The Elevated CK

ROBERT HAWKINS, M.D.

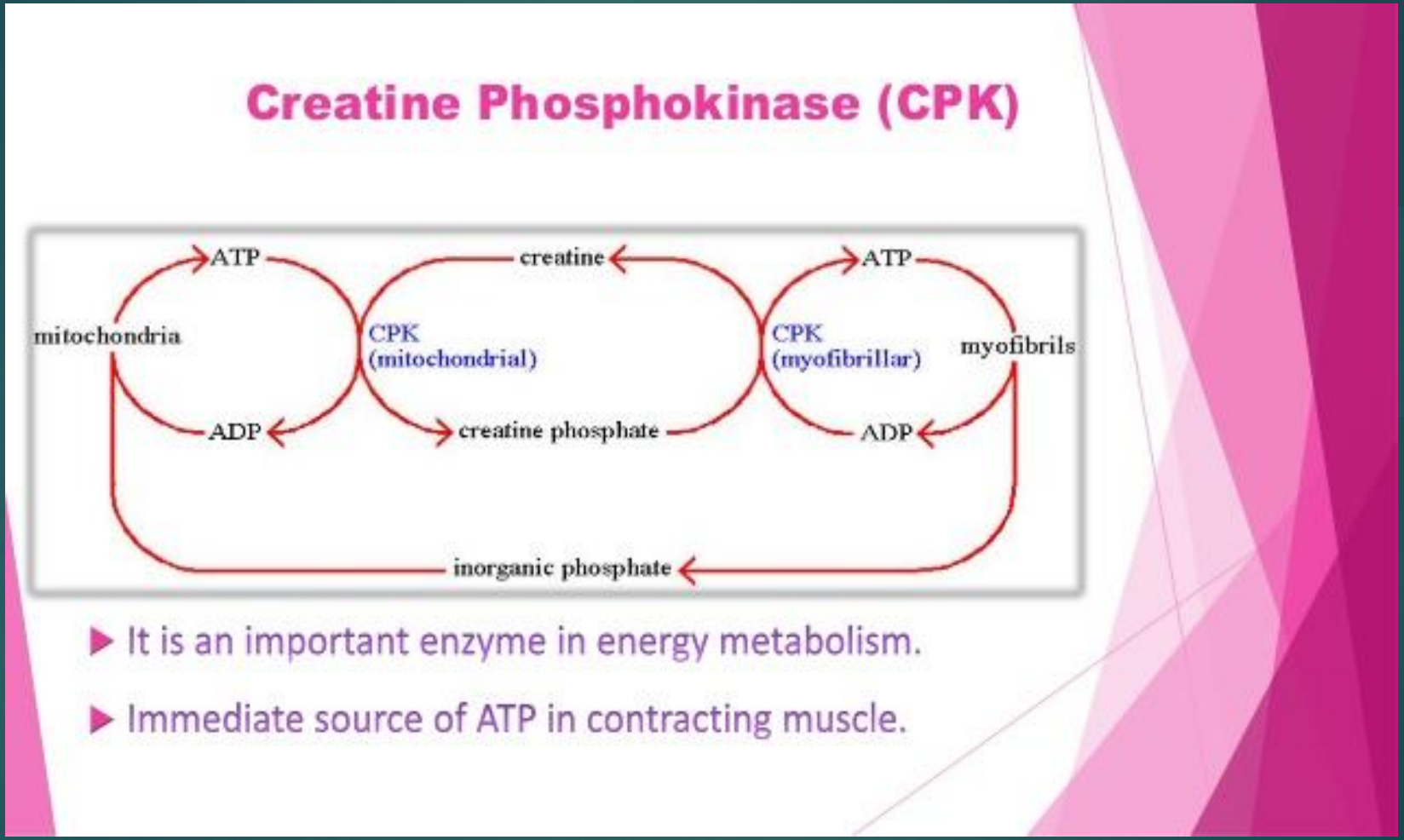
What is the difference between “CK” and “CPK”

- One has a “P” in it.
- One has “kinase” in it, the other has “phosphokinase” in it.
- There is no true difference.
  - A kinase is, by definition, an enzyme that phosphorylates a molecule.
  - So Creatine *Phosphokinase* is redundant.
- Like saying “Overbinging.”
- So just say CK.

What is the difference between “CK” and “CPK”

- The One Exception

What does CK do?



Where is CK located? Are there different isomers?

- CK-MM Skeletal muscle
  - Injury
  - Inflammation
- CK-MB Cardiac muscle
  - Cardiac injury
  - Defibrillation
  - Cardiac surgery
- CK-BB Brain and Lungs
  - Brain cancer, injury, seizure, ECT
  - Pulmonary infarction

What about Ethnicity and Gender?

Do they influence serum CK values?

Which of these famous individuals is likely to have the highest CK?

Distribution of serum CK in different population groups

Sex and ancestry	N	Age	BMI	Serum CK distribution			>ULN (N percent) *
				2.5th percentile	Median	97.5th percentile	
All subjects¶	1411	45 (7)	27 (5)	40	111	460	508 (36)
Women	831	45 (7)	28 (6)	36	95	349	304 (37)
Men	580	46 (7)	26 (4)	51	143	616	204 (35)
White subjects	503	48 (7)	26 (5)	35	88	286	64 (13)
Women	252	47 (7)	26 (5)	29	72	201	21 (8)
Men	251	48 (7)	26 (4)	47	110	322	43 (17)
South Asian subjects	270	44 (6)	27 (5)	40	104	382	62 (23)
Women	147	45 (6)	27 (5)	37	87	313	23 (16)
Men	123	44 (6)	26 (5)	47	143	641	39 (32)
Black subjects	570	44 (6)	28 (5)	51	149	627	278 (49)
Women	387	43 (6)	29 (6)	48	124	414	164 (42)
Men	183	44 (6)	26 (4)	71	213	801	114 (62)

Data for age and body mass index (BMI) are means (SD). Data are rounded to the nearest integer. CK is expressed as international units per liter.

* Number (percentage) of participants with a CK above the ULN, as recommended by the manufacturer (140 IU/L for women, 174 IU/L for men; with appropriately established reference intervals, 2.5 percent of the subjects are expected to have values above the ULN).

¶ Including participants of "other" ancestry (n = 68), with the exclusion of outliers (n = 3, 1 South Asian and 2 black participants) and those using statins (n = 30, 21 South Asian, 8 black participants, and 1 of other ancestry).

What is Rhabdomyolysis?

- Any process that damages muscle
- Any process that causes an elevated serum CK
- Any process that causes an elevated serum CK with myoglobinuria
- Any process that results in acute muscle damage
- Any process that causes persistent muscle damage

A Definition of Rhabdomyolysis

A Process of:

- *Acute* muscle necrosis
- *Five fold* elevation of CK above upper limit of normal
- *Maybe* myoglobinuria (seen in less than 50%)

CK and Myoglobin

CK

- Serum half life = 36 hrs
- Declines after reaching peak by 40%-50% / day

Myoglobin

- Serum half life = 2-3 hrs
- Serum levels may normalize in several hours

Myoglobinuria and the UA

- Serum level >1.5 mg/dl spills to urine
- Visible (Coke colored urine) >100-300 mg/dl
- Dipstick detects > 0.5-1.0 mg/dl
- Myoglobin *and* Hemoglobin detected as "blood"
- Absence of RBCs suggests myoglobin in urine
- Proteinuria seen in ½.
  - Myoglobin & other proteins from myocytes

The Elevated CK in the Hospital

Rhabdomyolysis in the Hospital*

Characteristic	
Age (yr) mean	47
Male	68%
Creatine Kinase IU/L (mean)	168,052
Creatine Kinase IU/L (range)	2,975 – 250,000
Urine myoglobin positive	19%
Multiple causes	60%
Acute renal failure	46%

*Rhabdomyolysis: An evaluation of 475 hospitalized patients. Medicine 2005;84(6):377-385

Rhabdomyolysis in the Hospital*

Primary Cause	%	Male %	Mean CK	Multiple Causes	ARF %
Illicit drugs/alcohol	34	82	17,781	80	65
Medical drugs	11	72	12,936	48	48
Muscle diseases	10	37	11,851	16	04
Trauma	09	58	9,779	68	45
Neuroleptic Malignant Syndrome	08	74	11,755	34	34
Seizures	07	75	22,001	72	38
Immobility	04	52	17,163	33	52

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Rhabdomyolysis in the Hospital*

Primary Cause	%	Male %	Mean CK	Multiple Causes	ARF %
HIV/AIDS	02	67	11,314	33	01
Metabolic Causes	02	56	13,989	44	01
ICU Myopathy	01	75	11,225	25	100
Exercise	01	56	13,989	68	45

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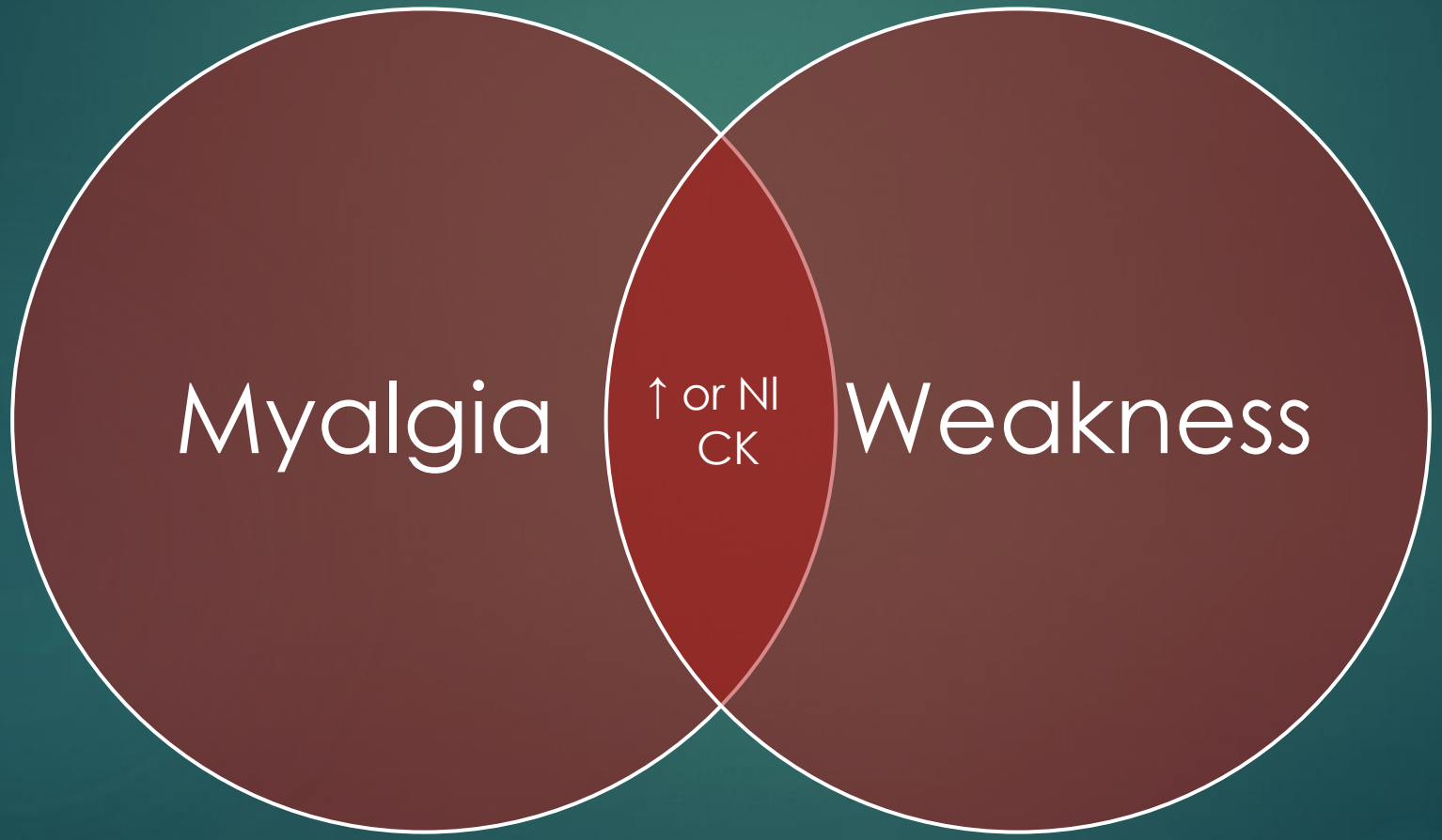
Statins in lipid Therapy

- HMG-CoA reductase inhibitors

Statin Myopathy:
A Spectrum Disorder

- Myalgia / Myopathy 2%-11%
- Severe myonecrosis 0.5%
- Rhabdomyolysis 0.1%

Statin Myopathy Clinical Findings



Statin Myopathy Risk Factors

- Higher doses
- Lipophilic vs hydrophilic
  - Lipophilic ↑ risk
    - Simvastatin
    - Lovastatin
  - Hydrophilic ↓ risk
    - Fluvastatin
    - Pravastatin
    - Rosuvastatin
- CYP3A4 metabolism
- Genetic
  - SLCO1B1 homozygotes
- Ethnic
  - Chinese / simvastatin niacin
- Age > 80 yrs
- Frailty
- Female
- Small body frame
- Liver / renal disease
- Concomitant drug therapy
  - Gemfibrozil, niacin, colchicine

Statins and the CYP3A4 System

Metabolized by CYP3A4

- Simvastatin
- Lovastatin
- Atorvastatin

Metabolized by Other

- Fluvastain
- Pravastatin
- Rosuvastatin
- Pitavastatin

Statins and the CYP3A4 System

Cytochrome P450 3A4 (CYP3A4) inhibitors and inducers*

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
Atazanavir	Amiodarone¶	Carbamazepine	Bexarotene
Boceprevir	Aprepitant	Enzalutamide	Bosentan
Ceritinib	Cimetidine¶	Fosphenytoin	Dabrafenib
Clarithromycin	Conivaptan	Lumacaftor	Dexamethasone¶
Cobicistat and cobicistat containing coformulations	Crizotinib	Mitotane	Efavirenz
Darunavir	Cyclosporine¶	Phenobarbital	Eslicarbazepine
Idelalisib	Diltiazem	Phenytoin	Etravirine
Indinavir	Dronedarone	Primidone	Modafinil
Itraconazole	Erythromycin	Rifampin (rifampicin)	Nafcillin
Ketoconazole	Fluconazole		Rifabutin¶
Lopinavir	Fosamprenavir		Rifapentine
Mifepristone	Fosaprepitant¶		St. John's wort
Nefazodone	Grapefruit juice		
Nelfinavir	Imatinib		
Ombitasvir-paritaprevir-ritonavir	Isavuconazole (isavuconazonium sulfate)		
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	Netupitant		
Posaconazole	Nilotinib		
Ritonavir and ritonavir containing coformulations	Ribociclib		
Saquinavir	Schisandra		
Telaprevir	Verapamil		
Telithromycin			
Voriconazole			

Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration. Specific drug interactions and management suggestions may be determined by using Lexi-Interact, the drug interactions program included with UpToDate. Refer to UpToDate topics on specific agents and indications for further details.

* The CYP3A4 inhibitors and inducers listed in this table are relevant for determining potential interactions of drugs that are CYP3A subfamily substrates.
¶ Weak effect on CYP3A4.

UpToDate®

Statin Myopathy Time Course

- Onset
  - Mean time to onset 6 months
  - Range 0.25 – 48 months
- Resolution
  - Mean time to resolution 2.3 months
  - Range 0.25 – 14 months

Does Statin Myopathy Always Resolve?

- Statin-associated immune mediated necrotizing myopathy
  - Antibody to HMG CoA reductase
  - Macrophage infiltrate engulfing necrotic muscle fibers
  - Responds to immunosuppressive Rx

Management of Suspected Statin Myopathy

- Stop the drug
- Look for co-conspirator drugs
- Evaluate for and treat AKI
- Consider restarting with statins not metabolized by CYP3A4
  - Fluvastatin
  - Pravastatin
  - Rosuvastatin

Other Prescribed Drugs

- Colchicine
- Anti-malarials
  - Chloroquine
  - Hydroxychloroquine
- Emetine
- Imatinib mesylate (Gleevic)
- Zidovudine
- Amiodarone
  - neuromyopathy
- Vincristine
  - Polyneuropathy
  - Rare myopathy

Colchicine Myopathy

- Acute overdose
- Chronic therapeutic doses
- Proximal muscle weakness
- ↑ CK 10-to 20 fold
- Bx Vacuolar changes

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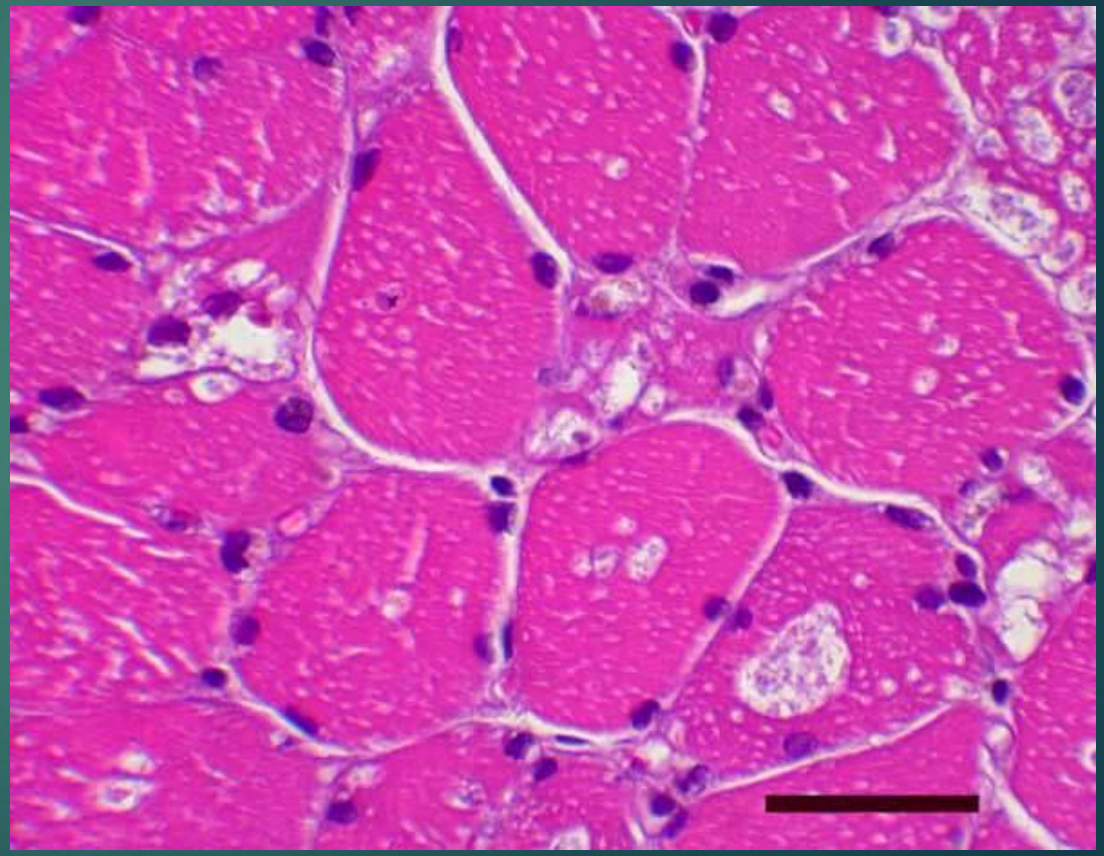
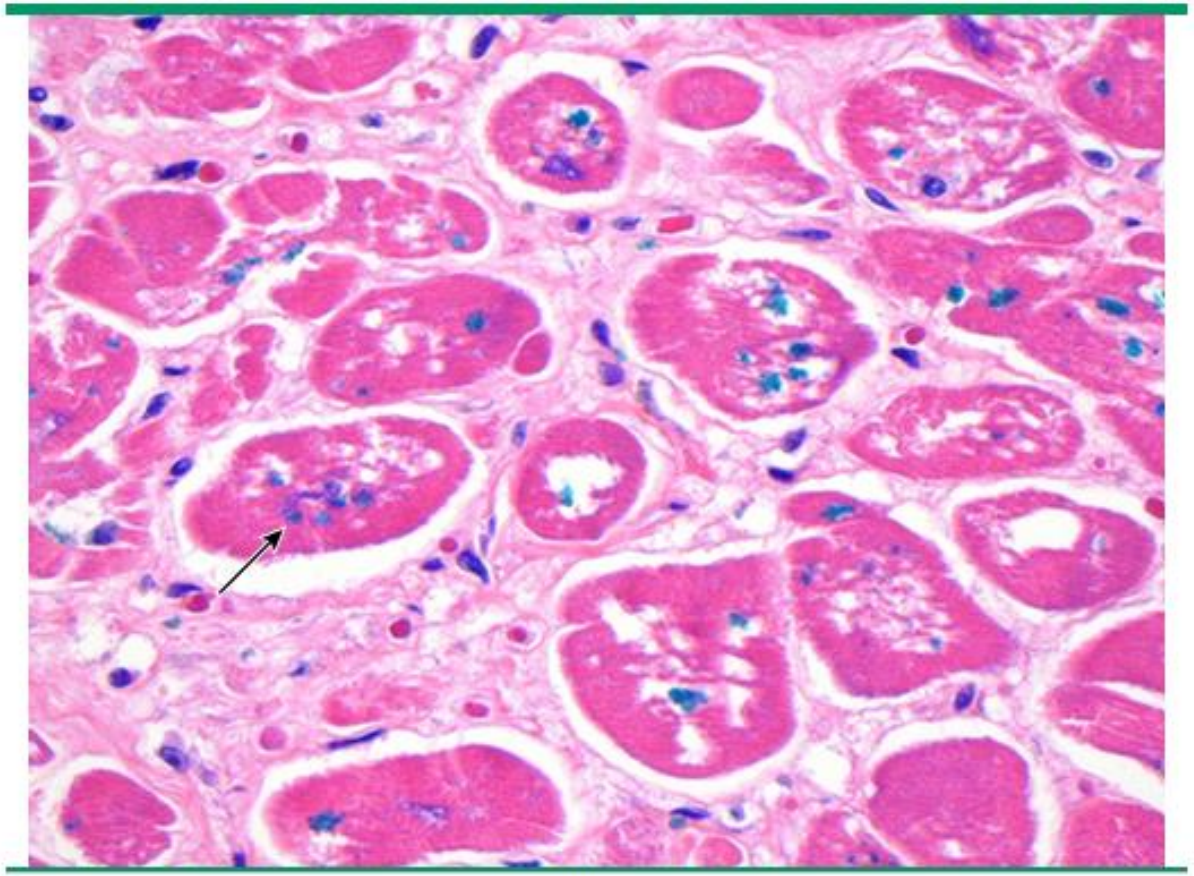


Antimalarial Myotoxicity Chloroquine Hydroxychloroquine

- Neuropathy
- Myopathy
- Cardiomyopathy
- Incidence unknown
  - Very low
- Clinical presentation
  - Proximal muscle weakness
  - Mild elevation of CK
  - Heart Failure
- Pathology

Hydroxychloroquine-induced cardiomyopathy showing cardiomyocytes with Luxol stain



The histopathology, using Luxol fast blue stain with 400x magnification, highlights the vacuolated myocardial cells which contain blue intracytoplasmic granules (arrow), characteristic of abundant lysosomes.

Courtesy of Aleksandr Perepletchikov, MD.

The "Malignant" Syndromes

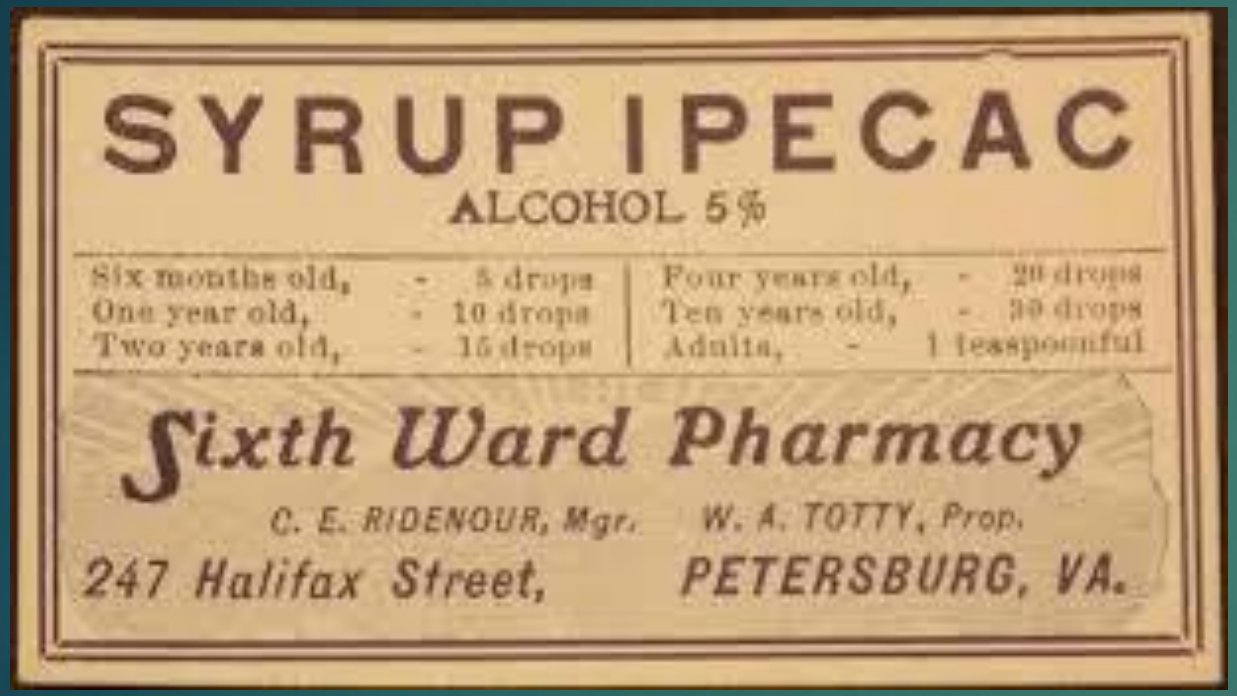
Neuroleptic Malignant Syndrome

- Neuroleptic medications
  - Haloperidol, fluphenazine
  - Less common
    - Chlorpromazine
    - Risperidone
    - Others
- Clinical findings
  - MS changes
  - Muscle rigidity
  - Fever
  - Autonomic dysfunction

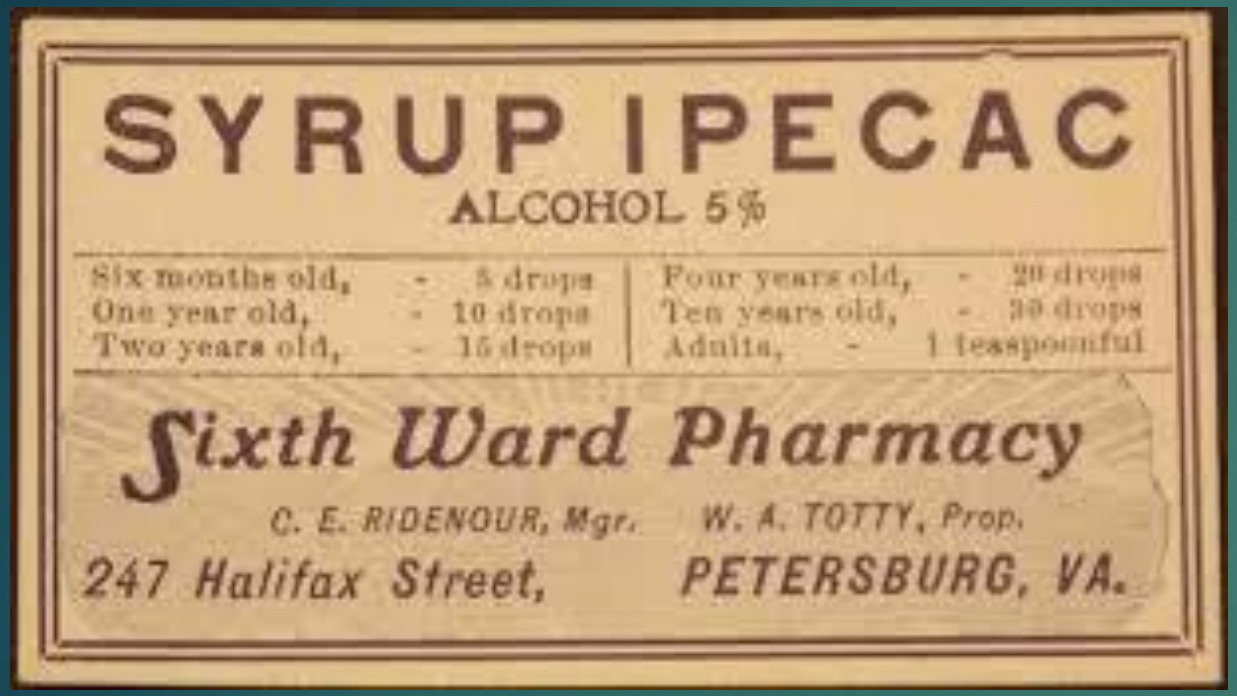
Malignant Hyperthermia

- Depolarizing muscle relaxants
  - Succinylcholine
  - Halothane
- Genetic susceptibility
- Clinical findings
  - Muscle rigidity
  - Fever
  - Cardiac arrhythmias

Emetine Myopathy



Emetine Myopathy



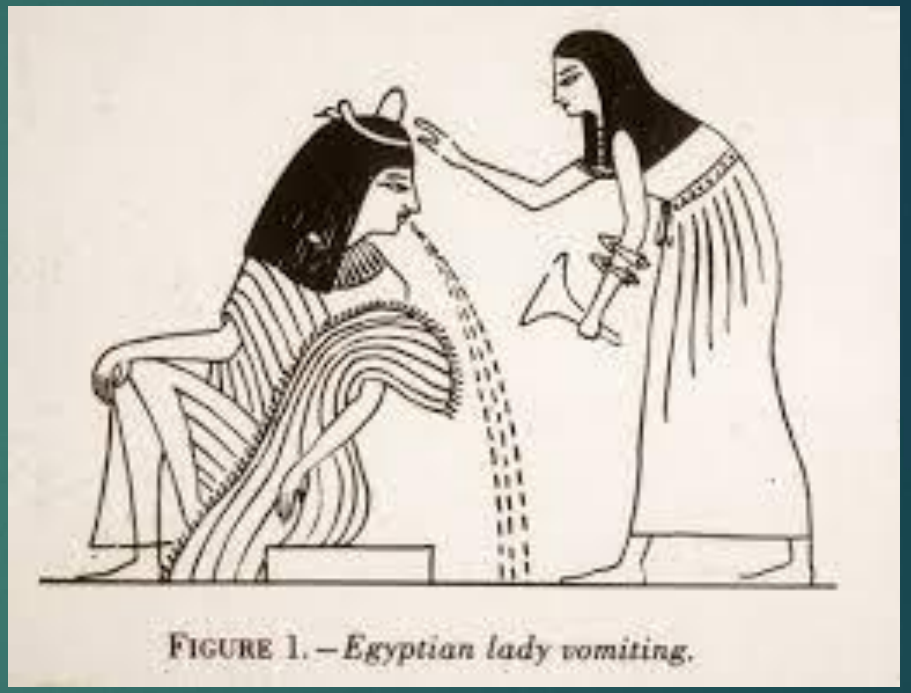


FIGURE 1.—*Egyptian lady vomiting.*

Emetine Myopathy

Karen Carpenter

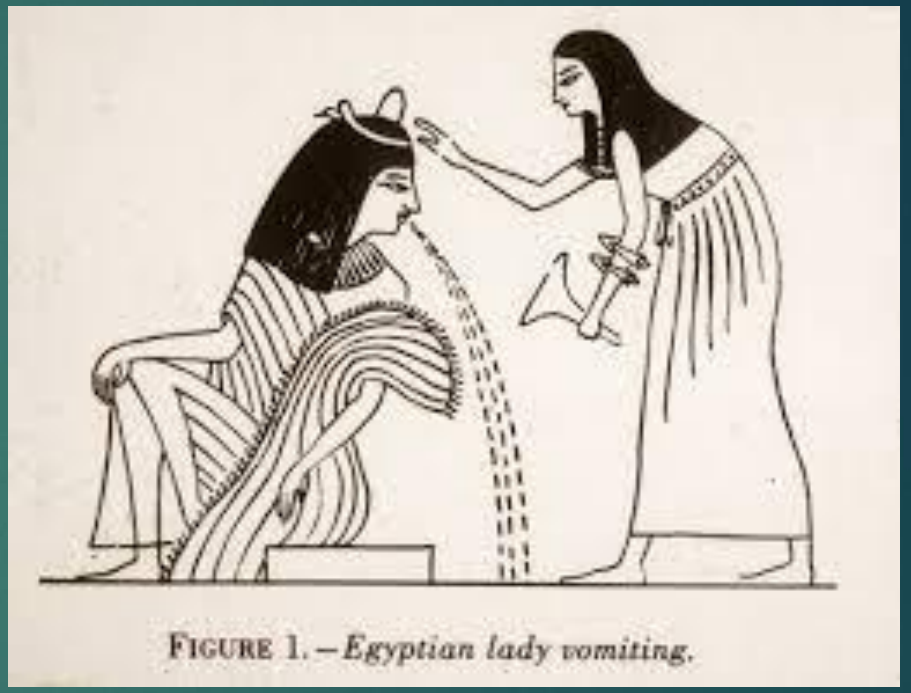
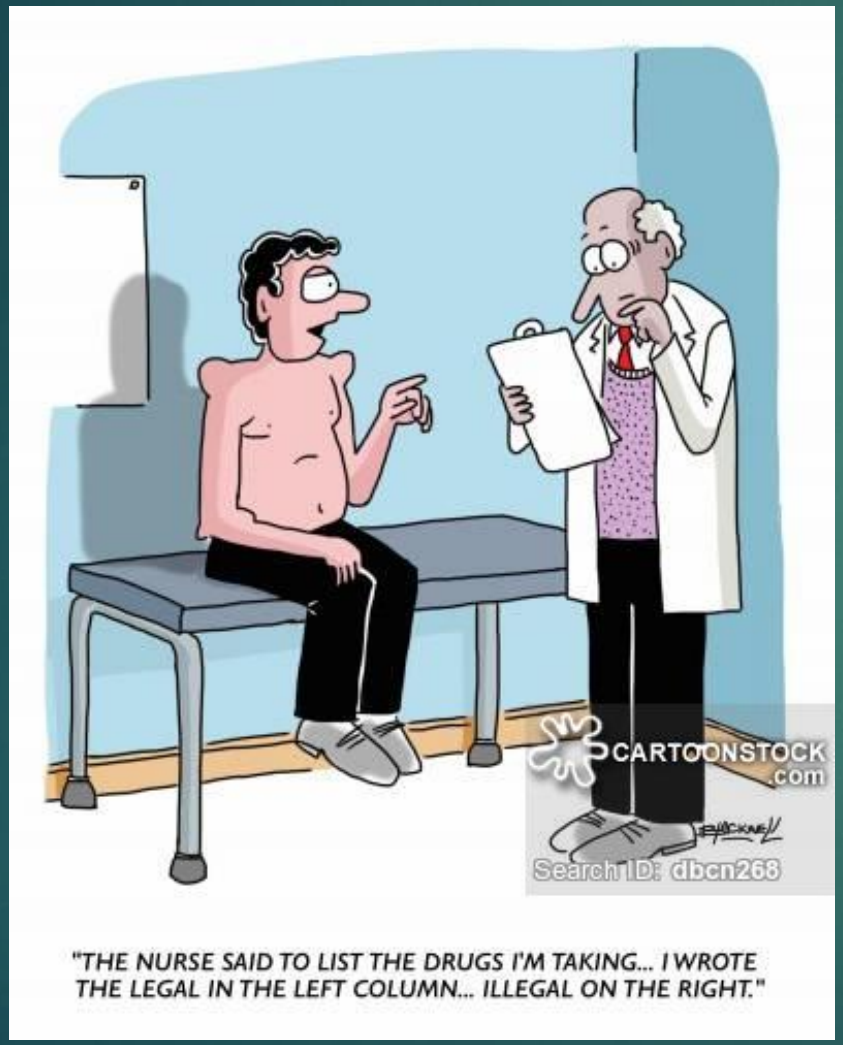


FIGURE 1.—*Egyptian lady vomiting.*

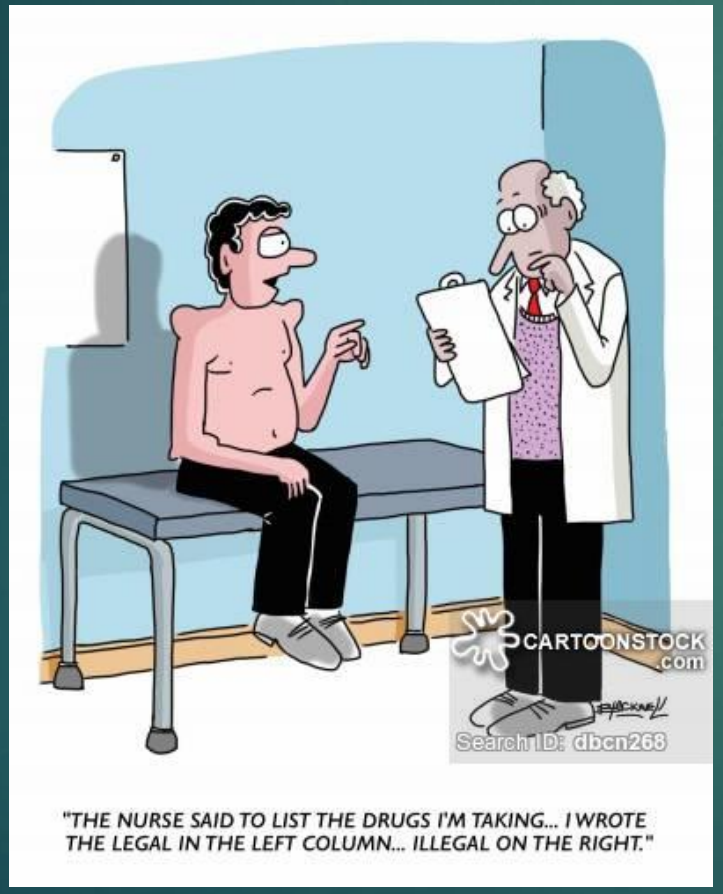
Emetine Myopathy

- Emetine still available
  - Local pharmacies
  - 1ounce limit without a prescription
- Online

Illicit Drugs



Illicit Drugs



No Doc, I swear I'm not on anything!

The KMC Urine Drug Screen

Myotoxins

- Amphetamine
- Cocaine
- Opiates

Non-Myotoxins

- Barbiturates
- Benzodiazepines
- THC

Serum/Urine Drug Screen

	Serum Half Life	Urine Metabolites Half Life	Urine Metabolites Detected (Days)
Amphetamine	3-24	11	Up to 7
Cocaine	1.5	4-8	2-4
Opiates	1.5-27	Variable	Variable

Cocaine Rhabdomyolysis

- Ranges from asymptomatic CK-emia to massive rhabdomyolysis
- Usually present with other issues
  - Chest pain
  - Delirium
  - Fever
  - Cardiovascular collapse
- Muscle injury due to:
  - Severe arterial vasoconstriction – ischemia
  - Inhibition of reuptake of catecholamines at alpha adrenergic receptors
    - ↑ intracellular Ca

Alcoholic Myopathy

Alcohol Effects on Striated Muscle

- Neuropathy more common
- Cardiomyopathy common
- Chronic alcoholic myopathy
- Acute hypokalemic myopathy
- Acute necrotizing myopathy

Alcoholic Acute Necrotizing Myopathy

- Intense binge drinking, several days
- Clinical
  - Myalgia
  - Cramping
  - Swelling
  - Weakness
  - ↑ CK
- Wide spread muscle fiber necrosis
- Multifactoral

Alcoholic Acute Necrotizing Myopathy

- Found down
- Unconscious for hours
- Muscle compression
- Compartment syndromes
- Other drugs of abuse

Acute Kidney Injury in Rhabdomyolysis

- Occurs in 15% - 33% or more
- Myoglobin & hemoglobin are the culprits
  - Mechanical injury to tubules
  - Toxic effect of free iron on tubules
  - Hypovolemia
- AKI correlates with severity of rhabdomyolysis
  - Rare if CK < 20K

AKI Correlates with Severity of Rhabdomylysis

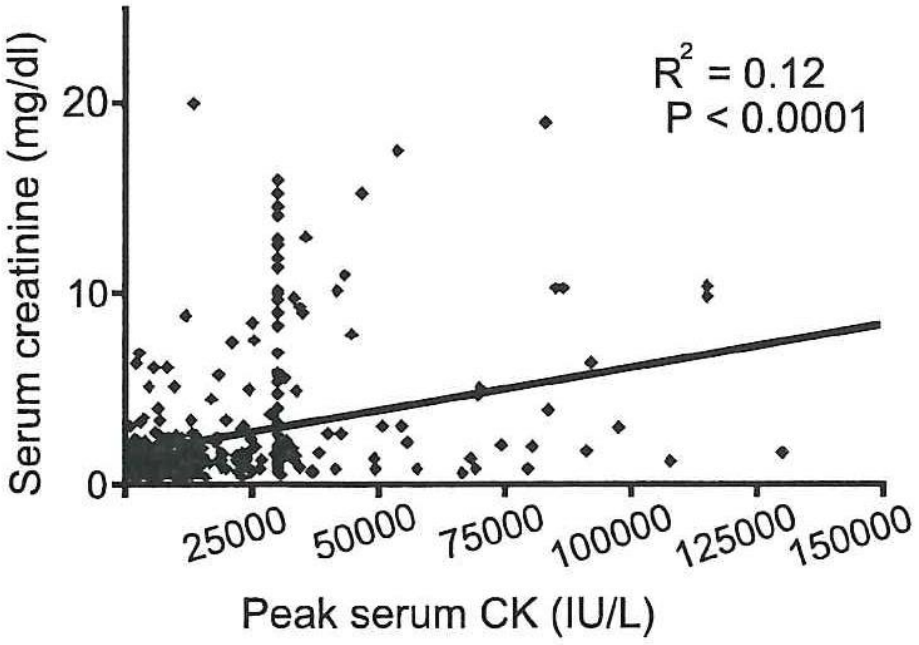


FIGURE 1. Correlation between peak serum creatine kinase and serum creatinine.

Rhabdomyolysis in the Hospital*

Primary Cause	%	Male %	Mean CK	Multiple Causes	ARF %
Illicit drugs/alcohol	34	82	17,781	80	65
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Poly / Dermatomyositis

- The ANA positive diseases
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjogren's syndrome
  - Scleroderma
  - Poly / Dermatomyositis

Clinical Features

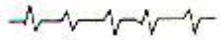
- Symmetrical proximal muscle weakness
- Elevated muscle enzymes
  - CPK, aldolase, transaminases, LDH
- Myopathic EMG abnormalities
- Typical changes on muscle biopsy
- Typical rash of dermatomyositis

Heliotrope Rash

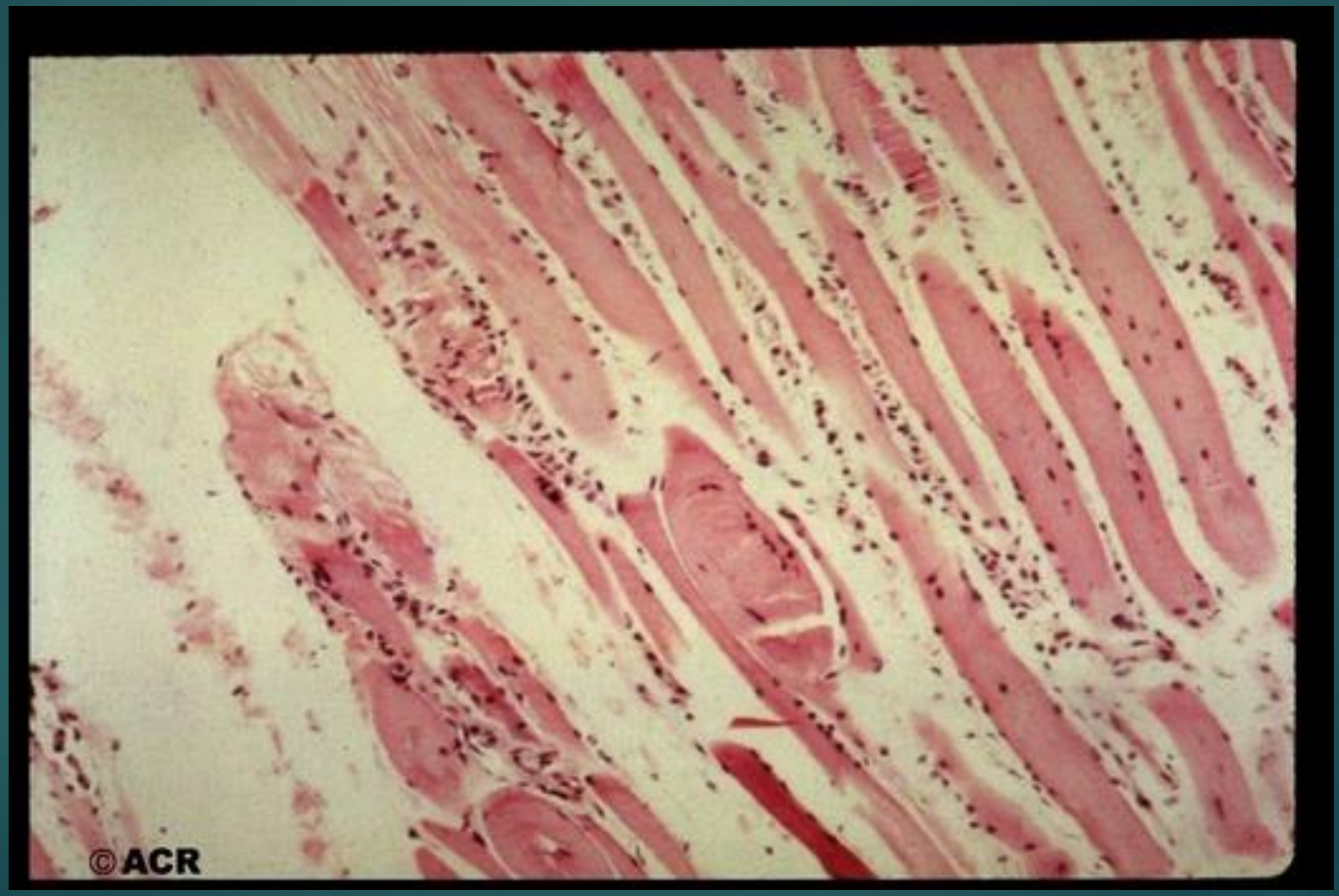
Heliotrope rash

Violaceous discoloration and puffiness of the eye lids

EMG

	Lesion / EMG Steps	Normal	Neurogenic Lesion		Myogenic Lesion	
			Lower Motor	Upper Motor	Myopathy	Polymyositis
1	Insertional Activity	Normal 	Increased 	Normal 	Normal 	Increased 
2	Spontaneous Activity		Fibrillation  Positive Wave 			Fibrillation  Positive Wave 
3	Motor Unit Potential	0.5-1.0 mv  5-10 msec.	Large Unit  Limited Recruitment	Normal 	Small Unit  Early Recruitment	Small Unit  Early Recruitment
4	Interference Pattern	Full 	Reduced  Fast Firing Rate	Reduced  Slow Firing Rate	Full  Low Amplitude	Full  Low Amplitude

Pathology of PM / DM



The Elevated CK in the Clinic

Asymptomatic Elevation of CK

- Why did I order this test???????

Asymptomatic Elevation of CK

It may be normal*

- Redefining elevated CK as 1.5 time beyond Upper Limit of Normal
- Adjust for ethnicity and gender
  - White women – 325 IU/L
  - White men – 504 IU/L
  - Black women – 621 IU/L
  - Black men – 1,200 IU/L

*European Academy of Neurology

Physical Activity Raises CK

- CK levels rise after heavy exercise or heavy manual labor
  - The P90X exercise program

Physical Activity Raises CK

- CK levels rise more in those who are couch potatoes

Physical Activity Raises CK

- CK levels rise more in those who are couch potatoes
  - If minimally elevated - Repeat 7 days after forced couch potato activity

Look for Non-neuromuscular Causes of elevated CK

- Take a careful history and review the chart for:
  - Illicit drugs & ETOH
  - Prescription drugs
- Order TSH/Free T4
- Macro CK
  - 1% of population
  - Atypical high molecular weight mass with reduced clearance
  - CK electrophoresis required

Look for Neuromuscular Causes of elevated CK

- Consider more Invasive studies
  - EMG / NCT
  - Muscle Biopsy
- When to biopsy?
  - CK more than 3 times Upper Limit of Normal
  - Age less than 25
  - Exercise intolerance
  - Abnormal EMG

What is the Yield of Invasive Testing in Asymptomatic Hyper-CK-emia

- Likelihood of specific diagnosis is 28%
- Diagnoses
  - Muscular dystrophies
  - Rare metabolic myopathies
  - Rare noninflammatory myopathies

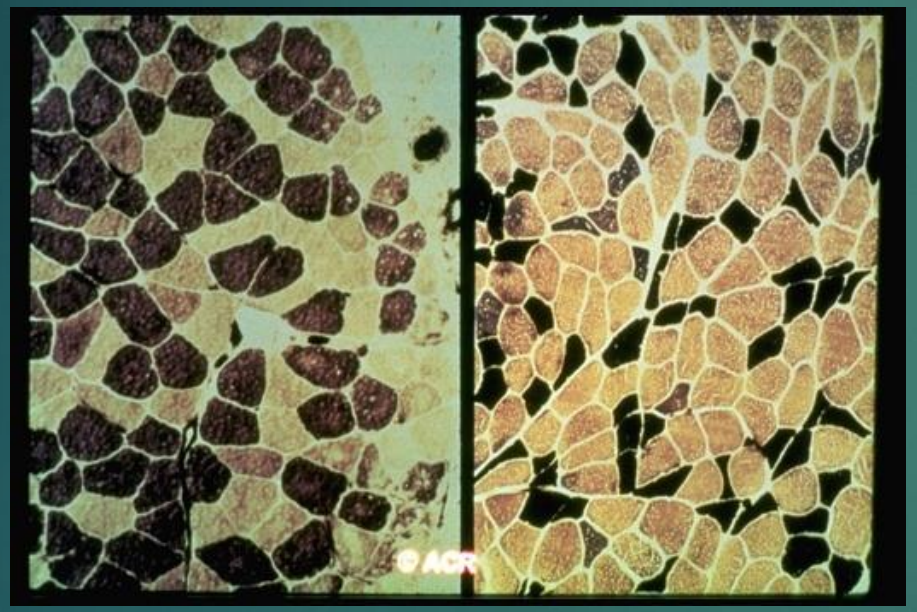
Idiopathic hyper-CK-emia*

- Defined as persistent elevation of CK despite:
  - No family history of neuromuscular disease
  - No clinical evidence of neuromuscular disease
  - Normal EMG, NCT and muscle biopsy
- 7 Year follow-up
  - 10% Malignancy
  - 10% Neuromuscular disorder
  - 80% No new condition

*Rowland et al: Muscular Dystrophy Research: Advances and New Trends. Excerpta Medica; Amsterdam: 1980. pp. 3-13.

Thank You for Your Attention

Corticosteroid Myopathy



- Prox muscle weakness
- Normal muscle enzymes
- Normal EMG
- Type II fiber atrophy

The ICU


He has been in the unit for 10 days and largely immobile...
Is there anything we can do to prevent ICU-related weakness?

Critical Illness Myopathy/Polyneuropathy

Who?

- Critically ill ICU
- Mechanically ventilated > 7 days
- Risk factors
  - Sepsis
  - Multiorgan failure
  - SIRS
  - High dose steroids?
  - Neuromuscular blockers

Clinical Features

- Flaccid quadriplegia (proximal)
- Failure to wean from mechanical ventilation
- Facial muscle weakness
- Relative sparing of cranial nerves*
- Decreased DTRs*
- Loss of peripheral sensation*

*CIP only

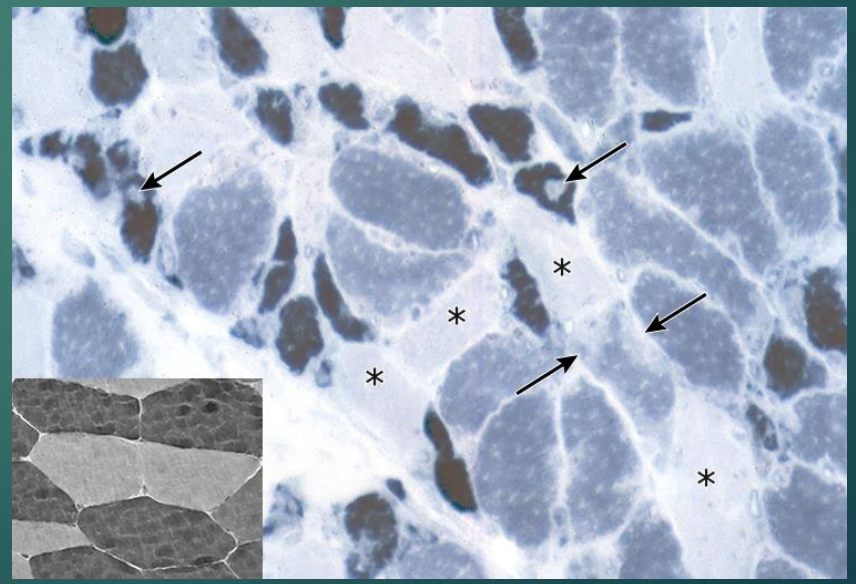
Critical Illness Myopathy/Polyneuropathy

CIP

- Reduced nerve excitability
  - Axon degeneration
  - Inactivation of sodium channels

CIM

- Selective loss of myosin
- Atrophy of type 2 > type 1 fibers



Critical Illness Myopathy/Polyneuropathy

Clinical Evaluation

- Muscle strength testing*
- Sensory examination*
- CK usually ↑ in CIM
- Electrodiagnostic testing*
  - EMG
    - Low motor amplitudes
    - Fibrillations
  - NCT
    - Low motor and sensory amplitudes

*Require alert, cooperative patient

Critical Illness Myopathy/Polyneuropathy Management/Prognosis