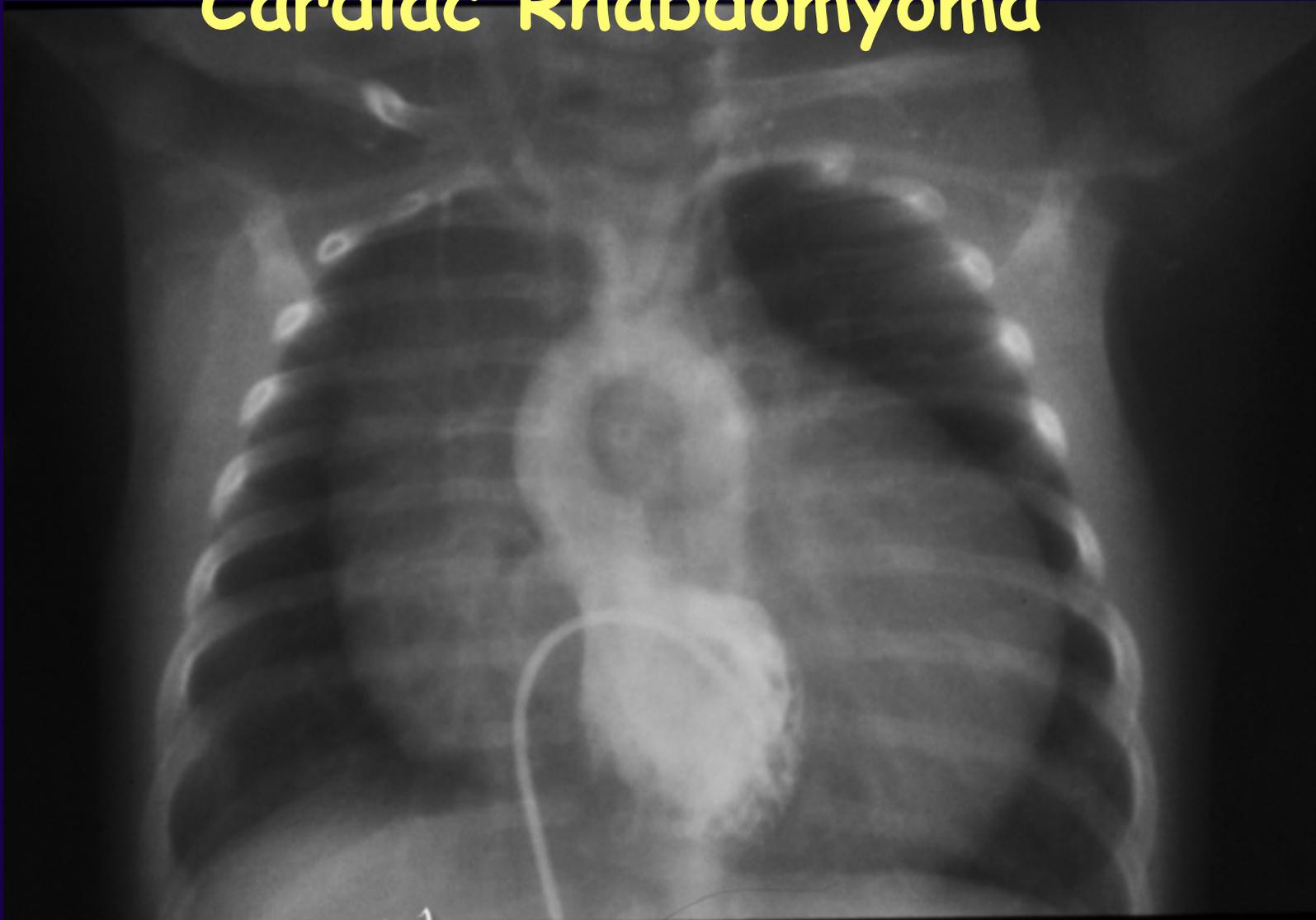
Renal Cysts



Subependymal Nodules



Cardiac Rhabdomyoma



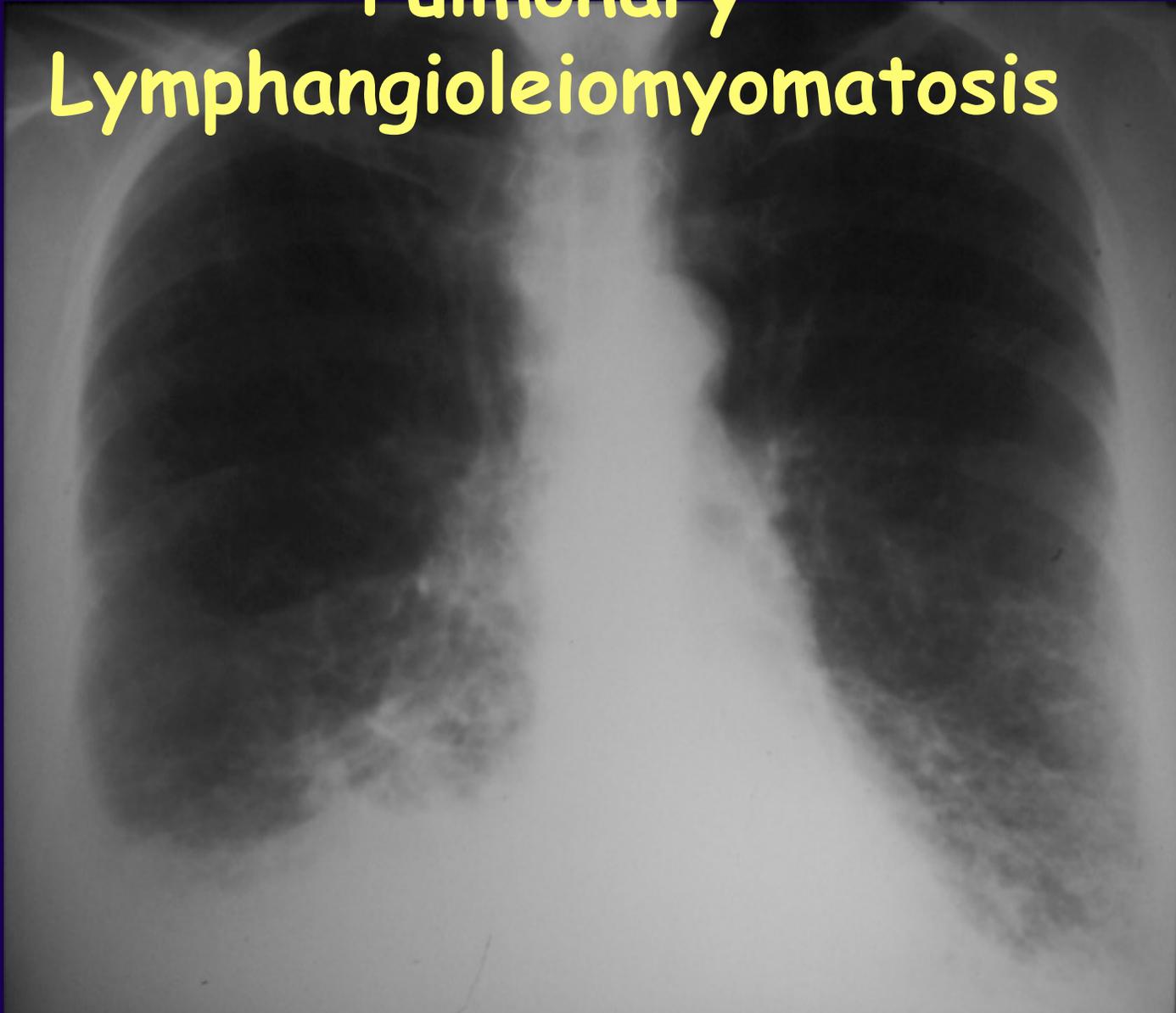
Cardiac Rhabdomyoma



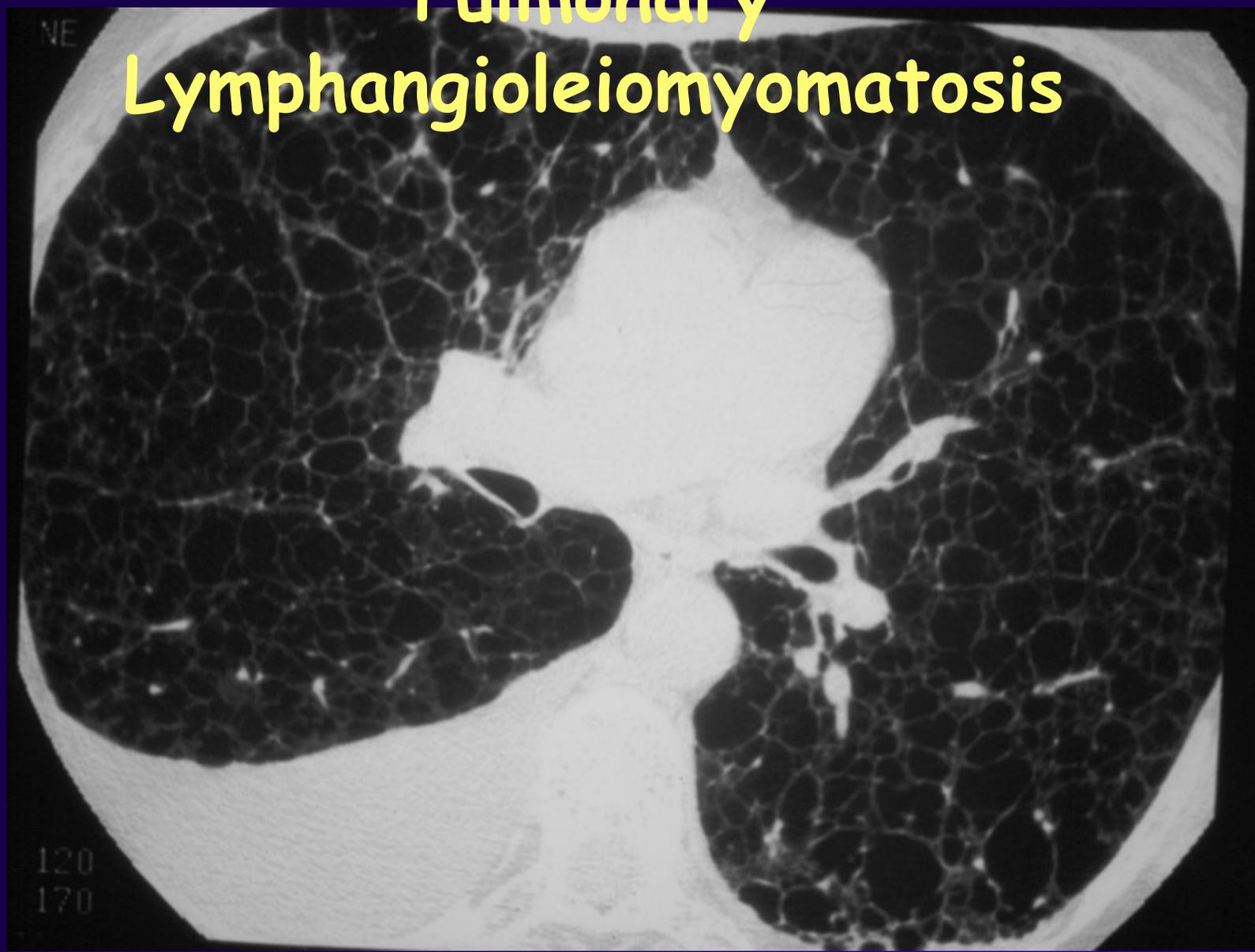
ANGIOMYOMATOSIS vs. LYMPHANGIOMYOMATOSIS

- "sporadic" cases, all are female
 - 50% chylothorax
 - Perilymphatic smooth mm.
 - May have abdominal LN involvement
- In TS, males can be affected
 - chylothorax is rare
 - Smooth mm around pulmonary aa

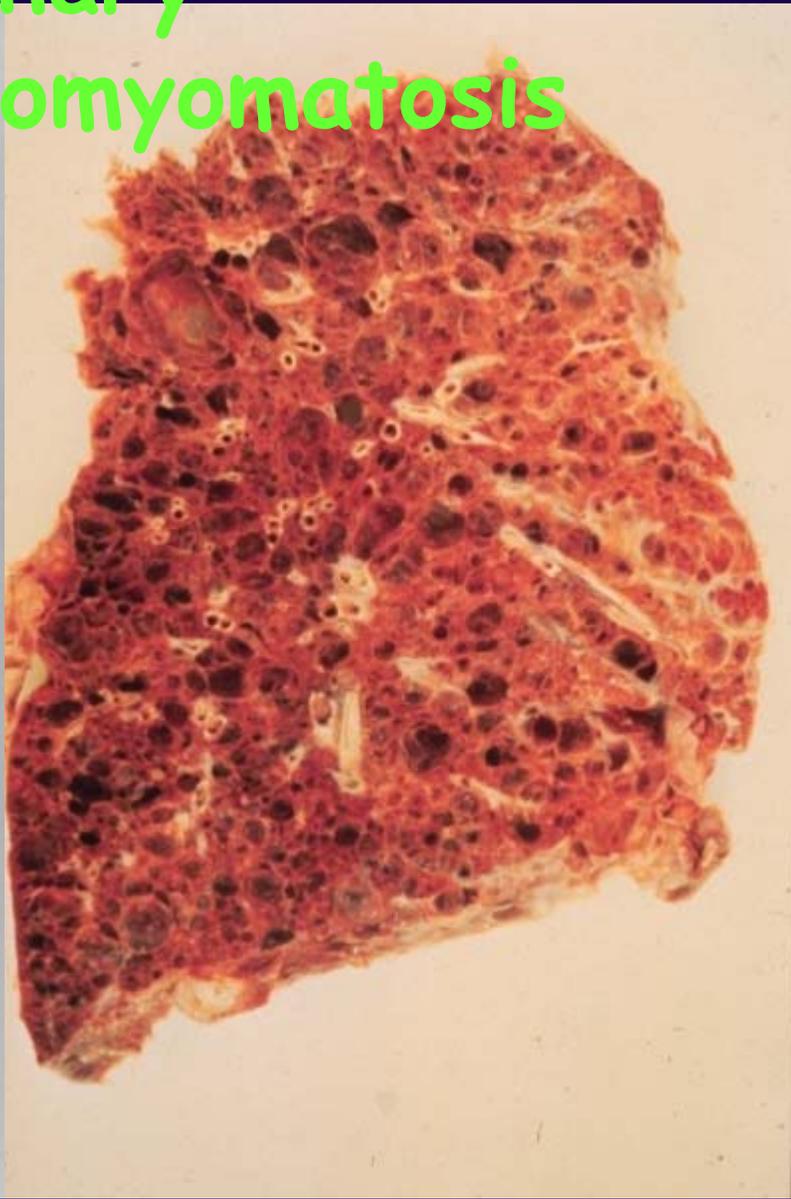
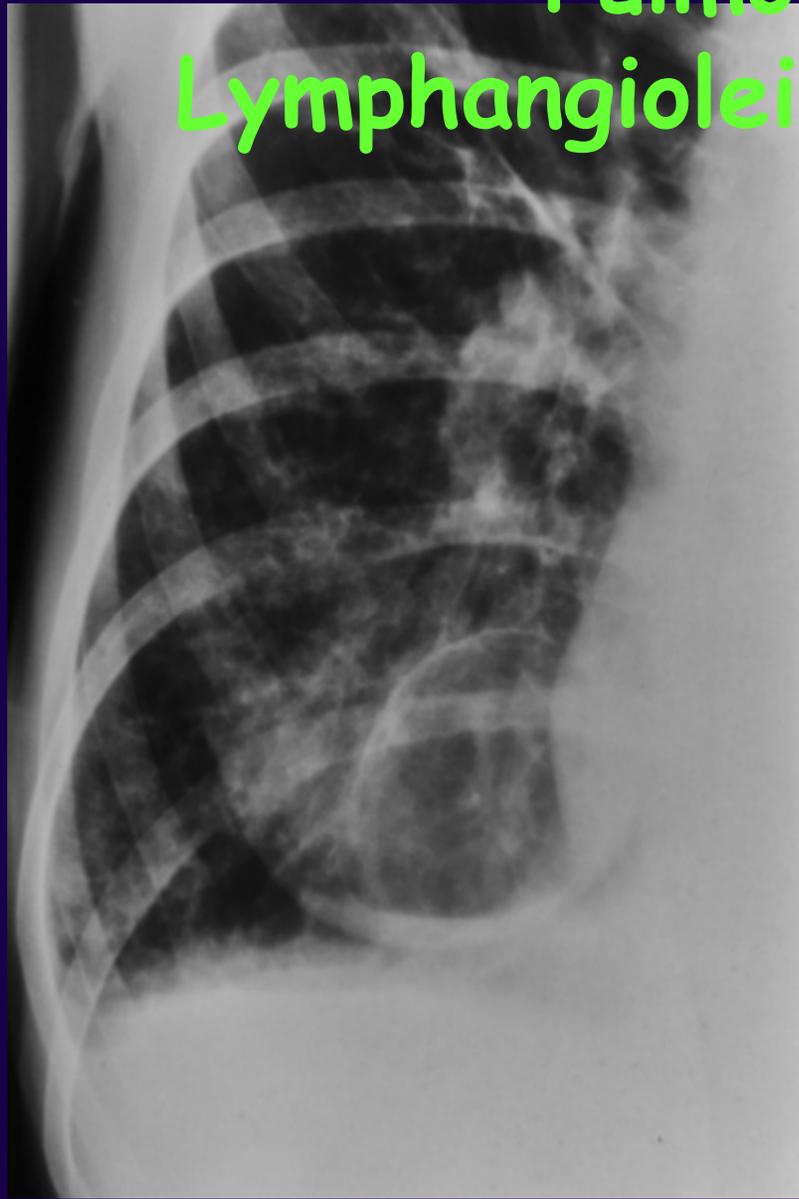
Pulmonary Lymphangiomyomatosis



Pulmonary Lymphangiomyomatosis



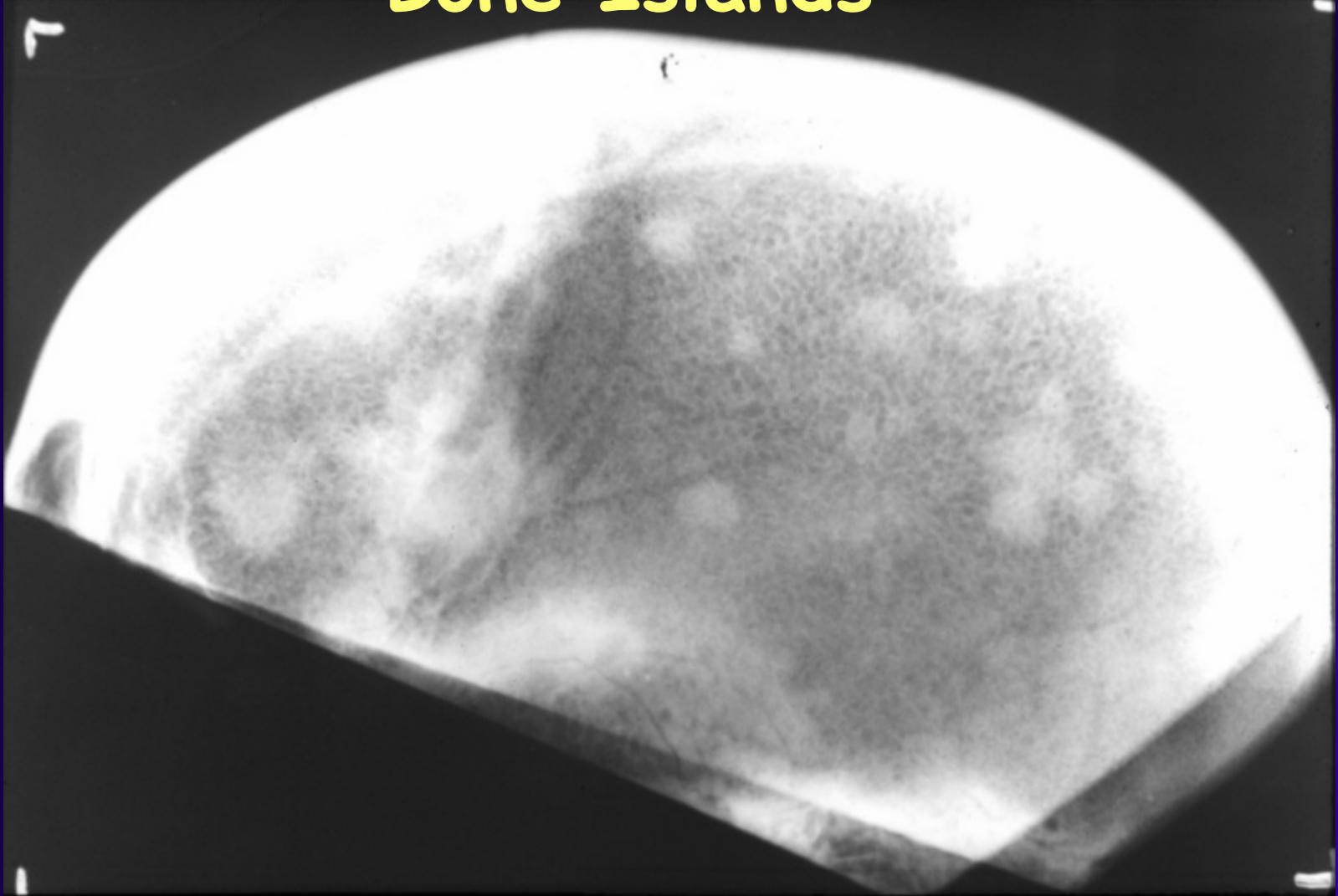
Pulmonary Lymphangiomyomatosis



Bone Islands



Bone Islands



Melorrheostosis



Bone Islands



Phakomatoses Mnemonic Tool

- NF-1 (von Reck's)
 - TRUE Neurofibromatosis #17
- NF-2 (Bilateral. VIII Syndrome)
 - M.I.S.M.E. #22
- STURGE-WEBER (Dimitri) Syndrome
 - Congenital Vascular Lesion, perhaps NOT inherited
- TUBEROUS SCLEROSIS
 - Pringle's "HAMARTOMA" Disease

Proband with Stigmata



Familial Syndrome



Radiology - <http://rad.medpix.net>

THE PHAKOMATOSES

James G. Smirniotopoulos, M.D.

Uniformed Services University
4301 Jones Bridge Road
Bethesda, MD 20814
Voice: 301-295-3145
FAX: 301-295-3893

Visit us on the WEB:
<http://rad.usuhs.mil>