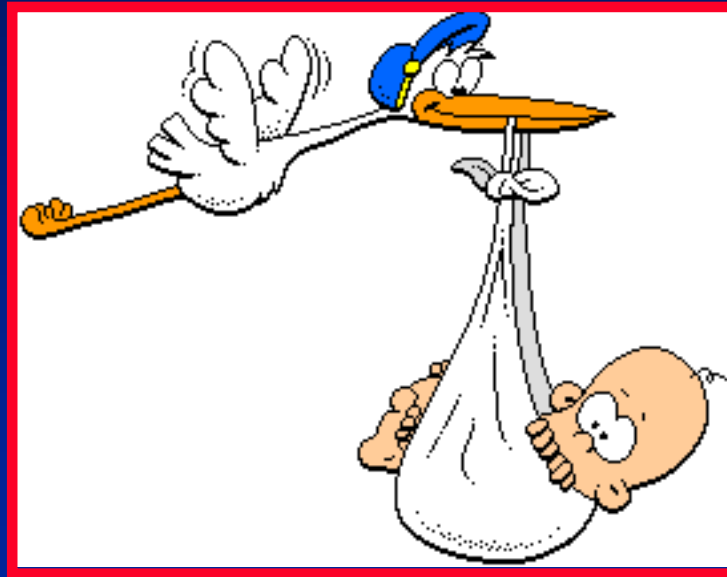


HYPOXIC-ISCHEMIC BRAIN INJURY of the NEWBORN & CEREBRAL PALSY



Jin S. Hahn, M.D.

Cerebral Palsy: Definition

Group of disorders that

- **present after birth**
- **characterized by abnormal control of movement or posture**
- **absence of recognized underlying progressive disease**

Not a single disease, but group of conditions

- **different parts of body involved**
- **other associated disabilities.**

Cerebral Palsy: History

William John Little

1861

Sigmund Freud

1889

William John Little

Orthopedic surgeon who observed that children with tone and developmental abnormalities often had prolonged labor, prematurity or breech delivery.

“Motor deformities resulted from difficulties in the birth process.”

1861

Sigmund Freud

“Cerebral palsy is not caused by a difficult birthing process or perinatal difficulties.”

“CP is the result of some injury to the brain that occurred during pregnancy which leads to CP and predisposes the infants to difficult deliveries.”

Cerebral Palsy: Epidemiology

- **1.2 to 2.3 children per 1000 by early school age**
- **10-15% of CP is acquired through known brain injury, infection or trauma after first month of life**

CP: Clinical Phenotypes

- **Spastic Quadriplegia**
- **Spastic Diplegia**
- **Spastic Hemiplegia**
- **Extrapyramidal CP**
- **Mixed CP**
- **Others**

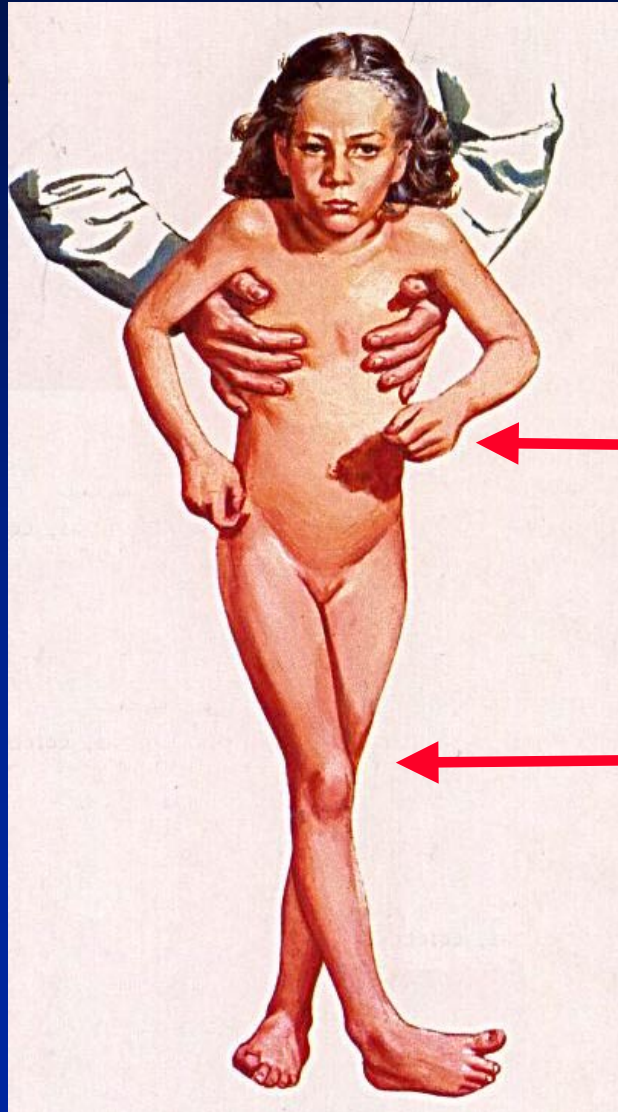
Hypotonic CP

Ataxic CP

Spastic Quadriplegia

- **aka double hemiparesis**
- **involves all four limbs, arms at least severely affected as legs**
- **bilateral hemisphere involvement, severely impaired and MR**
- **often have bulbar symptomatology**
- **9–43% of all CP**

CP: Spastic Quadriplegia



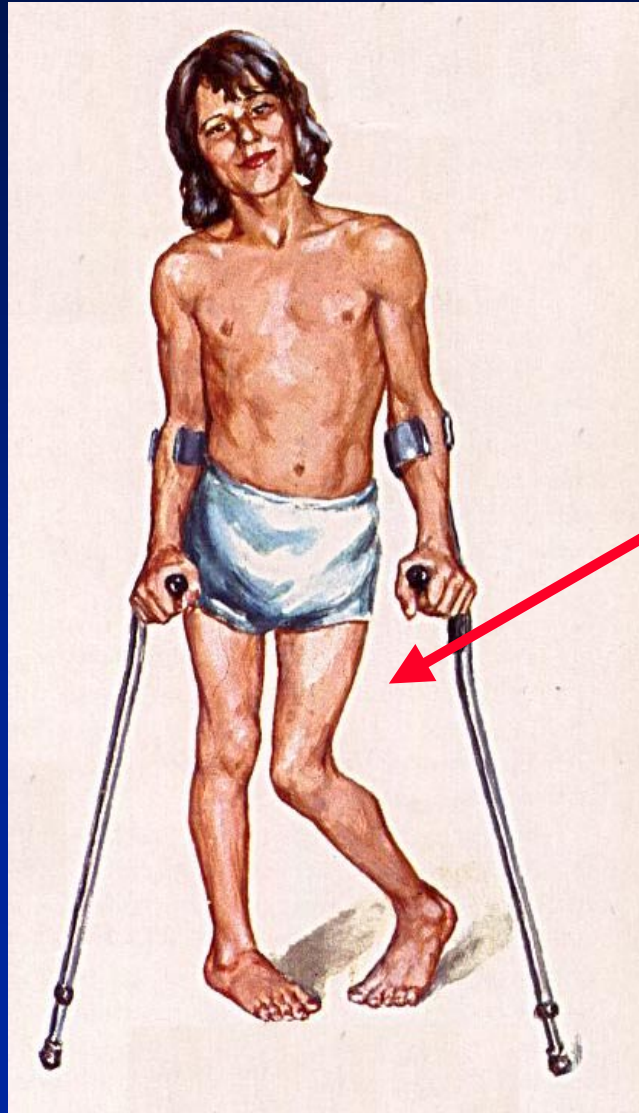
“Fisting”

***“Scissoring”
of lower limbs***

Spastic Diplegia

- **involves legs more than arms**
- **often associated with premature births**
- **only 11-20% are severely impaired**
- **MR not so profound**
- **10–33% of all CP**

CP: Spastic Diplegia



**Contractures
of hips, knees,
and feet (talipes
equinovarus)**

Spastic Hemiplegia

- **involvement of arm and leg on one side (arm>leg)**
- **motor handicaps least likely to be disabling**
- **intelligence is normal to dull**
- **25–40% of all CP**

CP: Spastic Hemiplegia

Hemiplegia on the right side.



Contractures of hip, knee and foot



Extrapyramidal CP

- defects of posture, involuntary movements (*i.e., athetosis, dystonia*), ataxia and hypertonus (*rigidity*)
- hallmark of bilirubin encephalopathy (*kernicterus*), now rarely seen
- 9–22% of all CP

CP: Athetoid



*Persistent
asymmetric tonic
neck reflex*

Neuropathology of Hypoxic-Ischemic Brain Injury

- Parasagittal brain injury
- Periventricular leukomalacia
- Focal/multifocal ischemic injury
- Status epilepticus
- Selective neuronal necrosis

Some Definitions:

Hypoxia = diminished oxygen supply to tissue

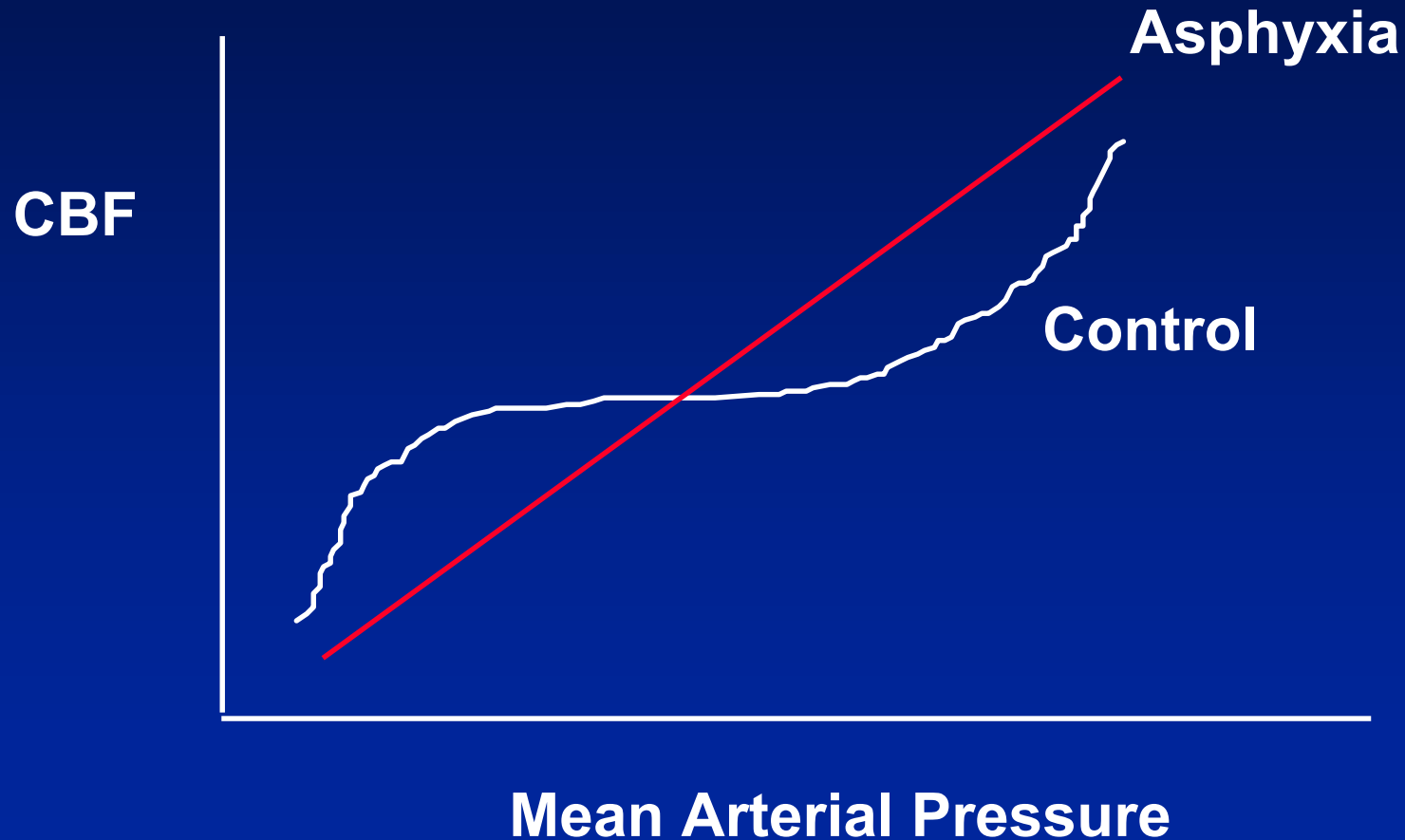
Ischemia = diminished blood flow to tissue or organ

Asphyxia = disturbance of gas exchange in fetal-maternal circulation resulting in
 \uparrow pCO₂ and \downarrow pO₂

Biochemical Response to Asphyxia

- **Cerebral Blood Flow is sensitive to**
 - **PaO₂ (inversely correlated with CBF)**
 - **PaCO₂ (hypercarbia increased CBF and hypocarbia decreases CBF)**
 - **Acid Base status (acidosis increases CBF and alkalosis decreases CBF)**

Autoregulation



Cardiovascular Response to Asphyxia

Asphyxia (\downarrow PaO₂, \uparrow PaCO₂, \downarrow pH)



REDISTRIBUTION OF CARDIAC OUTPUT



\uparrow Cerebral, Coronary,
Adrenal Blood Flow

\downarrow Renal, GI
Blood Flow



ONGOING ASPHYXIA

\downarrow CARDIAC OUTPUT



\downarrow CEREBRAL BLOOD FLOW

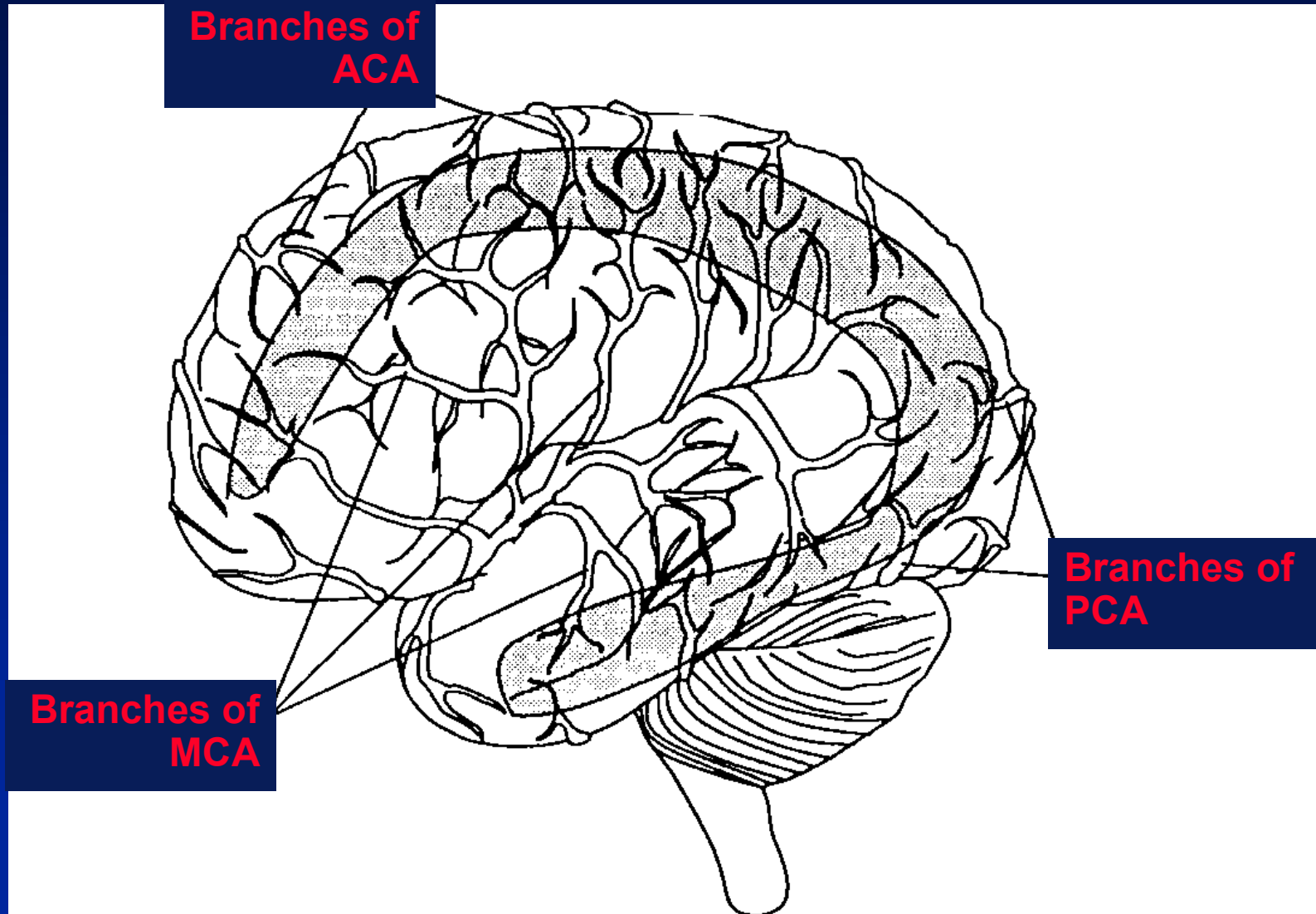
Pathophysiology of Hypoxic-Ischemic Brain Injury

- **Intrapartum Asphyxia results in:**
 - diminished oxygen content in blood
 - increased carbon dioxide
 - acidosis
 - decrease blood pressure
- **Loss of normal cerebrovascular *autoregulation* resulting in pressure-passive flow**
- **Results in decreased perfusion of brain**
- **Reperfusion injury and IVH**

Neuropathology of Hypoxic-Ischemic Brain Injury

- Parasagittal brain injury
- Periventricular leukomalacia
- Focal/multifocal ischemic injury
- Status marmoratus
- Selective neuronal necrosis

Parasagittal Watershed Area (Mature)



Selective Vulnerability to Ischemic Insult

- **PRETERM: Periventricular Areas**
 - Watershed Areas
 - White matter has higher metabolic demand
 - White matter more vulnerable to anaerobic conditions
 - Germinal Matrix
- **TERM: Parasagittal**
 - Arterial watershed distribution
 - Both cortex and white matter involvement

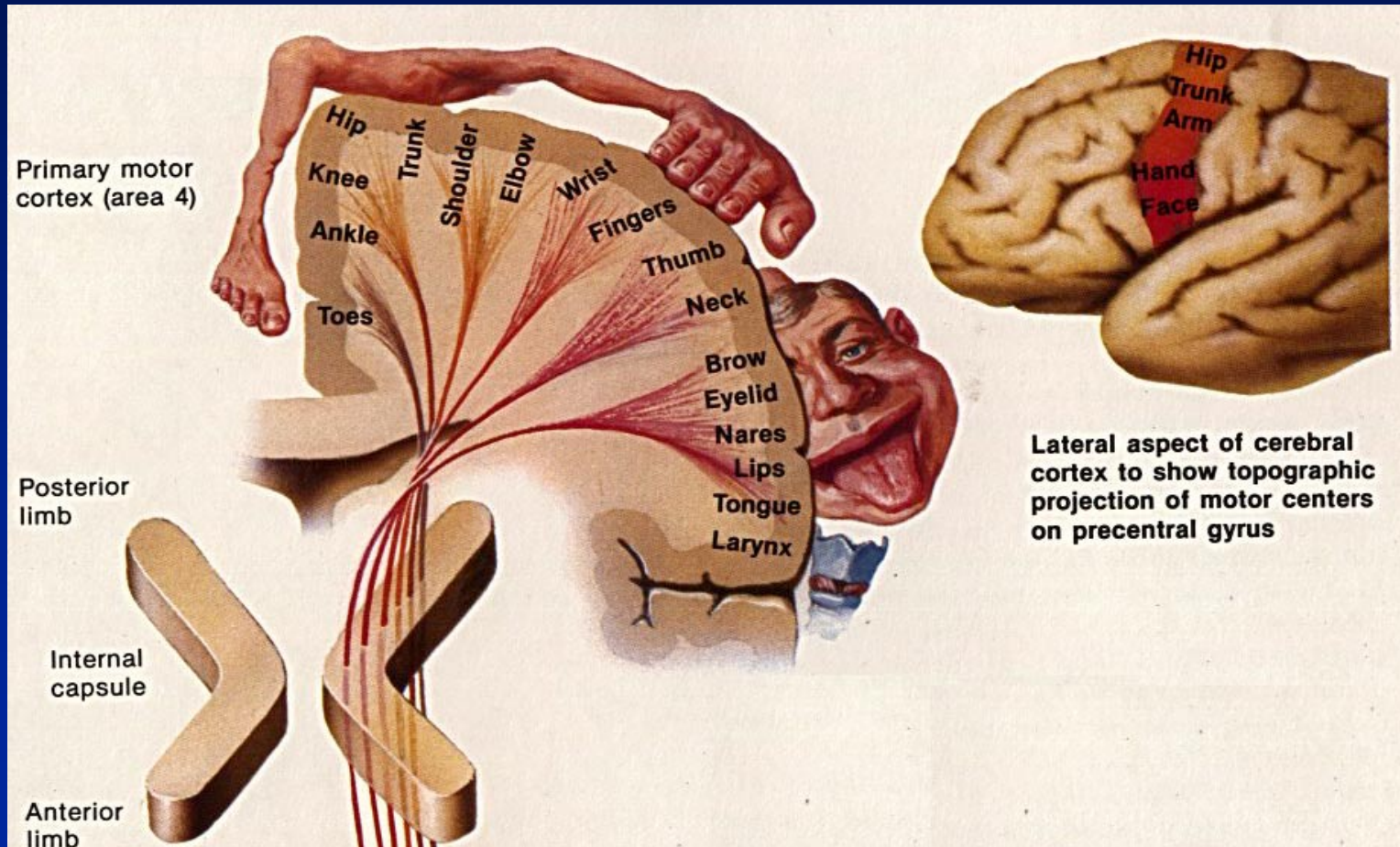
Cerebral Hypoperfusion (TERM): Example

- **B.A.: Term infant**
- **Pregnancy complicated by maternal hypertension**
- **1-2 days PTD, mom felt decreased fetal movements**
- **Placenta Abruptio noted at delivery**
- **Depressed at birth requiring resuscitation, Apgars 0/0/1**
- **Neonatal Course**
 - **neonatal encephalopathy**
 - **neonatal seizures**
 - **multiorgan failure**
- **CT scans at 2 days: diffuse edema and ischemic changes.**
- **F/U Exams shows Spastic Quad type of Cerebral Palsy**

Cerebral Hypoperfusion (TERM): Features

- **Acute brain injury during labor (abruptio)**
- **Severe compromise at birth**
- **Metabolic Acidosis**
- **Multiple Organ Compromise**
- **Prolonged Neonatal Encephalopathy**
- **Imaging**
 - **Parasagittal Watershed Infarction**
 - **Diffuse Neuronal Necrosis**

Map of the Homunculus



Cerebral Hypoperfusion (TERM): Outcome

- **Profound CNS injury**
- **Spastic Quadripareisis**
- **Epilepsy**
 - often infantile spasms
- **Mental Retardation**
- **Multiple handicaps**
 - cortical visual
 - hearing loss

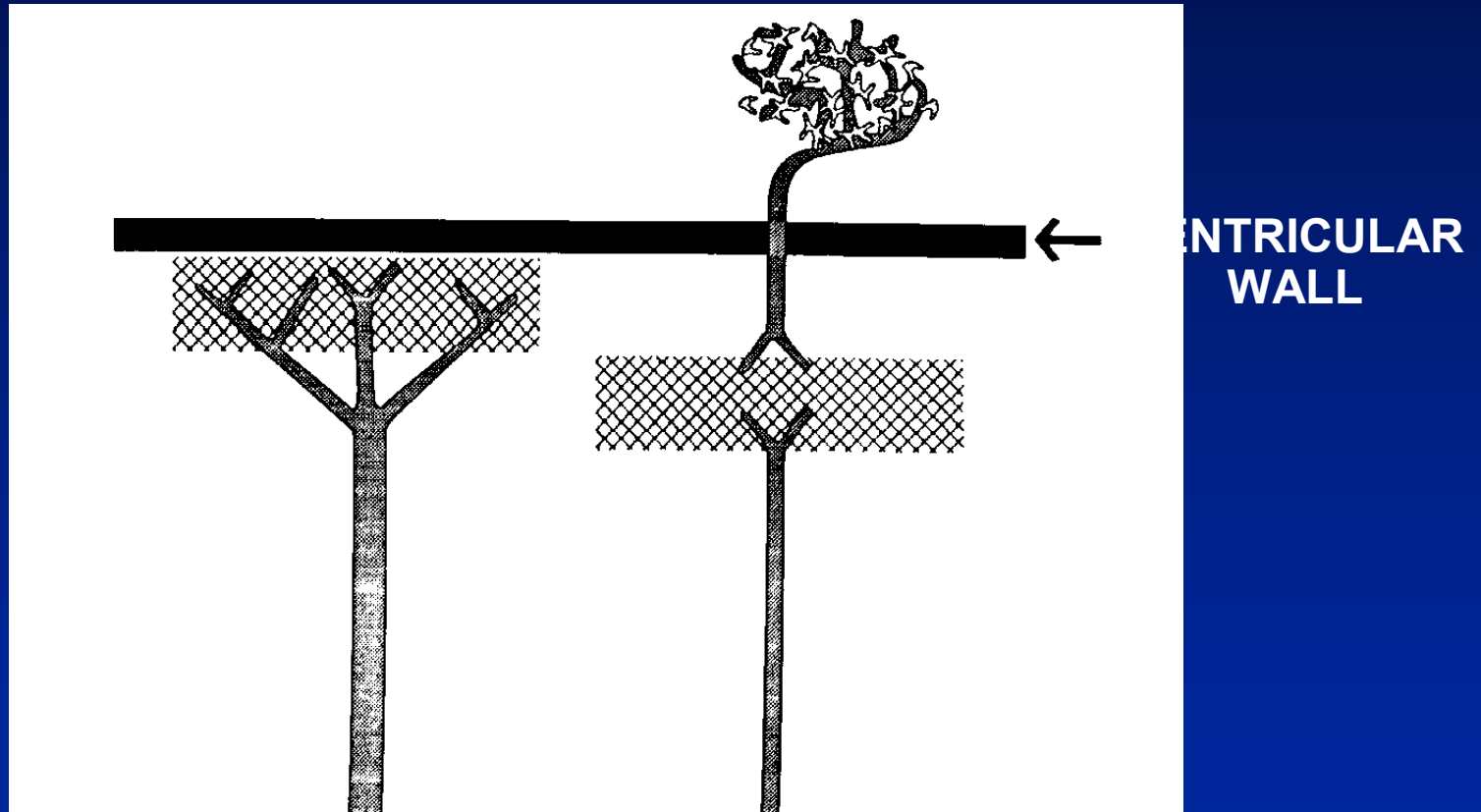
Neuropathology of Hypoxic-Ischemic Brain Injury

- Parasagittal brain injury
- **Periventricular leukomalacia**
- Focal/multifocal ischemic injury
- Status mamoratus
- Selective neuronal necrosis

Fetal Blood Supply to Cerebrum

IMMATURE PATTERN

MATURE PATTERN



CEREBRAL HEMISPHERE

Cerebral Hypoperfusion (PRETERM): Example 6079488

- **B.J.: 860 gm, 27-week gestation, Twin A**
- **Pregnancy complicated by twin gestation & premature rupture of membrane at 27 weeks**
- **Apgar scores: 7 (1-min) & 9 (5-min)**
- **Neonatal Course**
 - **RDS, chronic lung disease**
 - **Normal early HUS**
- **At 1.5 months, HUS: widespread cystic PVL**
- **F/U Exam shows spastic type of Cerebral Palsy, worse in LEs**

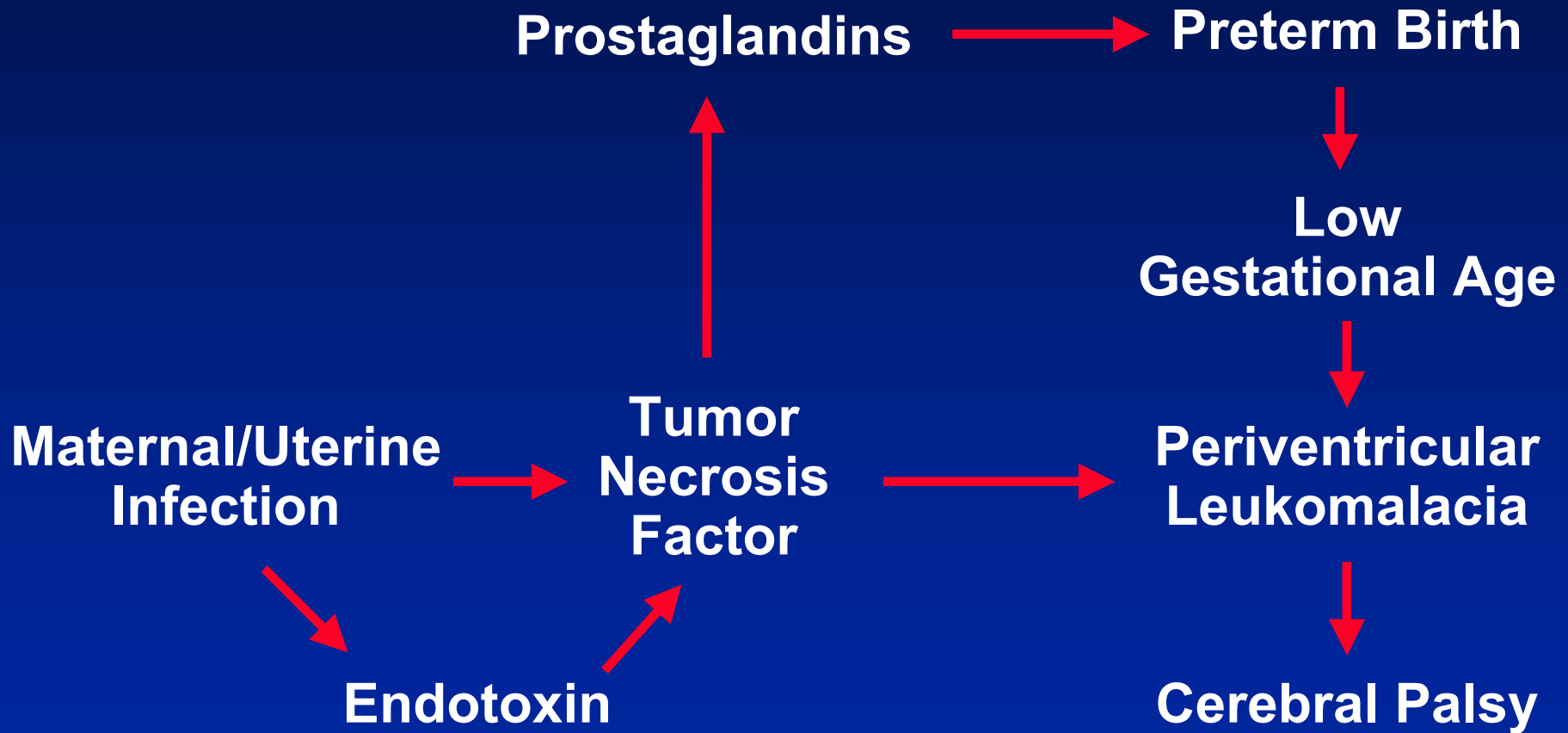
Periventricular Leukomalacia

- **MRIs at years later show:**
 - **Prolonged T2 signal in the periventricular areas (glial scars)**
 - **Distortion of normal contours of the lateral ventricle (glial scars)**
 - **Ventriculomegaly (reflects hydrocephalus ex vacuo caused by inadequate myelination of periventricular axons)**

Cerebral Hypoperfusion (PRETERM)

- **Widespread cystic PVL**
 - May or may not be associated with IVH
 - Parenchymal lesions are nonhemorrhagic
- **Possible causes of cerebral hypoperfusion**
 - Group B streptococcal sepsis (shock and endotoxins)
 - Maternal antepartum hemorrhage
 - Birth Asphyxia
 - Seizures
 - Recurrent Apneas

PVL and Maternal Infection



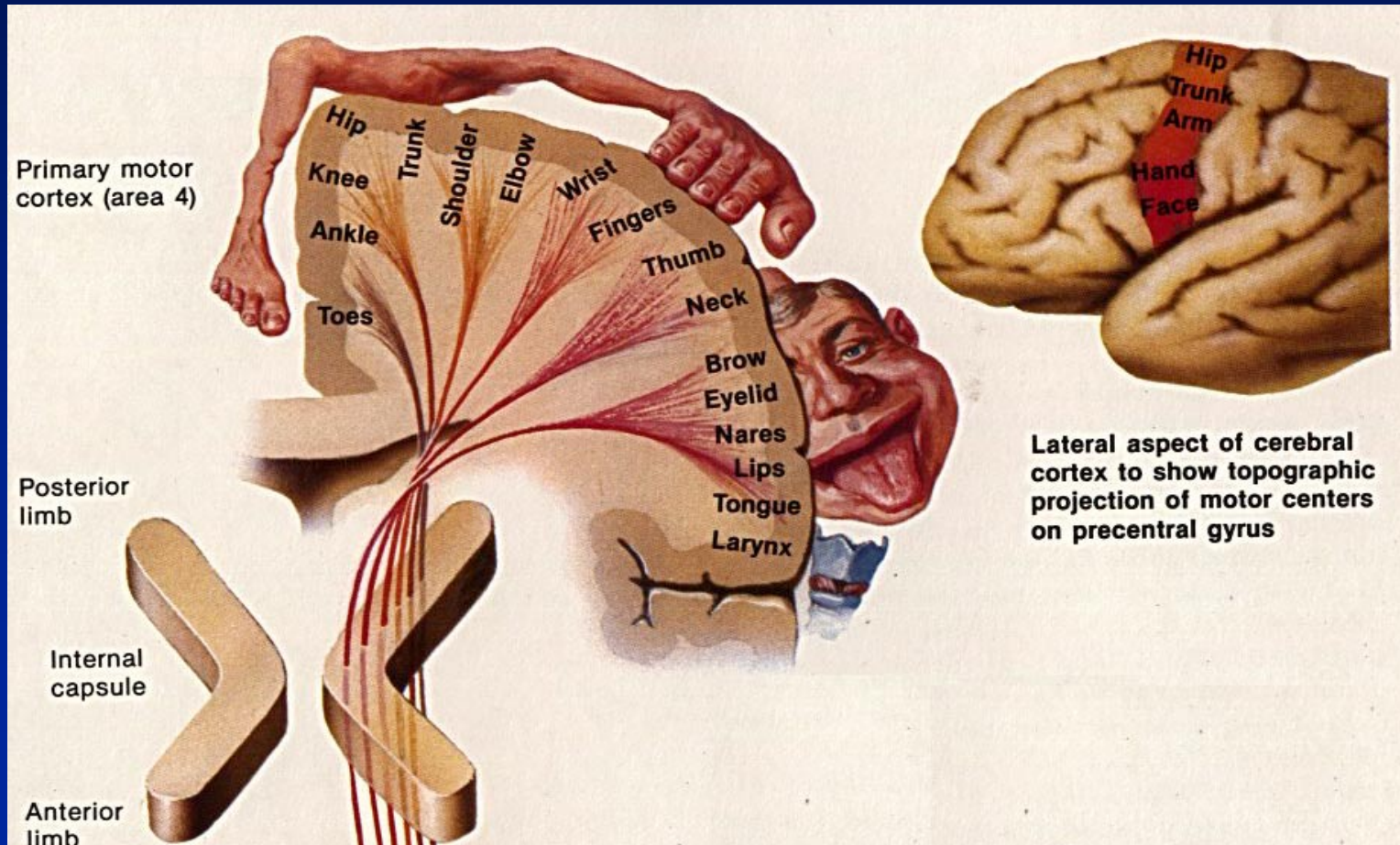
Tumor Necrosis Factor and PVL

- **Cells in the brain produce TNF produces hypotension, leading to ischemia**
 - TNF promotes disseminated intravascular coagulation, leading to vessel obstruction and multiple foci of ischemia
 - TNF promotes production of *Platelet Activating Factor* which has cytotoxic properties
 - TNF promotes destruction of oligodendrocytes

Cerebral Hypoperfusion (PRETERM): Outcome

- **Cerebral Palsy highly likely**
 - Spastic diplegia most commonly
 - Spastic quad less common
- **Spectrum of other neurologic dysfunction**
 - Mental retardation
 - Cortical visual problems

Map of the Homunculus



Neuropathology of Hypoxic-Ischemic Brain Injury

- Parasagittal brain injury
- Periventricular leukomalacia
- **Focal/multifocal ischemic injury**
- Status epilepticus
- Selective neuronal necrosis

Arterial Distribution Infarct (TERM): Example

- **A.S.: 4281 gm LGA infant born at Term**
- **Pregnancy complicated by gestational diabetes mellitus**
- **Apgars 9 and 9**
- **At 48 hours of life noted to have clonic seizures of right arm and legs**
- **CT scan revealed stroke in Left Middle Cerebral Artery distribution**
- **Treated with phenobarbital**
- **F/U exam 4 months, mild head lag, no major asymmetry, no seizures on phenobarbital**

Arterial Distribution Infarct (TERM)

- **Due to occlusion of major artery**
 - embolic or thrombosis
 - late intrauterine event
- **Benign neonatal course**
- **Focal cortical ischemic lesions do not interfere with mechanisms of consciousness**
- **Subtle neuro signs in newborn period**

Arterial Distribution Infarct (TERM): Outcome

- **Hemiparetic cerebral palsy**
- **Normal to near normal mental ability**
- **Few have severe handicap**

Etiology of Cerebral Palsy (1990s)

- Cause of most CP unknown, but majority seems to be *prenatal* in etiology (such as congenital malformations and genetic causes)
- Most children with CP did not sustain intrapartum asphyxia (only about 10-24%)
- *However, intrapartum asphyxia does occur and is an important mechanism of brain injury and CP.*

Hypoxic-Ischemic Insults and C.P.

- Intrapartum hypoxic-ischemic insults do lead to C.P.
- However, most C.P. are not due to cerebrovascular or hypoxic-ischemic insults
- Although obstetric and neonatal care has improved, prevalence of C.P. has *not* decreased

Antepartum HIBI

- **Only about 20% of CP attributed to *intrapartum asphyxia***
- **70 – 80% of CP is *antepartum* in origin**
- **Timing of HIBI**
 - **Before 20th week results in migrational defects (e.g., schizencephaly)**
 - **Between 27 and 30 weeks results in PVL**
 - **Between 34 and 40 weeks results in FOCAL or bilateral PARASAGITTAL INJURY**

Future Therapeutic Approaches

- **Prevent intracellular calcium accumulation**
- **Antagonism of excitatory amino acids**
- **Inhibition of nitric oxide production**
- **Scavenging of free radicals**
- **Hypothermia, regional**

Etiology: 1990's

Nelson and Ellenberg, 1986

Prematurity and severe birth asphyxia are important risk factors for CP, but most children with CP did not experience either of these risk factors

Mild or brief intrapartum asphyxia does not produce lasting brain damage; severe or prolonged intrapartum asphyxia is required to produce a substantial risk of CP

Most children with CP did not have low Apgar scores or other markers of intrapartum asphyxia

Most surviving children with low Apgar scores or birth complications do not develop CP

Full-term neonates at risk of neurologic sequelae from intrapartum asphyxia will demonstrate signs of neurologic dysfunction at least within the first week of life

Cause of most CP unknown, but majority seems to be prenatal in etiology

High frequency of congenital malformations, cerebral and noncerebral, in person with CP

Etiology of Cerebral Palsy (cont'd)

- *Severe asphyxia* (defined as Apgar @ 20 min ≤ 3) in term
 - Risk of CP 250-fold
- *Prematurity* is an important risk factors for CP
 - Risk of CP 20-fold in infants ≤ 1500 gm
- **Mild or brief intrapartum asphyxia does not produce lasting brain damage and CP**
- *Full-term neonates* at risk of neurologic sequelae from intrapartum asphyxia will demonstrate signs of neurologic dysfunction at least within the first week of life

CP: Diagnosis

- **initial complaint is failure to meet early developmental milestones**
- **no evidence of progressive disease**
- **no loss of milestones acquired previously**
- **criteria**
 - delayed milestones**
 - persistence of primitive reflexes**
 - pathologic reflexes**
 - failure to develop protective reflexes**

Associated Problems with CP

Mental retardation is common associated problem

50% of CP children have psychometric scores in MR range

25% of CP children are below educable

Seizure disorders

25-33% of CP children have some type of seizure

Visual and visual-motor abnormalities

Deafness associated with athetoid CP (bilirubin encephalopathy), now rare

Speech and learning defects

Evaluation of Child with CP

Assignment of Etiology

- Consistent evidence of a marked degree and substantial duration of intrapartum asphyxia?
- Newborn course consistent with moderate or severe hypoxic-ischemic encephalopathy?
- Can outcome be explained by intrapartum asphyxia?

Exclusion of other plausible explanations

- Congenital Brain Anomaly
- Genetic and Dysmorphic Syndrome
- Congenital Infection
- Inborn Errors of Metabolism
- Post-natal anoxic, infectious, traumatic lesions

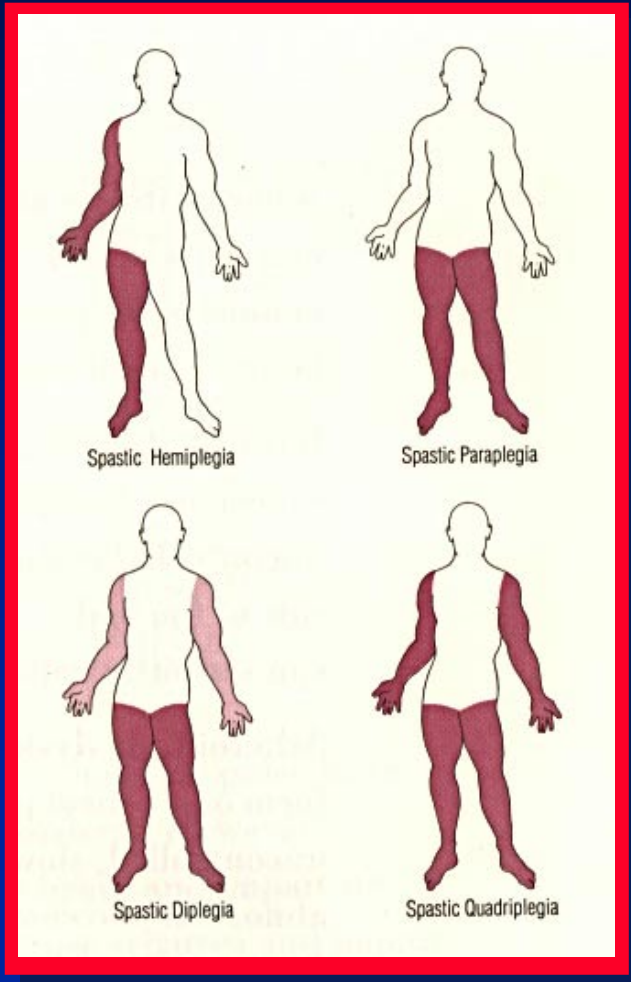
Prognosis in CP

- **Children with hemiplegia but no other major problems walk by 2 y.o.**
- **More than 50% of spastic diplegia learn to walk**
- **Of spastic quadriplegia 25% will require total care, 33 will walk (after 3 y.o.)**
- **Most children who sit by 2 y.o. will walk**

Table 1. Timing of CNS insult and neonatal encephalopathy

	TIMING OF INSULT(S)			
	Antepartum	Antepartum and intrapartum	Intrapartum	Postnatal
Approximate percent of Total	20-30	30-35	30-40	10
Possible Causes	Maternal hypotension Uterine hemorrhage Maternal hypoxia Antenatal white matter necrosis Maternal chorioamnionitis Certain brain malformations (porencephaly, hydranencephaly)	Maternal diabetes Preeclampsia Intrauterine growth retardation Dysmorphic syndromes	Abruptio placentae Uterine rupture Cord prolapse Velamentous insertion of cord and vasa previa Traumatic delivery	Postnatal cardiac arrest Severe pulmonary disease

Forms of Spastic Cerebral Palsy



- Spastic Hemiplegia
- (Spastic Paraplegia)
- Spastic Diplegia
- Spastic Quadriplegia

Extrapyramidal CP

- defects of posture, involuntary movements (i.e., athetosis, dystonia), ataxia and hypertonus (rigidity)
- hallmark of kernicterus (no longer seen)
- 9–22% of all CP

Cerebral Hypoperfusion (TERM): Example

- **E.C.: 3145 gm Term infant girl**
- **Contractions for 1 week, meconium at ROM**
- **Fetal heart rate deceleration with poor variability**
- **Depressed at birth requiring resuscitation, Apgars 3/5**
- **Neonatal Course**
 - **neonatal encephalopathy**
 - **neonatal seizures**
 - **renal and liver dysfunction**
- **CT scans at 2 days: diffuse edema**
- **F/U scan at 3 months, diffuse cystic encephalomalacia**
- **F/U: Spastic Quad and Infantile Spasms**

Cerebral Hypoperfusion (PRETERM): Example

- **J.T.: 1025 gm, 29-week gestation**
- **Pregnancy complicated by severe maternal hypertension.**
- **Neonatal Course**
 - **RDS, pulmonary hemorrhage**
 - **Grade I-II IVH and evolving ventriculomegaly**
- **At 2 months, HUS and MRI: widespread cystic PVL**
- **F/U Exam shows spastic type of Cerebral Palsy, worse in LEs**

IVH and IPH (PRETERM): Example

- **R.C.: 1250 gm, 30 wk premie**
- **Maternal thyrotoxicosis and severe pre-eclampsia**
- **Emergent ceasarian section**
- **Apgars 2/5/7**
- **Intubated and given ventilation**
- **Neonatal course complicated by necrotizing enterocolitis, sepsis, and shock**
- **Large IVH/IPH at 3 days of age**

Intraventricular and Intraparenchymal Hemorrhage (PRETERM)

- **Germinal Matrix is a common site of hemorrhage in preterm infants**
- **Leads to intraventricular hemorrhage (IVH)**
- **Often, ipsilateral intraparenchymal hemorrhage (IPH)**
- **Venous congestion periventricular region due to IVH causes hemorrhagic infarction**

IVH and IPH (PRETERM): Outcome

- **Spastic Diparesis**
 - Leg Fibers are more affected in periventricular region
- **May be Asymmetric**
- **Bilateral Parenchymal Lesions associated with worse prognosis**

Mechanism of Ischemic Brain Injury

- **Depletion of high energy metabolites**
- **Electrolyte fluxes**
- **Calcium entry and excitotoxic neuronal injury**
- **Acidosis and hyperglycemia**
- **Free radical and reperfusion injury**
 - Nitric Oxide (NO)
- **Cerebral Blood Flow alterations**

Pathophysiology of Cerebrovascular Insults

- **Neonatal Asphyxia results in:**
 - diminished oxygen content in blood
 - increased carbon dioxide
 - acidosis
 - decrease blood pressure
- **Loss of normal cerebrovascular *autoregulation* resulting in pressure-passive flow**
- **Results in decreased perfusion of brain**
- **Reperfusion injury and IVH**

Major Parenchymal Cerebrovascular Lesions in Perinatal Period – TERM

Disease Type	Abnormalities	Cerebral Palsy Type
Cerebrovascular hypoperfusion	Widespread cortical/subcortical infarcts in parasagittal region and white matter	Spastic quadriparesis
Large artery thrombosis	Wedge-shaped infarction in single vascular territory	Spastic hemiparesis

Major Parenchymal Cerebrovascular Lesions in Perinatal Period – PRETERM

Disease Type	Abnormalities	Cerebral Palsy Type
Intracerebral hemorrhage	Hemorrhagic infarction in periventricular white matter contiguous to IVH	Spastic diplegia
Cerebral hypoperfusion	Ischemic infarction of periventricular white matter ± cystic change (PVL)	Spastic diplegia