Mitochondrial Disease: Can Bioenergetic Disorders be Involved in Psychiatric Disorders?

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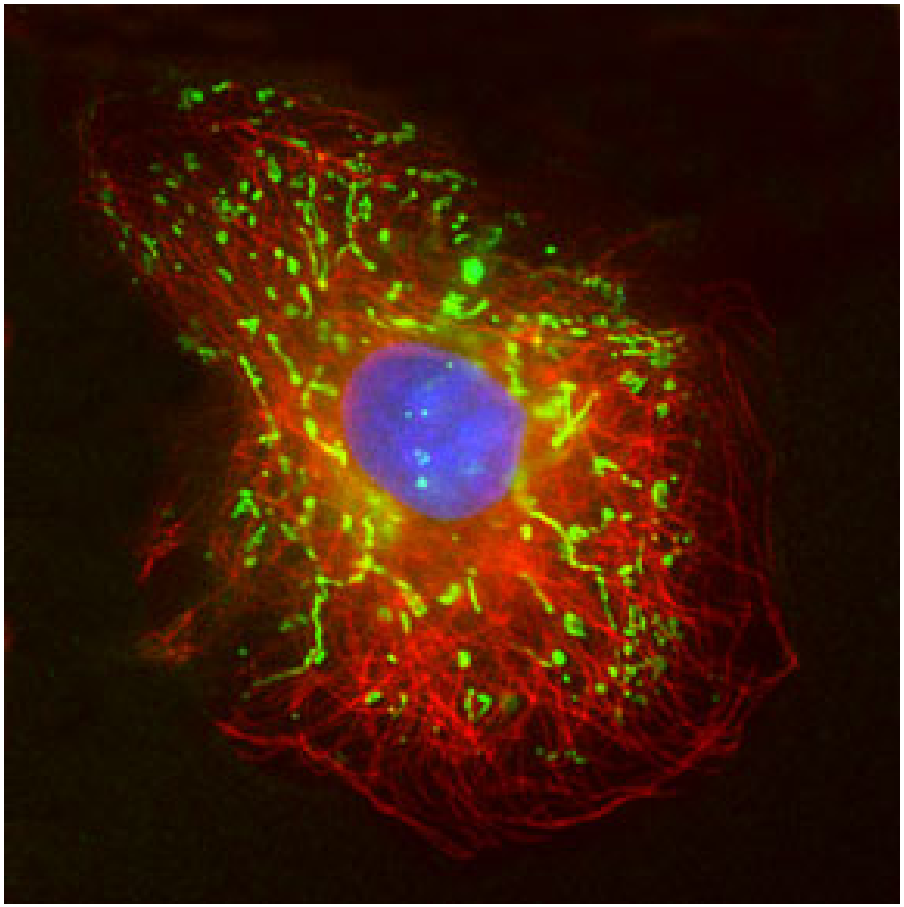
Objectives

- Learn to define mitochondrial disorders.
- To define at least two mechanisms of how mitochondrial disorders disrupt energy production.
- Learn cognitive/neuropsychological presentations of children/adolescents with mitochondrial disorders.
- To keep you awake for the next 90 minutes.

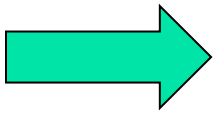
What are mitochondria?

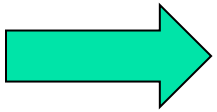


What are mitochondria?

- An intracellular organelle.
- There are 100 to 1000s of mitochondria/cell.
- All mitochondria come from the mother.
- Mitochondria have their own DNA.
- Found in all cell types, except the RBC.
- Major functions of mitochondria:
  - Makes energy in the form of ATP.
  - Programmed cell death (apoptosis).

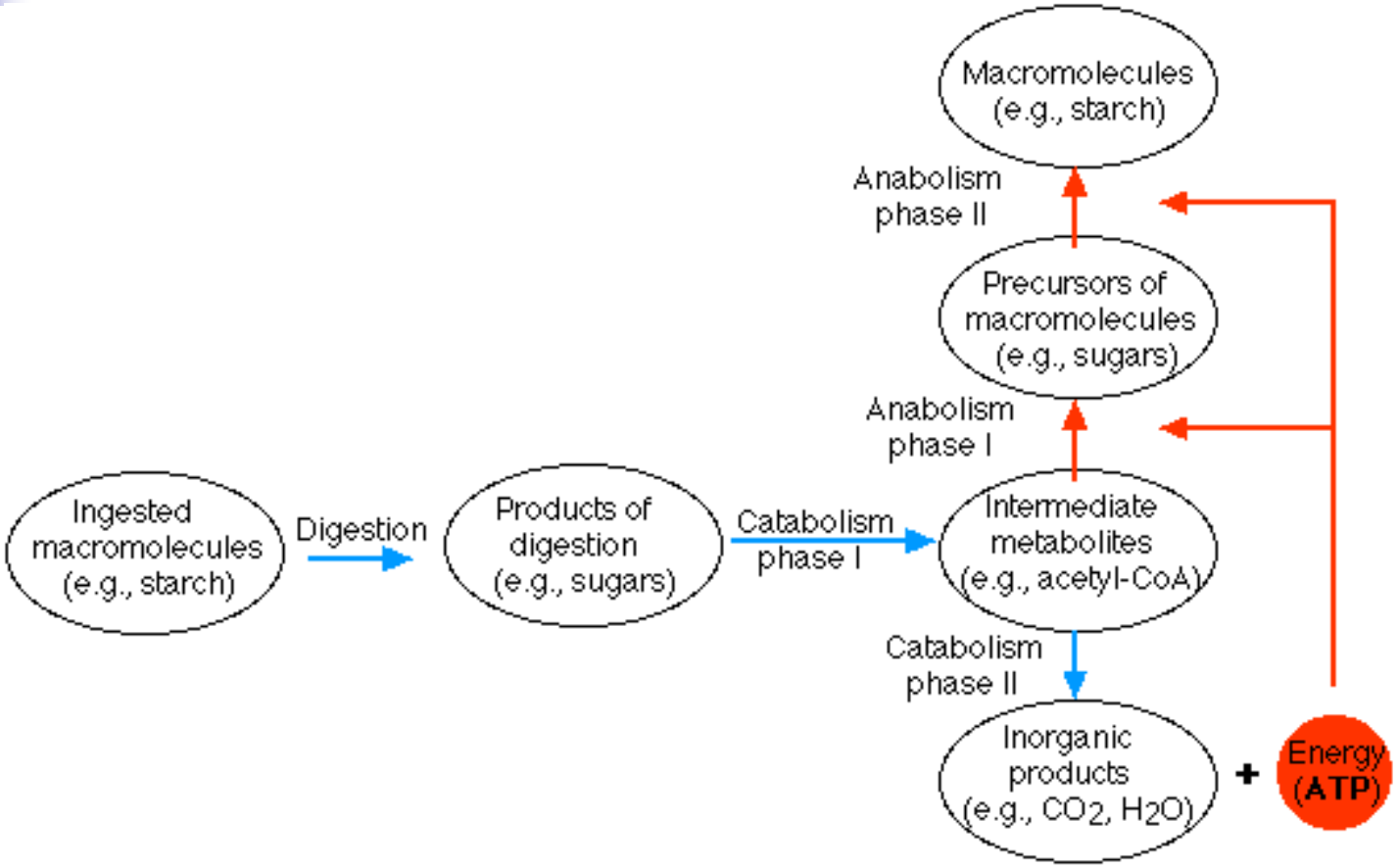
Chemical Energy

Cars  Gasoline

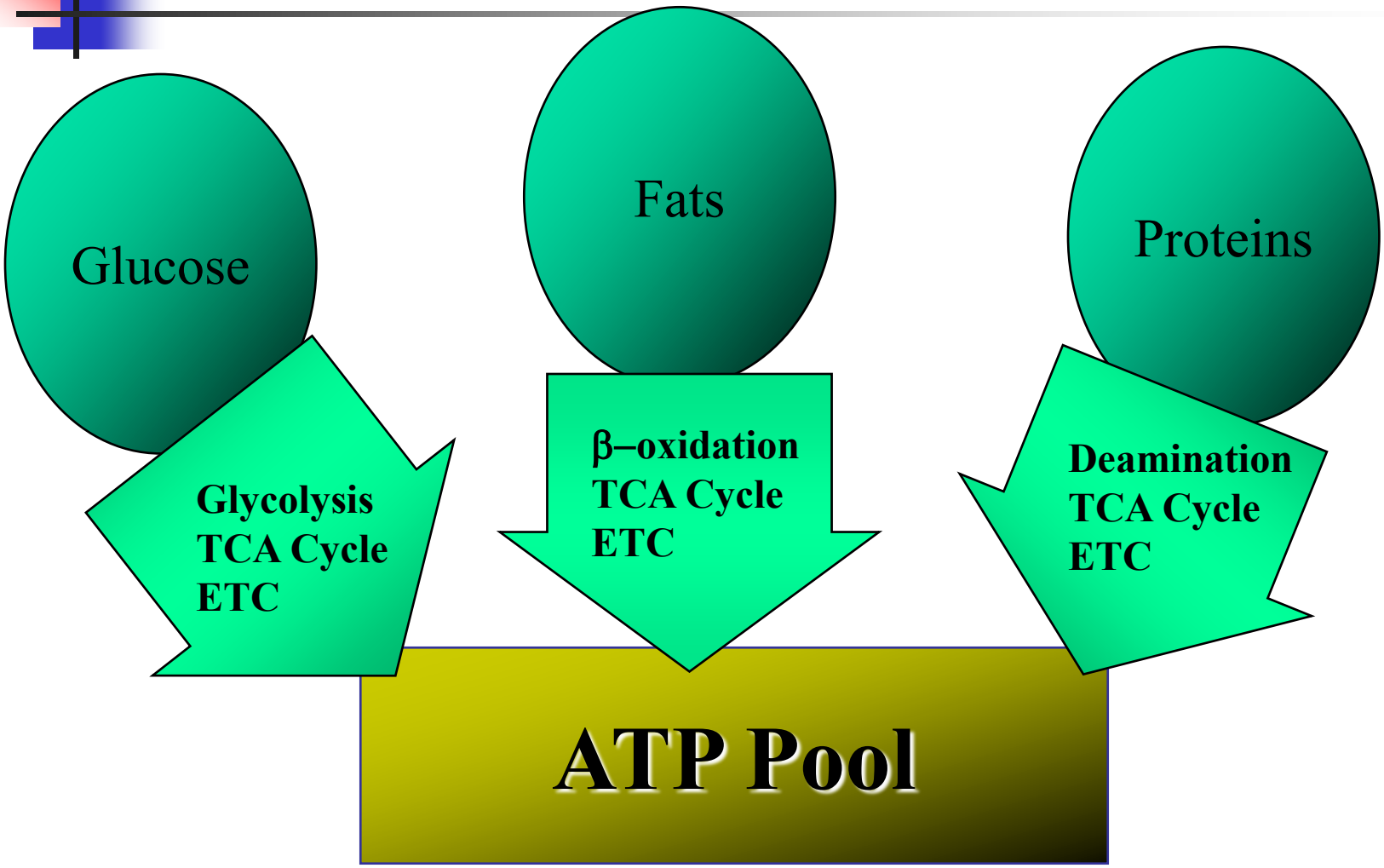
Cells  ATP

Mitochondrial Substrates

Fate of Ingested Food



Intermediary Energy Metabolism



Why is energy so important?

- Role of ATP (energy)
  - Mechanical Work
    - Muscle contraction
  - Chemical Work
    - Na^+/K^+ Ion Pump
  - Synthetic Work [Anabolism]
    - Macromolecules
      - Nucleic Acids
      - Proteins
      - Lipids
      - Complex carbohydrates

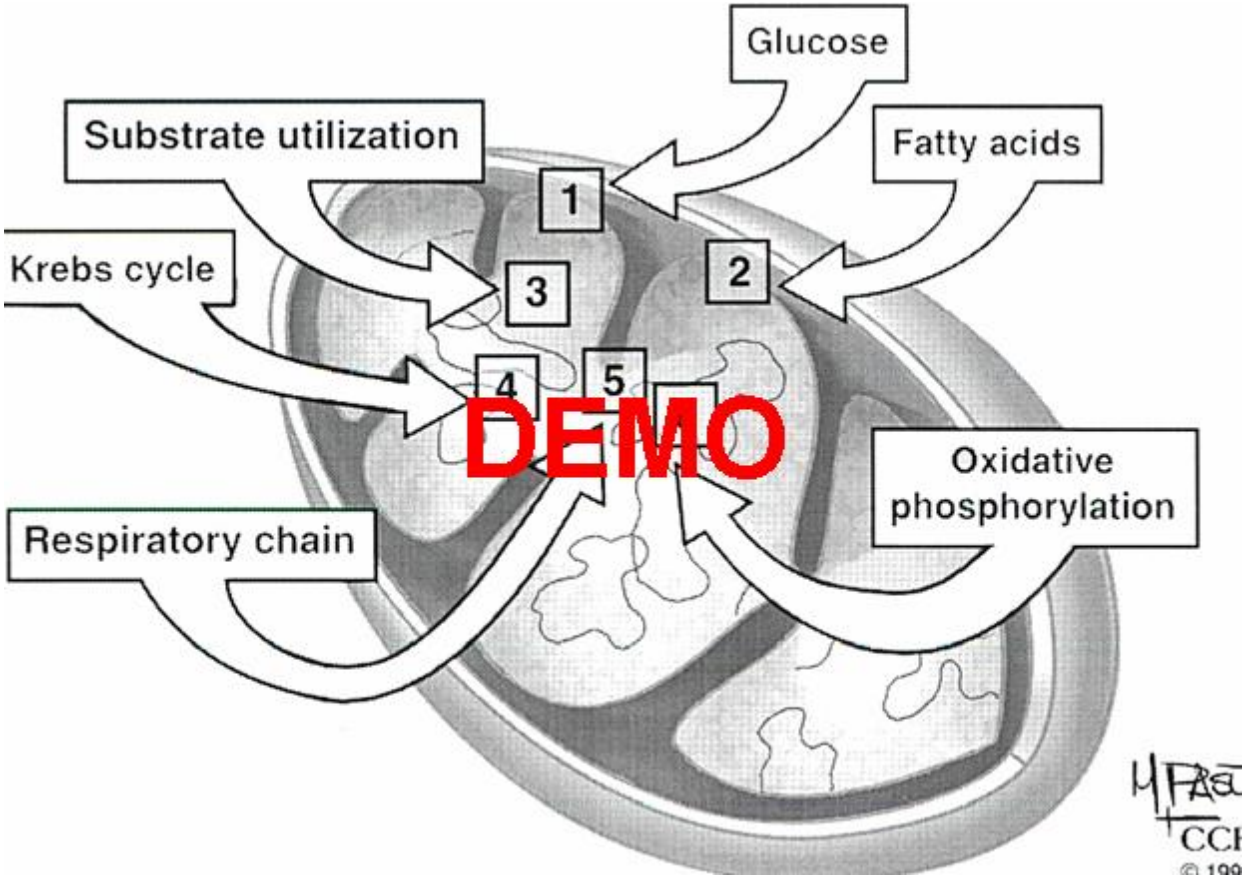
Bioenergetics: Energy

- 1 teaspoon of sugar weighs 5 gm and contains 20 calories of energy
- 1 teaspoon of sugar contains 10×10^{21} molecules of sugar or sucrose
  - 10,000,000,000,000,000,000,000 molecules
- 1 teaspoon of sugar forms about 3.6×10^{23} molecules of ATP
  - 360,000,000,000,000,000,000,000 molecules

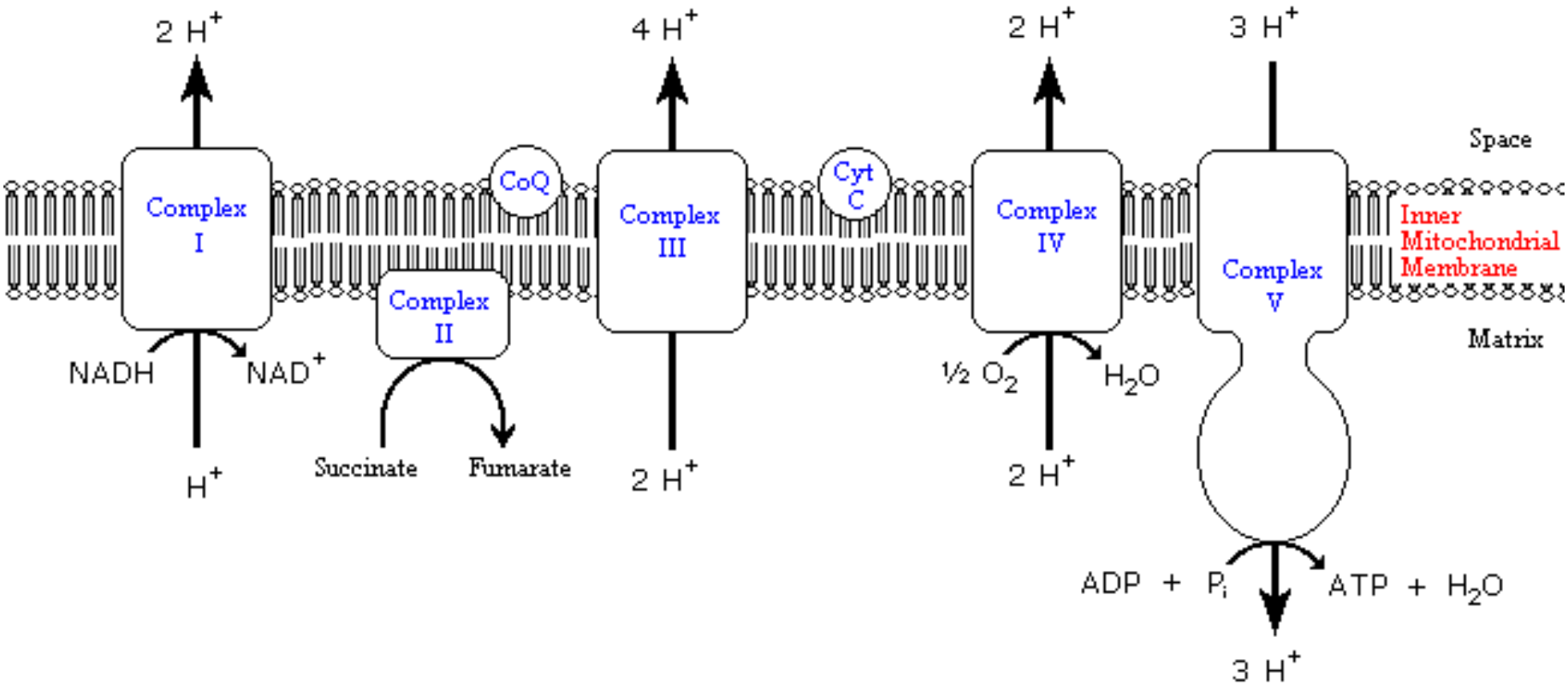
Bioenergetics: Energy

- At rest, the average adult male will need 3.0×10^{18} molecules of ATP per second for normal organ functioning.
- The body produces and makes approximately 70 Kg of ATP daily (average adult male).
- The brain uses approximately 70% of all ATP produced.

Bioenergetics



Bioenergetics



Bioenergetics: Summary

- Mitochondria function is to produce ATP for energy.
- The mitochondria use electrons and protons from metabolism and molecular oxygen to reduce water and generate proton-motive force to produce ATP from ADP: oxidative phosphorylation.
- When this process is dysfunctional, then disease can occur.
- Bottomline: mitochondrial cytopathies are diseases of energy production.

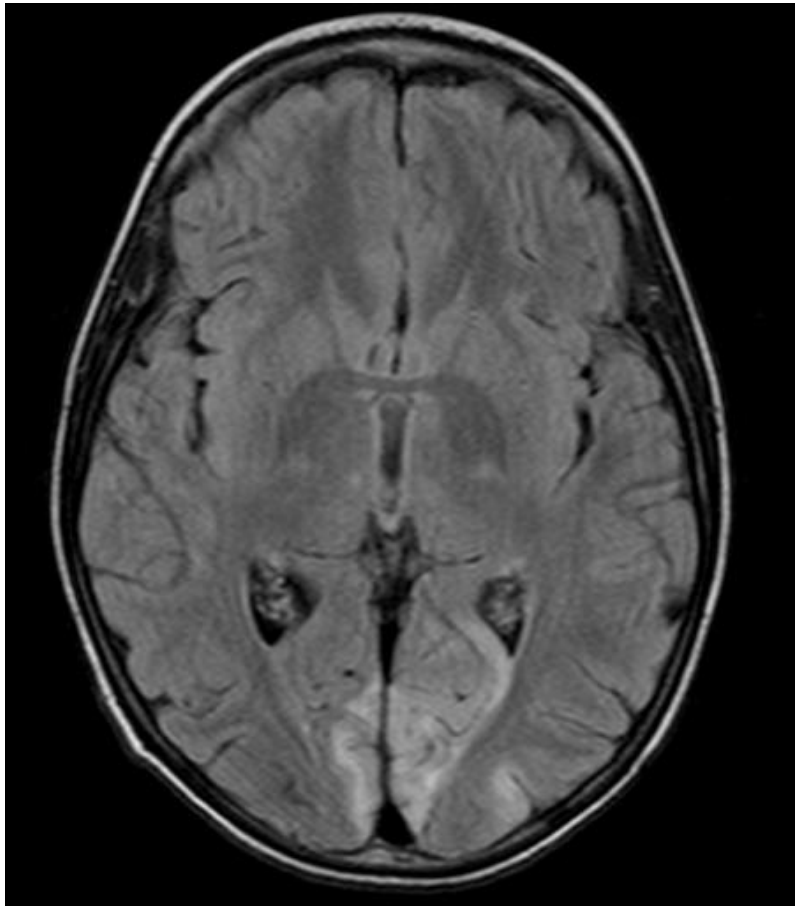
Bioenergetics: Summary

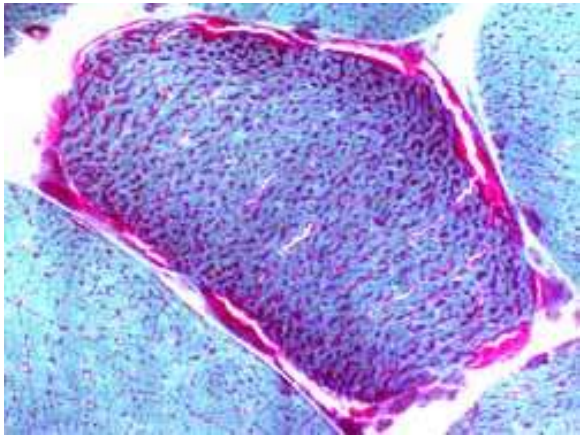
- What happens when an organ does not get enough ATP or energy?
  - Brain dysfunction: when the brain doesn't get it's 70% of energy required:
    - Seizure
    - Mental Retardation
    - Cognitive dysfunctions
    - Psychological dysfunctions?

History: Bioenergetics

- 1924: Warburg: Cell Respiration
- 1929: Lohmann: Discovery of ATP
- 1929: Warburg and Negelein: Oxidation-Reduction Processes
- 1957: Krebs and Kornberg: Oxygen Consumption and ATP
- 1961: Mitchell: Chemiosmotic Theory

History: Disease





History: Disease

- 1962: Luft et al. (J Clin Invest 1962;41:1776)
  - Described a woman having a hyper-metabolic state, structurally abnormal mitochondria, and abnormalities of oxidative phosphorylation.
- 1963: Nass and Nass (J Cell Biol 1963;19:593)
  - Described mitochondrial DNA.

History: Disease

- 1963: Engle and Cunningham (Neurology 1963;13:919)
  - Described ragged red fibers.
- 1988: First description of mitochondria DNA mutations, insertion-deletions and base substitutions, causing disease.
  - Kearns-Sayre/Chronic progressive external ophthalmoplegia (Holt et al., Nature 1988;331:717).
  - Leber's Heredity Optic Neuritis (Wallace et al., Science 1988;242:1427).

Mitochondrial Cytopathies

- Why call the disease mitochondrial cytopathy?
  - "Mitochondrial encephalomyopathy" limits the true spectrum of the disorder. It encompasses more than just brain and muscle. Since all tissues transfer electrons from substrate to oxygen in the oxidative-phosphorylation reaction, a better name for the disorders of energy or bioenergetics would encompass all tissues.

Epidemiology

Are these diseases common?

Epidemiology

- Three large studies looking at the prevalence of mitochondrial disorders have shown:
  - The majority of adults with mitochondrial disease have an underlying mtDNA mutation.
  - The majority of children with mitochondrial disease have an underlying nuclear DNA mutation.

Minimum Prevalence of Mitochondrial Electron Transport Chain Disease

		Prevalence/ 100,000	Approximate Disease Frequency
ADULTS	MtDNA Disease in North East England[1]	6.57 (5.30 – 7.83)	1 in 15,000
CHILDREN	ETC Disease in Victoria Australia[2]	4.7 (3.2 – 5.0)	1 in 21,000
CHILDREN	ETC Disease in Western Sweden[3]	4.7 (2.8-7.6)	1 in 21,000
TOTAL		**11**	**1 in 9,000**

1-Chinnery et al., Ann Neurol 2000; 2-Skladal et al., J Inher Metab Dis 2000; 3-Darin et al., Ann Neurol 2001

Epidemiology

- Disorders involving electron transport chain complex dysfunction or mtDNA mutations likely have a prevalence of 1/9000.
- However, primary mitochondria functioning involves more than just electron transport chain function.

Epidemiology

- Substrate Utilization (fatty acid oxidation)
  - SCAD
  - MCAD
  - LCAD
  - Trifunctional Protein/LCHAD
  - Carnitine deficiency
  - Carnitine palmitoyltransferase I and II
- Cofactor production
  - Pyruvate dehydrogenase complex
  - Kreb cycle intermediates
- Defects in the mitochondria lipid milieu
  - G4.5-acyl-coenzyme A synthetase (tafazzins) that are involved in cardiolipin synthesis (Barth syndrome).
- Defects in mitochondrial protein importation
  - TIMM8A-encodes deafness-dystonia protein a component of the mitochondria import machinery.
  - HSP60-import chaperon associated with hereditary spastic paraplegia.

Epidemiology

- Defects in mitochondrial motility
  - OPA1-mitochondrial dynamin-related guanosine triphosphatase (AD form of optic atrophy).
- Defects in intergenomic signaling
  - Nuclear control of factors needed for mitochondria integrity and replication.
    - Mutations in the mitochondria-specific **DNA polymerase gamma** (progressive external ophthalmoplegia).
    - Mutations in **thymidine phosphorylase** (MNGIE).

Epidemiology

- Structural proteins of the mitochondria
  - SURF1 gene-involved in assembly of complex IV (Leigh disease).
  - SCO2 and COX15-involved in synthesis of complex IV (infantile cardiomyopathy and brain disease).
- Cation homeostasis
  - Iron
    - Friedreich Ataxia
    - Neurodegeneration with brain iron accumulation (NBIA) mutation in pantothenate kinase 2 (Hallervorden-Spatz).
  - Copper
    - Wilson disease
  - Calcium
    - Apoptosis

Epidemiology

- If one just thinks of electron transport complex dysfunction, then mitochondrial cytopathies would be the most frequent inborn error of metabolism (Smeitink, J Inherit Metab Dis 2003;26:199).
- If you include genes involved in mitochondrial biogenesis and maintenance, then some think the prevalence is much higher, up to 1/1000 (Naviaux and Shoffner, personal communication).

Clinical Manifestion of Mitochondrial Dysfunction

Multiple organ disease

Mitochondrial Cytopathies: Clinical Features

- CNS
  - Myoclonus
  - Generalized Seizures
  - Stroke
  - Migraine Headache
  - Ataxia
  - Mental Retardation
  - Psychiatric Disease (?)
- Skeletal Muscle
  - Myopathy (hypotonia)
  - CPEO
  - Recurrent Myogloburia
  - Weakness/Fatigue
- Bone Marrow
  - Siderblastic Anemia
  - Pancytopenia
- Renal Function
  - Fanconi Syndrome
- Systemic Symptoms
  - Lactic Acidosis
  - Short Stature
  - Fatigue
  - Failure to Gain Weight
  - Asthma
  - Intermittent Air Hunger

Mitochondrial Cytopathies: Clinical Features

- Endocrine
  - Diabetes Mellitus
  - Hypoparathyroidism
  - Exocrine Pancreatic Failure
  - Thyroid Disease
- Heart
  - Cardiomyopathy
  - Conduction Defects
- Vision
  - Optic Neuropathy
  - Retinitis Pigmentosa
- Hearing
  - High-frequency Hearing Loss
  - Aminoglycoside-induced Deafness
- Gastrointestinal
  - Pseudo-obstruction
  - Constipation
  - Vomiting
- Liver
  - Hypoglycemia
  - Gluconeogenic Defects
  - Liver Failure and Cirrhosis

Case: Family with disease

- Family members with progressive external ophthalmoplegia (CPEO). (Suomalainen et al., Neurology 1997;48:1244)
- Pedigree demonstrated autosomal dominant transmission, linked to chromosome 10q 23.2-24.3.
  - Multiple deletions of mitochondrial DNA.
  - Likely a primary defect in a nuclear gene, which results in multiple deletions in mitochondrial DNA.
  - Mutation in polymerase gamma.

Case: Family with disease

- Clinical expression of the disease
  - Grandmother with the disease.
  - First Generation: 3/5 of her sons; 2/3 of her daughters with the disease.
  - Second Generation: 6/9 boys; 0/5 girls with the disease.
- Disease symptoms
  - Ptosis, ophthalmoparesis, and muscle weakness.

Case: Family with disease

- Examinations
  - MRI of brain:
    - 1 member had abnormal scan-hyperintensity in the lentiform nuclei, others were normal.
  - Blood work:
    - Lactate acidemia in 3 patients, others were normal.
  - Muscle:
    - Electron transport chain enzymatic activities were not significantly decreased.
    - Abnormal mitochondria in all affected siblings and in 4 asymptomatic siblings.

Case: Family with disease

- Examinations (continued)
  - Brain mtDNA studies
    - Autopsy-derived tissue from two affected siblings.
    - Basal ganglia (caudate) 60% of mtDNA, frontal cortex > 50% mtDNA, cerebellum 10% mtDNA of total mtDNA.

Case: Family with disease

- Psychiatric evaluation
  - 7/11 of the siblings with mtDNA deletions in their muscle, filled the criteria for psychiatric diagnosis by DSM-IIIR criteria.
    - 4 had avoidant personality traits.
    - 1 had avoidant personality disorder.
    - 1 had major depressive disorder with histrionic features.
    - 1 had major depressive disorder with psychotic features.

Case: Family with disease

- Psychiatric evaluation
  - 6 of the family members without mutant mtDNA:
    - 1 had personality disorder (explosive behavior) and depression.
    - 1 had dysthymia and depression.
    - 1 had a past stress-induced depression NOS.
    - None had avoidant personality features.

Case: Family with disease

- Is there a possible connection with mitochondrial cytopathy and psychiatric disease?
  - 2 of the patients with mtDNA mutations expressed their disease before the clinical manifestations became apparent. Not likely disease induced.
  - Avoidance may be inherited, and in families of patients with unipolar major depression, 2% of relatives have avoidant traits.
    - This family has a frequency of 50% of avoidance and depression.

Case: What does it show us?

- Mitochondrial disease can express psychiatric abnormalities.
- There were 4 asymptomatic siblings with mtDNA mutations.
  - Why would some patients with mtDNA mutations not express the disease?
- Different brain regions had varying amounts of mtDNA mutation percentages.
  - If genetic defect is nuclear, then why the variability?

Have I lost anyone?

Mark J. Terrill / AP file

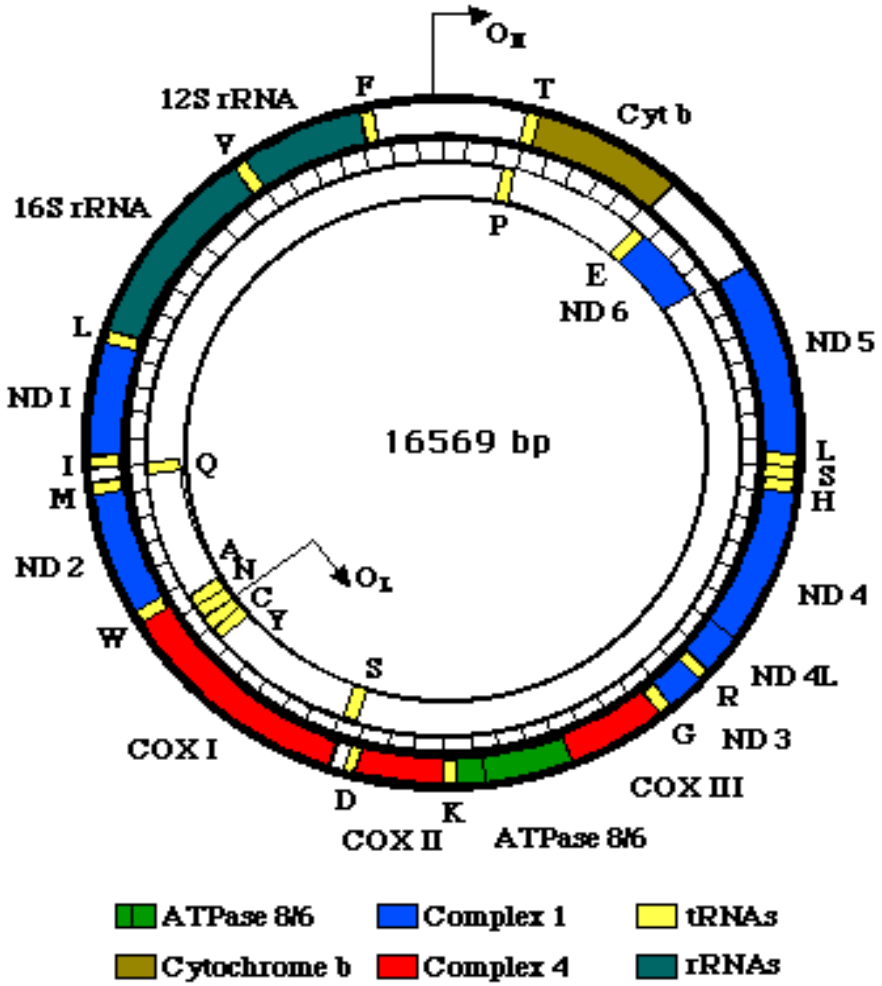
Phenotypic Variability

Phenotype and Genotype

Phenotypic Variability

- How can a simple dysfunction in production of ATP induce such a variety of clinical phenotypes?
  - Mitochondrial DNA
  - Cell biology of mitochondrion
  - Mitochondrial inheritance

Mitochondria DNA: Basics



Mitochondria DNA: Basics

- Unique DNA structure
  - Double stranded polycistronic circular DNA
    - 16.5 kb in length
  - Genes for only protein synthesis and electron transport chain (ETC)
    - 22 tRNAs (distinct genetic code)
    - 2 rRNAs
    - 13 subunits of the electron transport chain

Mitochondria DNA: Basics

- Polycistronic genes
  - $tRNA^{leu}$ is also the terminator of transcription.
- Few introns
- Multiple copies of mtDNA genome per mitochondrion (2-10 copies)
- All mtDNA is maternally inherited.
  - Sperm mtDNA is ubiquitinated and degraded.
  - One case report of paternally inherited mitochondrial cytopathy, so paternal inheritance is possible.

Mitochondria DNA: Basics

- Symbiotic relationship with nuclear DNA products
  - Replication of mtDNA is controlled by nuclear DNA products
  - Transcription of mRNA is polycistronic and RNA endonucleases are nuclear DNA products
  - DNA repair mechanisms are nuclear DNA products

Mitochondria DNA: Basics

- mtDNA replication is not strictly coupled to S phase
- Mutation index is likely higher than for nuclear DNA
  - Oxidative process generates free radical formation and possible DNA damage
  - Few introns, therefore mutational damage to exons is greater
  - Fewer DNA repair mechanisms

Mitochondria DNA: Basics

- Complementation of mtDNA
  - Nakada et al., (2001) Nature Medicine 7:934
  - They introduced COX^- (complex IV) mitochondria into COX^+ mitochondria and wild-type mtDNA zygotes, and created transgenic mice (using cybrids introduced with COX^- and electofusion COX^+ zygotes).

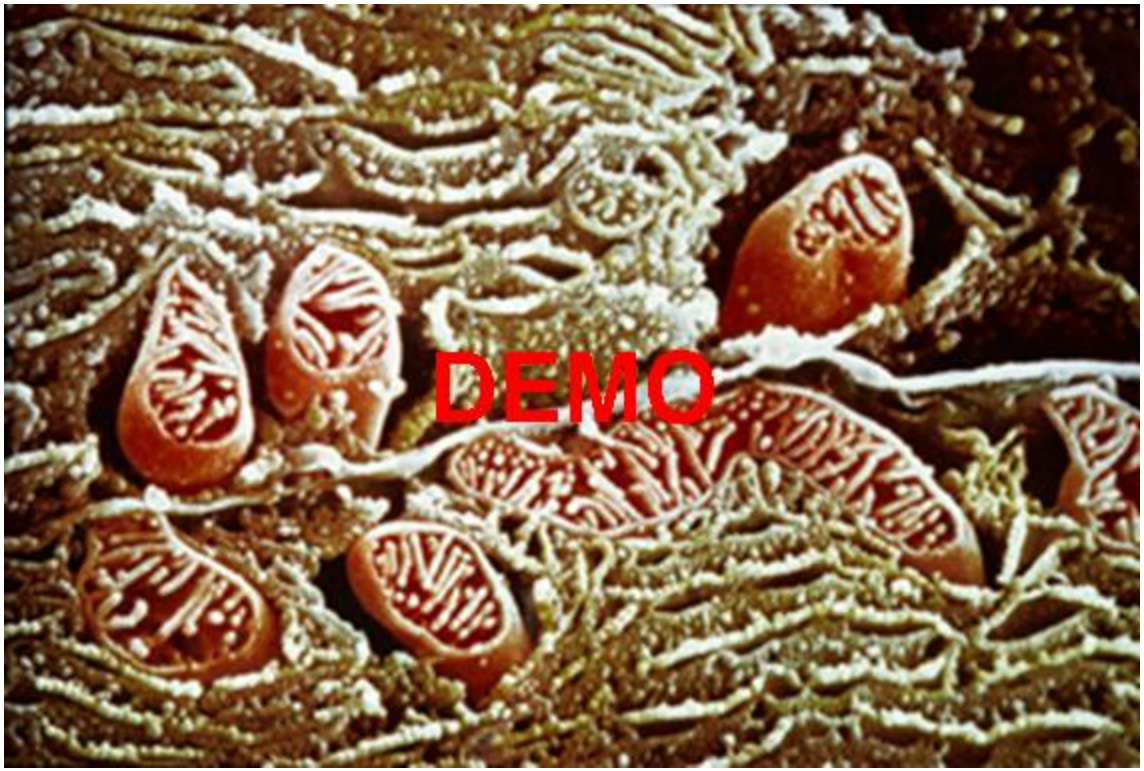
Mitochondria DNA: Basics

- Complementation of mtDNA (cont'd)
  - They did not observe co-existence of COX^- and COX^+ mitochondria within single cells.
  - However, mitochondrion with large (>60%) COX^- mtDNA became uniformily negative for staining.
    - Less than 60% remained stained for COX^+.
  - This would indicate that complementation took place at a genetic level and within a particular organelle.

Mitochondria DNA: Basics

- Complementation of mtDNA (cont'd)
  - Also, data gives evidence that "threshold" is found at the mtDNA level in a particular mitochondrion.
- Stochastic redistribution of mtDNA
  - At mitochondrion organelle division, redistribution of daughter mtDNA is random and therefore, proportion of mutated mtDNA per organelle is random.

Cell Biology of Mitochondria



Cell Biology of Mitochondria

- Multiple mitochondrion per cell
- Complementation
- Heteroplasmy
- Threshold
- Stochastic Redistribution
- End Organ Susceptibility

Cell Biology of Mitochondria

- Multiple mitochondrion per cell
  - Varies between 100s to 1000s, depending on energy demand.
- Complementation
  - As with mtDNA, normal mitochondria can complement or "normalize" abnormal mitochondria function within a cell. As with mtDNA, there is a threshold effect. Mitochondria with ETC dysfunction can also complement one another with mitochondria proliferation to compensate for mildly compromised ATP production.

Cell Biology of Mitochondria

- Homoplasmy
  - Homoplasmy is a condition of complete "wild type" or normal mitochondra per cell. It can also be completely abnormal mitochondria per cell (at the mtDNA and organelle level).
- Heteroplasmy
  - Presence of both normal and abnormal mitochondria within a cell or organ.

Cell Biology of Mitochondria

- Threshold
  - The energetic minimum at which a cell or organ or organism needs to function.
    - Changes during development
    - Changes during stress or illness (i.e. brown outages during peak electrical use)
    - Varies between organs (e.g. brain activity versus mature epidermal cell)
  - High energy demand tissues/states are more sensitive to heteroplasmy.

Cell Biology of Mitochondria

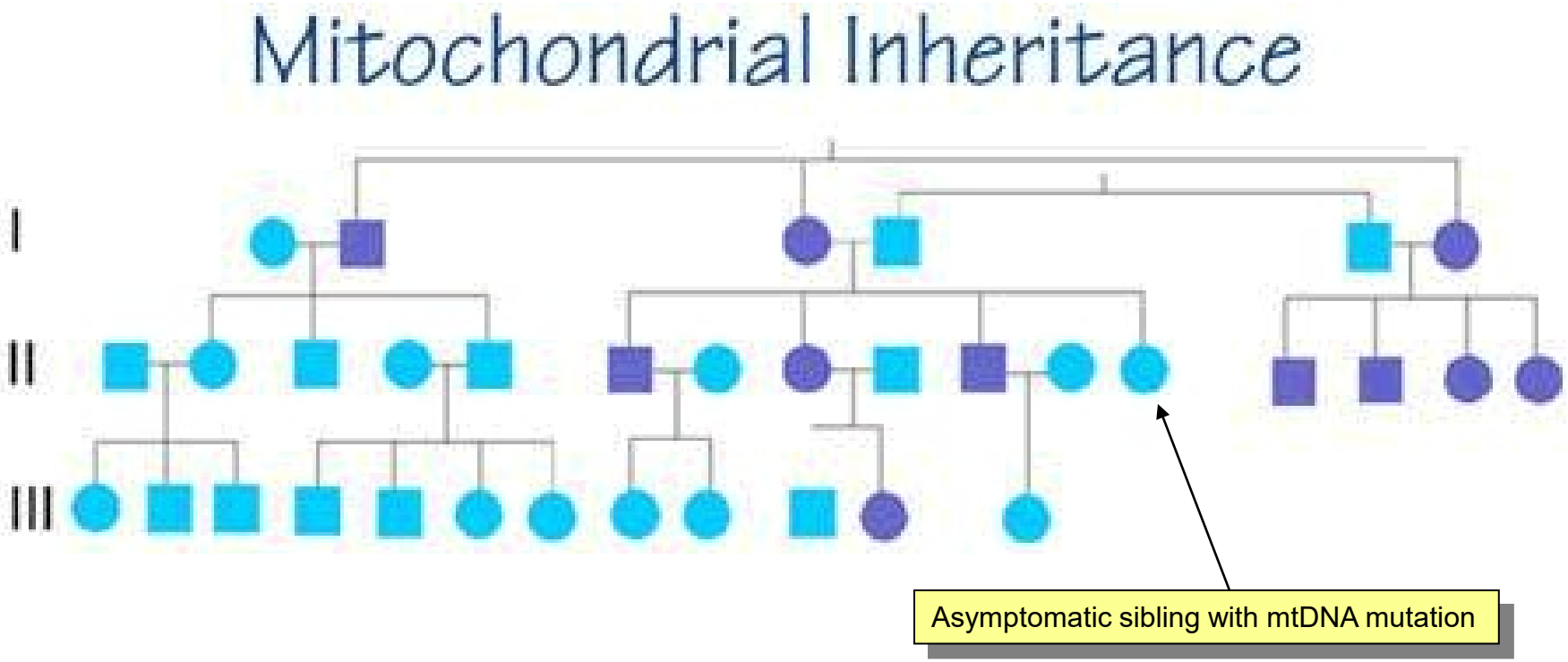
- Stochastic Redistribution
  - At cell division, redistribution of mitochondria is random.
  - This changes the degree of heteroplasmy from cell generation to cell generation.
  - Obviously, those cells that do not undergo cell division do not change their heteroplasmy by redistribution.
    - Brain and muscle.
      - Collect abnormal mitochondria.

Cell Biology of Mitochondria

- Organ Susceptibility
  - Dividing cells tend to select against abnormal mitochondria.
  - Non-dividing cells tend to collect abnormal mitochondria.
  - High energy demanding organs are more sensitive to heteroplasmy
  - Conditions of growth, stress, and illness lower threshold for bioenergetic disease.

Mitochondrial Inheritance

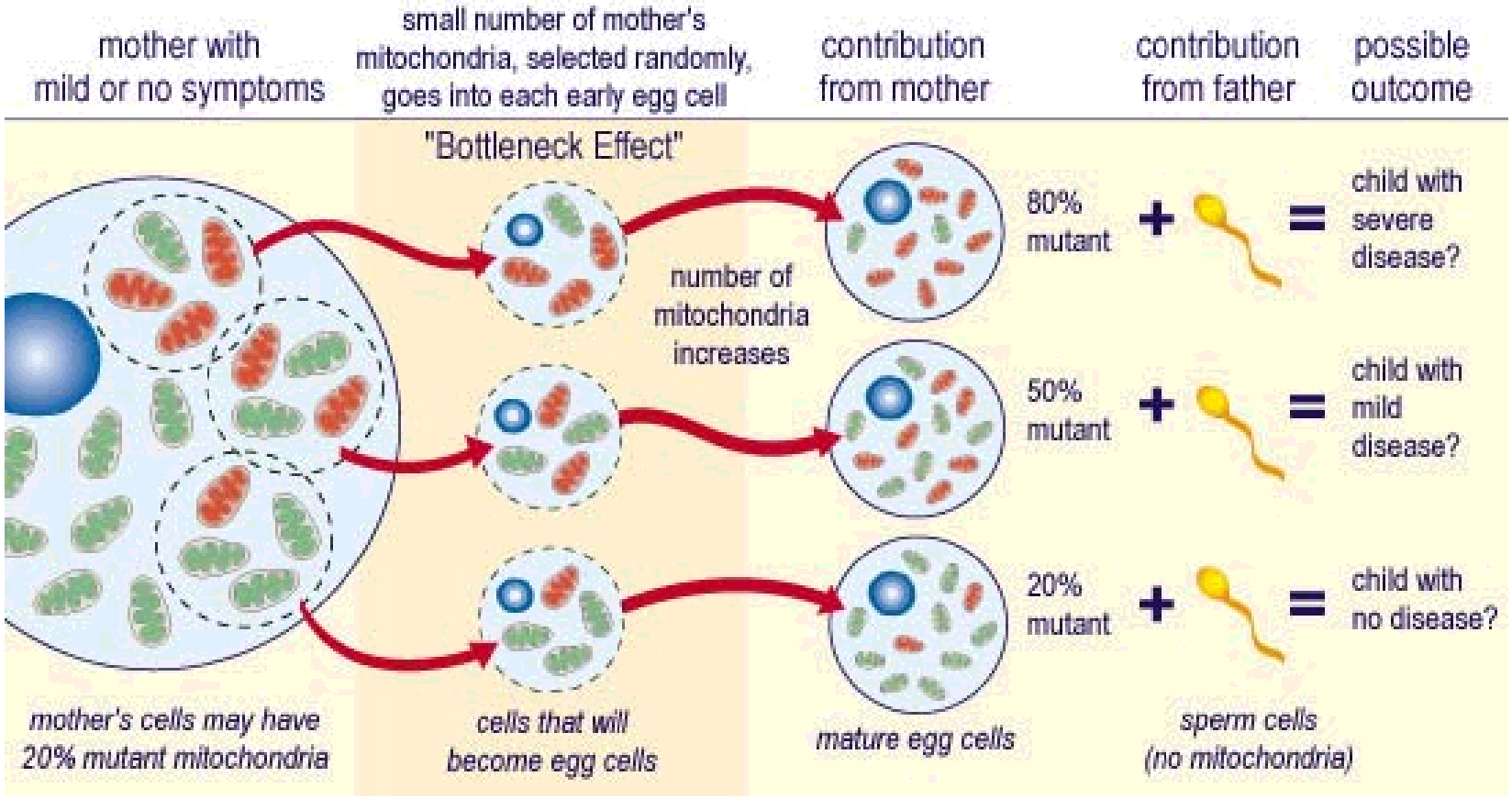
Mitochondrial Inheritance Patterns



Mitochondrial Inheritance

- Remember our family with CPEO:
  - Grandmother had the disease.
  - Some of her offspring had the mtDNA mutations but not the disease.
  - If all mitochondria are inherited from the mother, why did only some of the offsprings have the disease?
    - Threshold, complementation, and ….

Mitochondrial Inheritance



Mitochondrial Inheritance

- Paternal mtDNA is ubiquitinated and degraded.
- Oogenesis-”bottleneck” effect where random selection of mitochondria occurs, thereby changing heteroplasmy.
- Theoretically, only mothers can pass on mtDNA traits.
  - All children would receive mtDNA mutation.

Mitochondrial Inheritance

- Therefore, clinical expression of a genetic disorder comprises both unique gene inheritance (mitochondria) and standard autosomal and x-linked processes.
- Clinical expression of the disease represents the integration of both unique and common genetic processes, and the unusual cell biology of mitochondria.

Have I lost anyone?

Putting it all together

- CC: 12 year old girl with rapid cycling bipolar disease.
- HPI: Mood difficulties began at the age of 8 years with diagnosis of bipolar disease made at 9 years of age. Seizure started at 10 years of age. Academic achievement has been very good but her work toward these goals was often obsessive. She has shown some decline in academics over the last 2 years. Her motivation to be socially accepted has deteriorated.

Case

- HPI: She has shown decline in coordinated motor movements with increased clumsiness.
- PMHx: Chronic constipation (multiple episodes of fecal impaction), hypothyroidism, and seizures.
- Family Hx: Lives with mother and two siblings.
  - Mother has neuropathy of unclear etiology.
  - Brother has been diagnosed with ETC complex III dysfunction and myopathy. (brother has a different father)
  - Sister has just been diagnosed with bipolar disorder.

Case

- PE:
  - CN II-XII intact
  - Motor: Axial hypotonia
  - DTRs: Trace in all tendons tested
  - Cerebellar: Normal
- Neuroimaging
  - Normal MRI

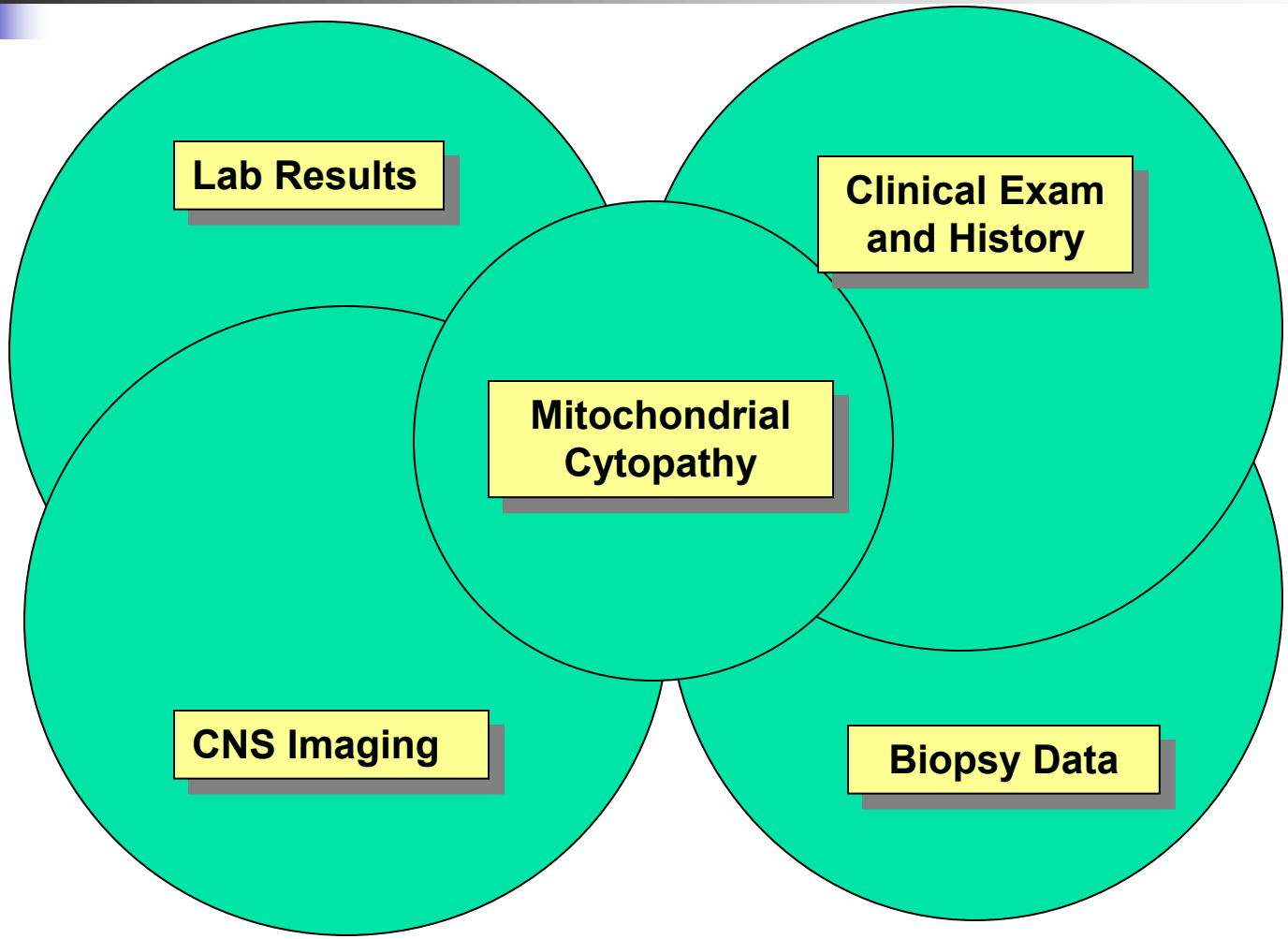
Case

- Labs
  - Elevated lactate > 2 blood draws.
  - Elevated alanine.
  - Reduced level of free carnitine.
  - Presence of ethylmalonic acid in urine organic acid profile.

Case

- Muscle biopsy
  - Decreased activity of complex III of the electron transport chain.
  - Normal mtDNA
  - Normal histology on light microscopy examination.

Diagnosis of Mitochondrial Cytopathies



Case

- Our patient has a mitochondrial cytopathy:
  - PE: Hypotonia, decreased DTRs
  - Systemic involvement: Hypothyroidism, chronic constipation, bipolar disease, seizures
  - Muscle: ETC abnormality
  - Family Hx: Brother with ETC abnormality, mother with neuropathy

Important points

- Diagnosis is not based on a single test, but using multiple tests.
  - History, Physical exam, Lab, Neuroimaging, & Muscle biposy.
- Note that there is multi-systemic illness that is not unified by a single syndrome or disease.
- Our patient had less muscle findings and more CNS and systemic findings than our first family case.
  - Variation in phenotypic presentation.

Important Points

- Mitochondrial Cytopathies
  - Suspect when > 2 unrelated organ systems are involved.
  - Suspect when inheritance seems maternal.
  - Suspect when the neurological exam seems paradoxical.
  - Suspect when the usual presentation of a syndrome is not “usual” and history is suspect for a bioenergetic disorder.

Important Points

- Diagnosis of a Mitochondrial Cytopathy
  - History (history, history, history)
  - Good neurological examination
  - Multiple labs (best drawn when ill)
  - Subtle findings, even within the "normal range"
  - No standard, therefore, clinical acumen of extreme importance

Conclusions

- Psychiatric disorders may be associated with a mitochondrial cytopathy.
- Mitochondrial cytopathies are common diseases.
- Phenotypic expression of mitochondrial diseases are varied and high index of suspicion is necessary for diagnosis.
- When greater than two systems are involved without a logical explanation, think of mitochondrial disease.

References

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