DILI: Diagnostic and Treatment Challenges

(also Featuring the use of Statins for Liver Disease)

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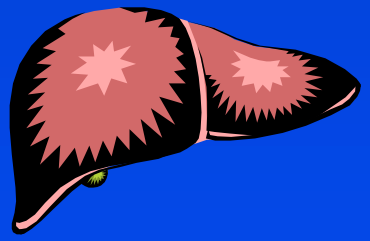
davernt@sutterhealth.org



Timothy J. Davern, MD
California Pacific Medical Center Liver Transplant Program

I have no financial relationships to disclose within the past 12 months relevant to my presentation

AND

My presentation includes discussion of off-label or investigational use of NAC.

AASLD | Access by **Sutter Resource Library**

Hepatotoxicity

Drug Metabolism, Toxicity and Therapeutics	
Aldehyde Dehydrogenase-2 Act	2062
Analysis of Immune-Related A	2067
Causes, Clinical Features, O	2050
Drug Induced Liver Injury (D	2054
Echinacoside and Verbascosid	2068
Elevated Camp Protects Again	2053
Farnesoid X Receptor and Bil	2055
Hepatic Adverse Events of Im	2058
High Incidence of Cholestati	2060
Impact of Change In the Alan	2065
Increasing Episodes of Hepat	212

Outline

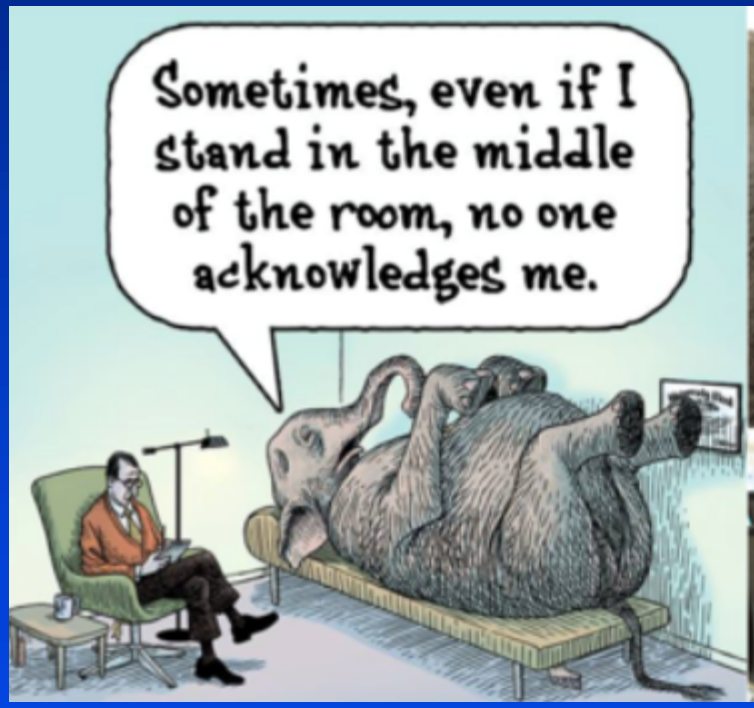
- Causality Assessment in DILI
- Acetaminophen – “Elephant in the Room”
- LiverTox – “Virtual Hy”
- Augmentin – “An Incredibly Intense Yellow Itch”
- Nitrofurantoin – “Autoimmune Mimic”
- INH – “Yellow Consumption”
- Anabolic Steroids – “The Incredible Bulk”
- Occult HEV Infection Masquerading as DILI
- DILI from statins

Causality Assessment
CSI Analogy

- Was the drug in the right place at the right time?
- Does the drug have a prior record?
- Are the characteristics of the apparent DILI event (the ‘crime’) consistent with the modus operandi of the implicated drug?
- Are there other explanations for the liver injury other than DILI?
- Is the clinical course consistent with DILI?

Clin Liver Dis 16 (2012) 231–245

Acetaminophen Poisoning
"The Elephant in the Room"

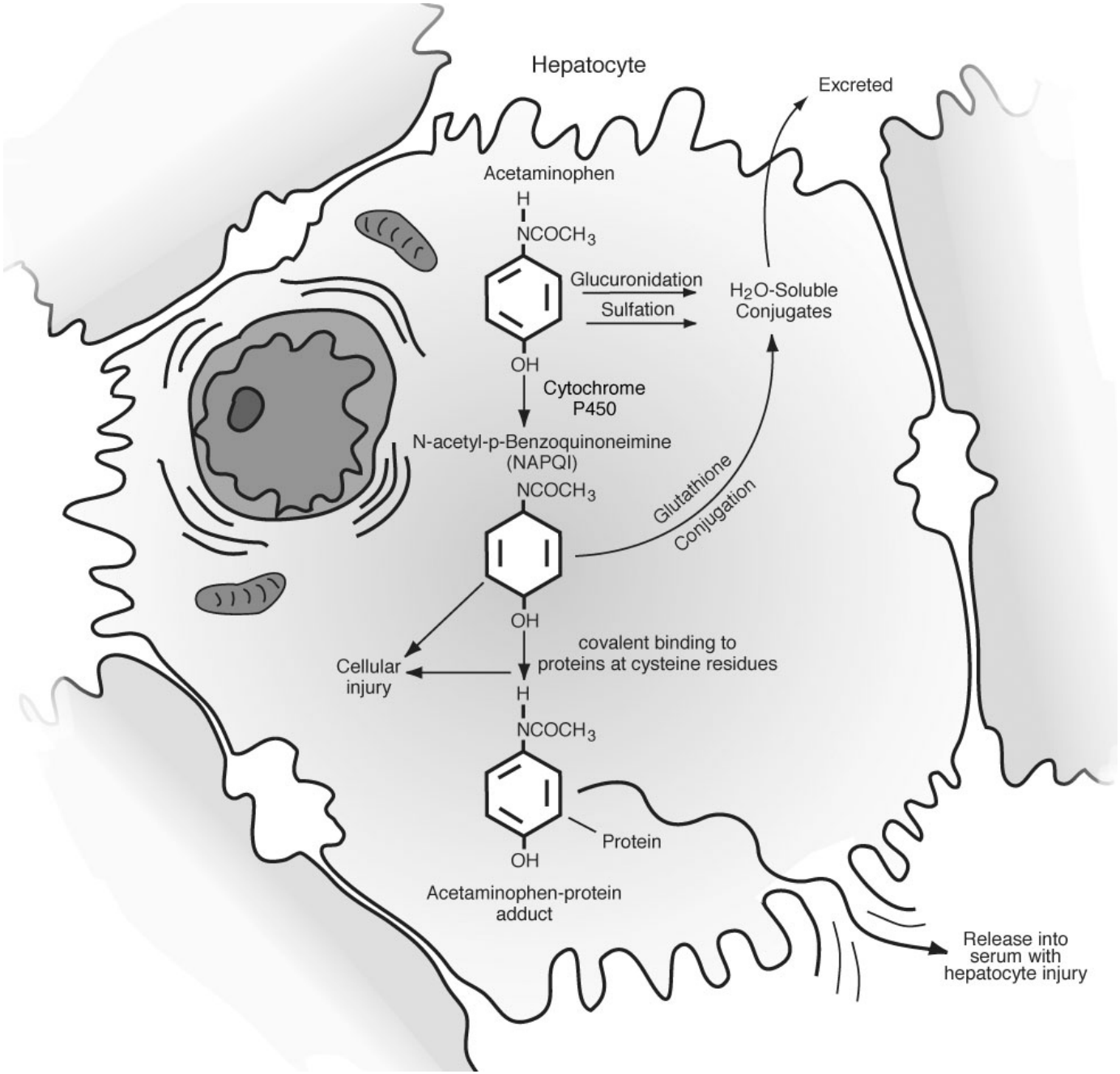


Acetaminophen Poisoning
"The Elephant in the Room"

"*Ok, is there anything about DILI that we haven't covered?*"

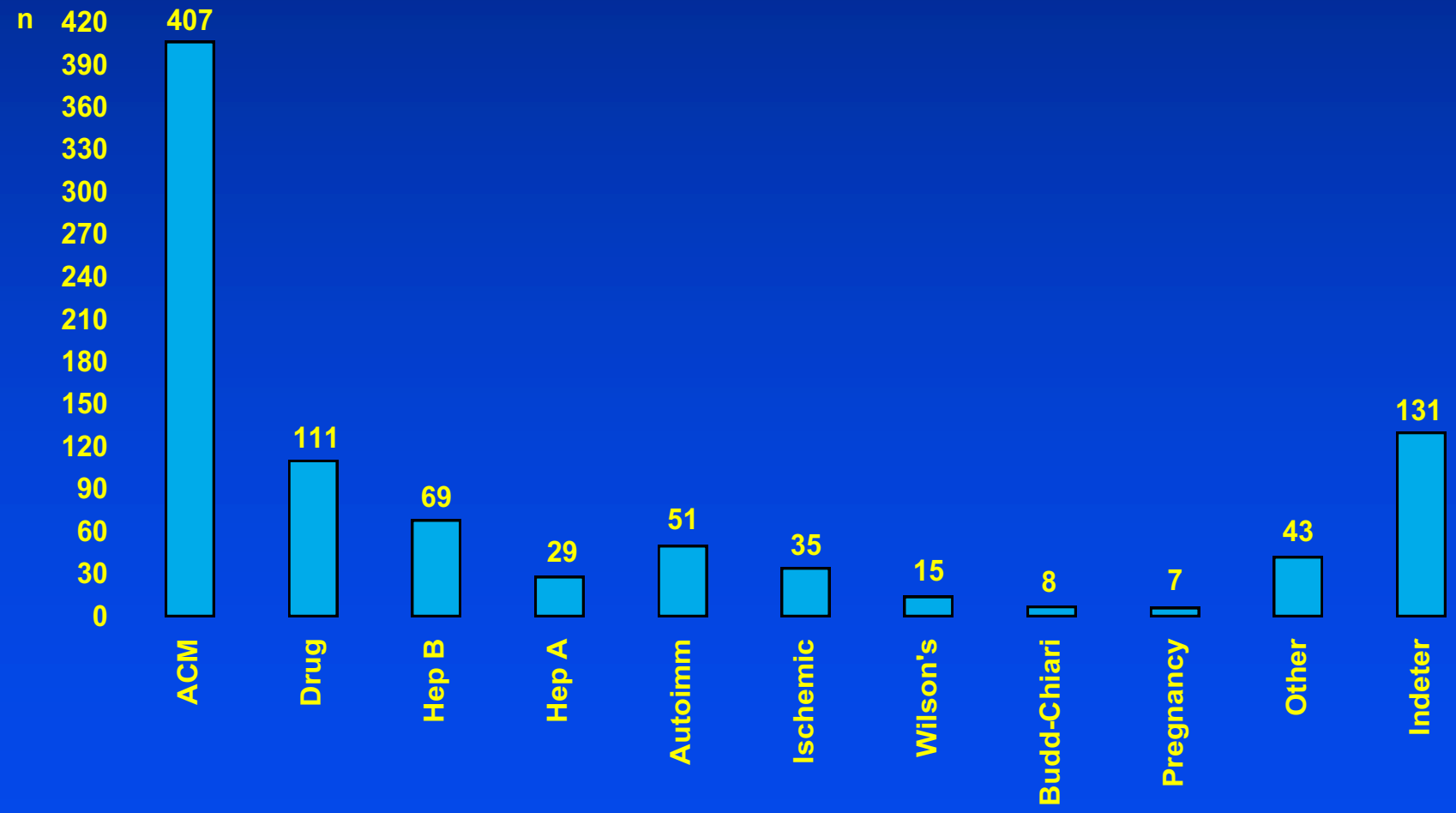
Acetaminophen Poisoning
"The Elephant in the Room"

- Acetaminophen is a dose-dependent liver toxin
- The most common cause of ALF in the US
- Increasing incidence over last 15 yrs?
- Many misconceptions:
  - "The acetaminophen level is zero so the patient's liver injury can't be from acetaminophen."
  - "It is too late to give NAC since the patient already has ALF"


Hepatocyte
Excreted
Acetaminophen
H
NCOCH3
Glucuronidation
Sulfation
H2O-Soluble
Conjugates
OH
Cytochrome
P450
N-acetyl-p-Benzoquinoneimine
(NAPQI)
NCOCH3
Glutathione
Conjugation
OH
covalent binding to
proteins at cysteine residues
Cellular
injury
H
NCOCH3
Protein
OH
Acetaminophen-protein
adduct
Release into
serum with
hepatocyte injury

Etiology of ALF in the USA:

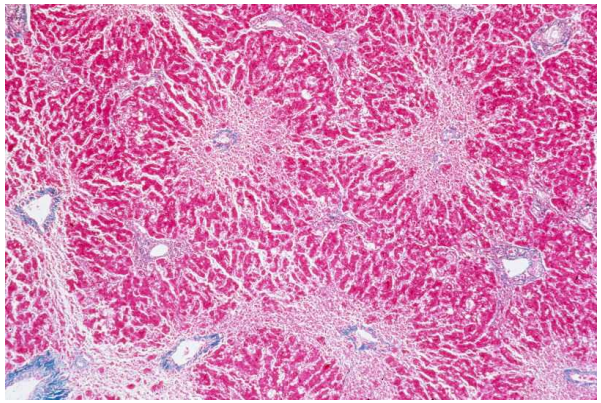
Adult Registry (n = 906)



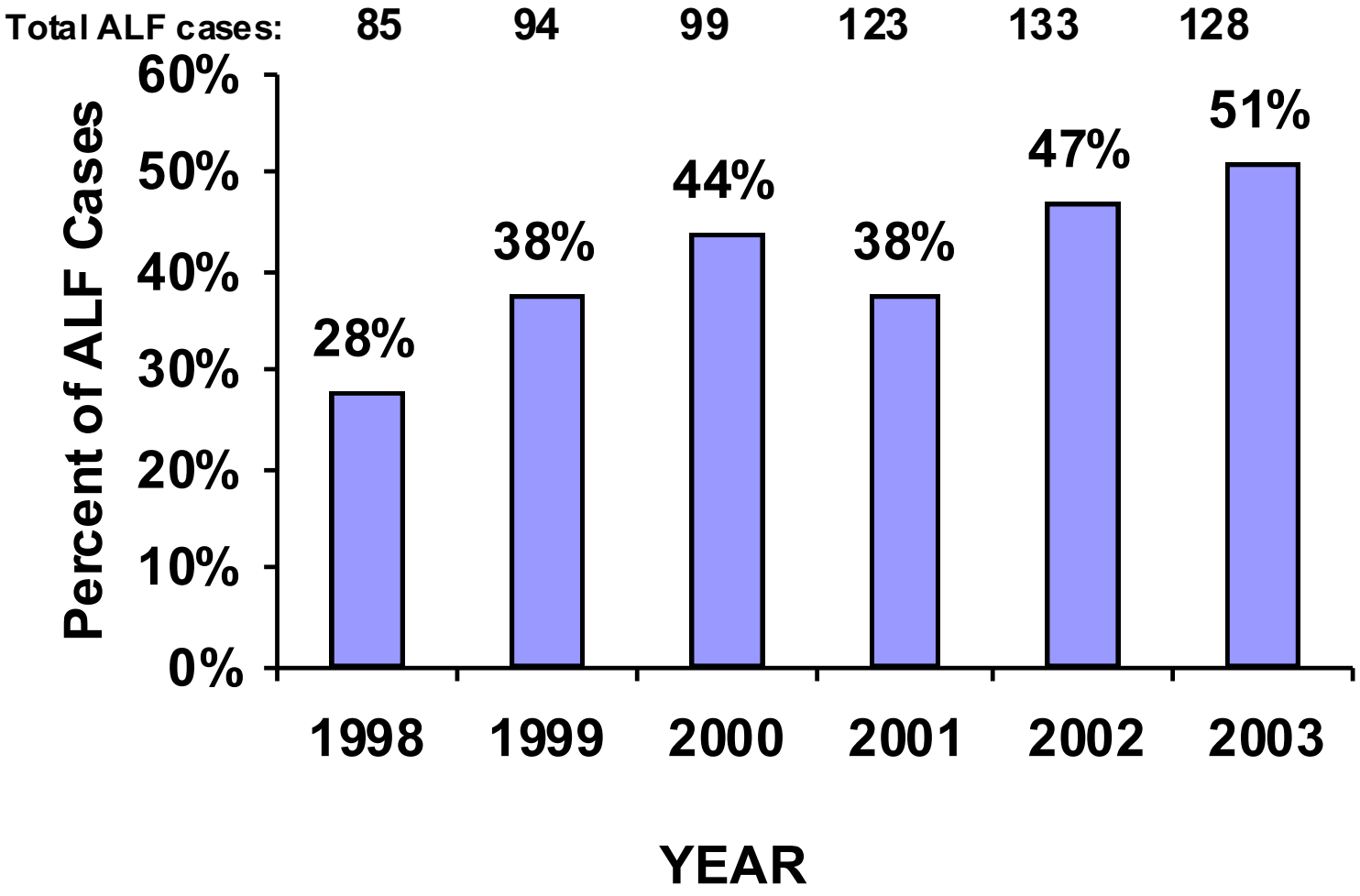
TYLENOL®
ACETAMINOPHEN

THE TYLENOL® COMPANY

"Meet the Family"



Increasing Incidence of APAP-related ALF in US



Comparison of Different Etiological Groups

Variable	APAP n=262	Drug n=76	Indeterminate n=90	Hep A/Hep B n=22/47	All Others n=113
Age	36	42	37	48/40	42
Sex (% F)	74	72	57	55/47	79
Jaundice (Days)	1	12	10	4/5.5	8
Coma 3/4 (%)	52	43	48	50/60	43
ALT	4055	491	1015	2658/1707	709
Bili	4.6	21.3	23.5	11.7/18.8	14.7
Tx (%)	8	44	40	18/51	34
Spont. Survival (%)	65	20	26	64/28	31
Overall Survival (%)	71	60	62	82/70	58

Suicidal vs. Accidental APAP cases

	Suicidal (n = 101)	Unintentional (n = 109)	p Value
Female (%)	75	76	NS
APAP (g)	28	34	NS
APAP/day (g)	28	10	0.001
Coma (% > 3)	39	55	0.026
ALT (IU/L)	6,118	3,975	0.001
Spont Surv (%)	67	66	NS
Antidepressant (%)	35	36	NS
APAP/opiate (%)	19	62	0.001

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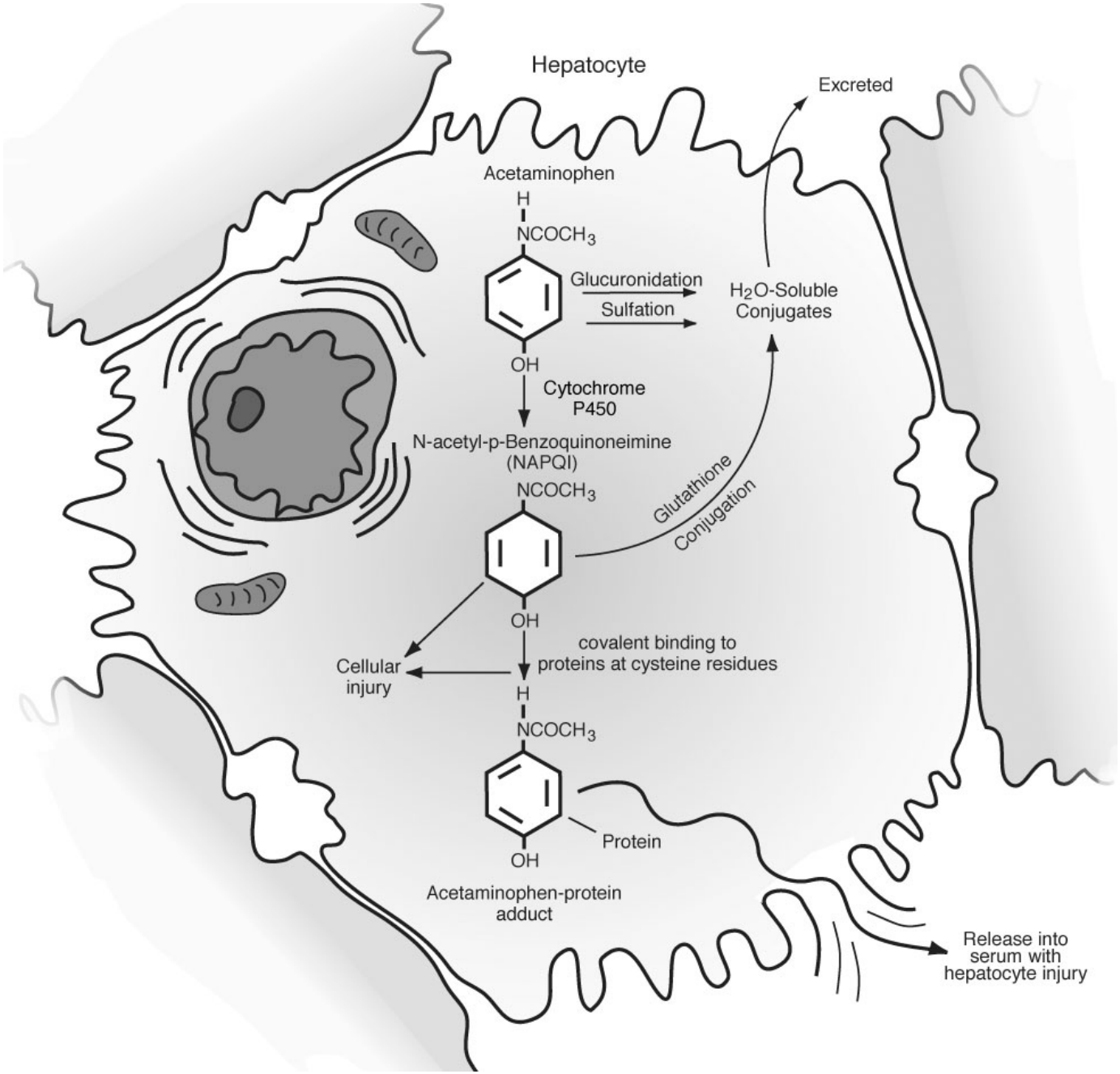
Hepatocyte
Excreted
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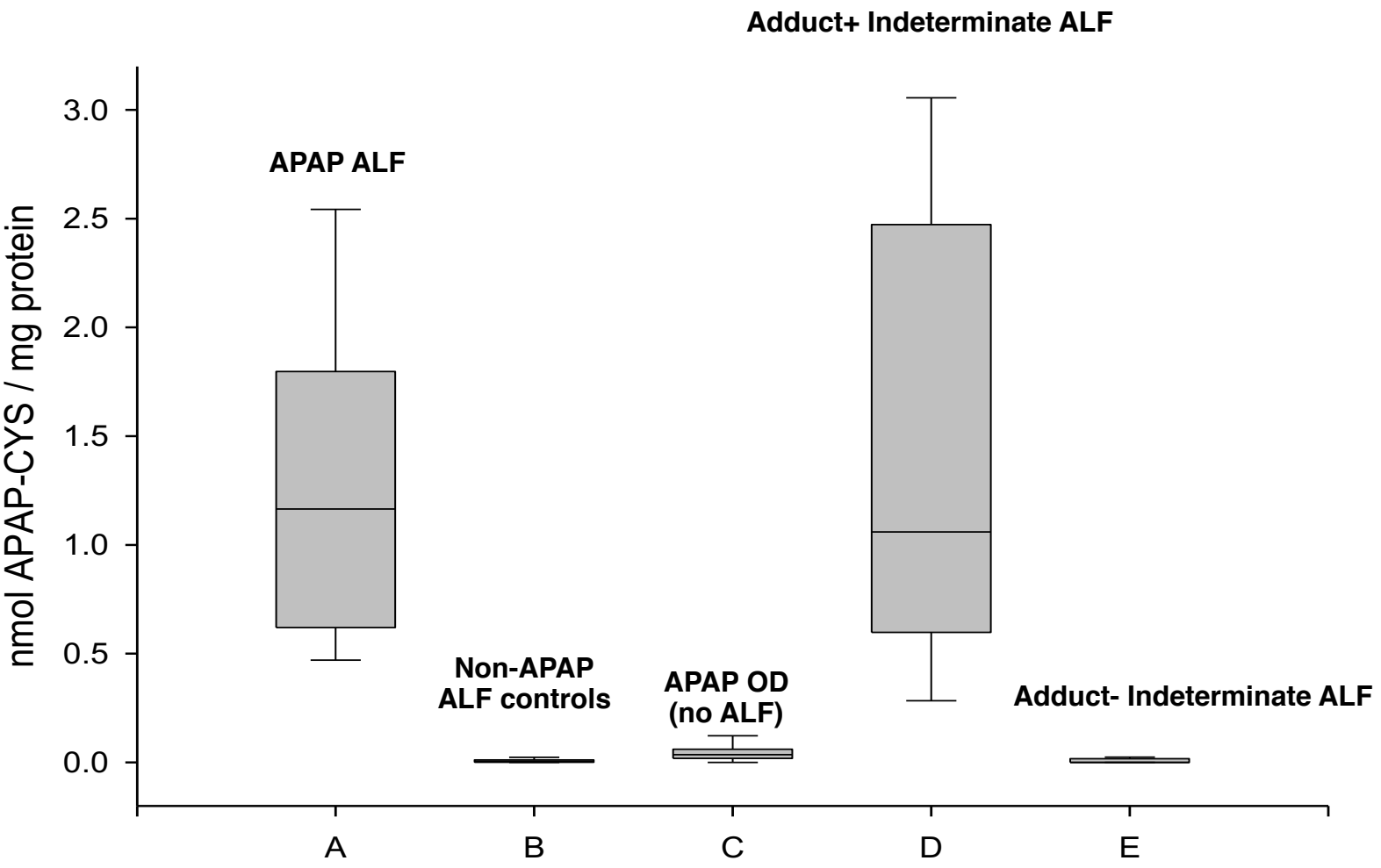
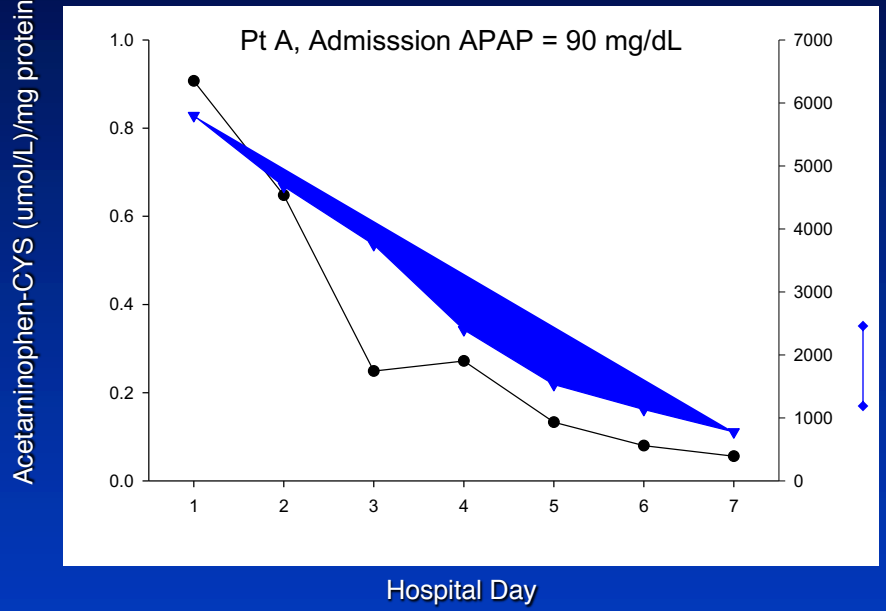
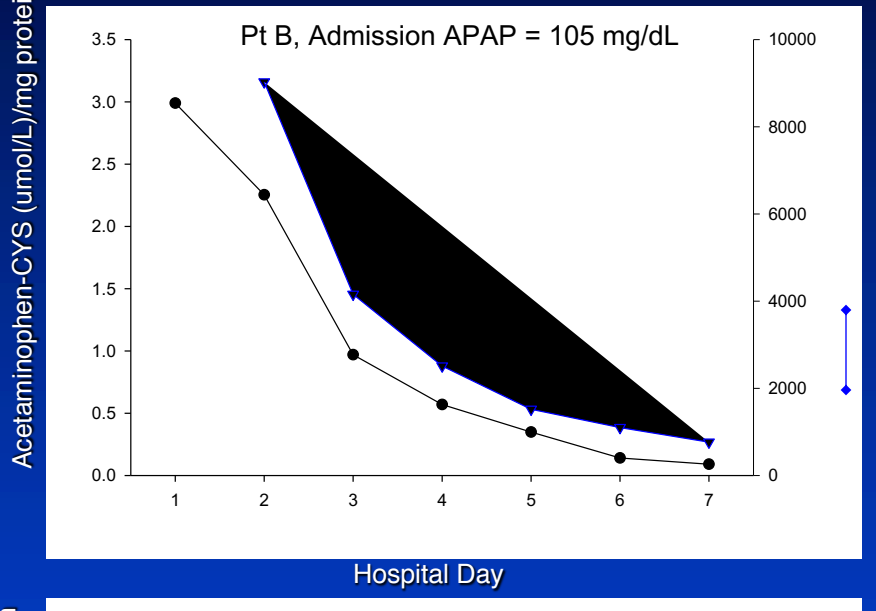
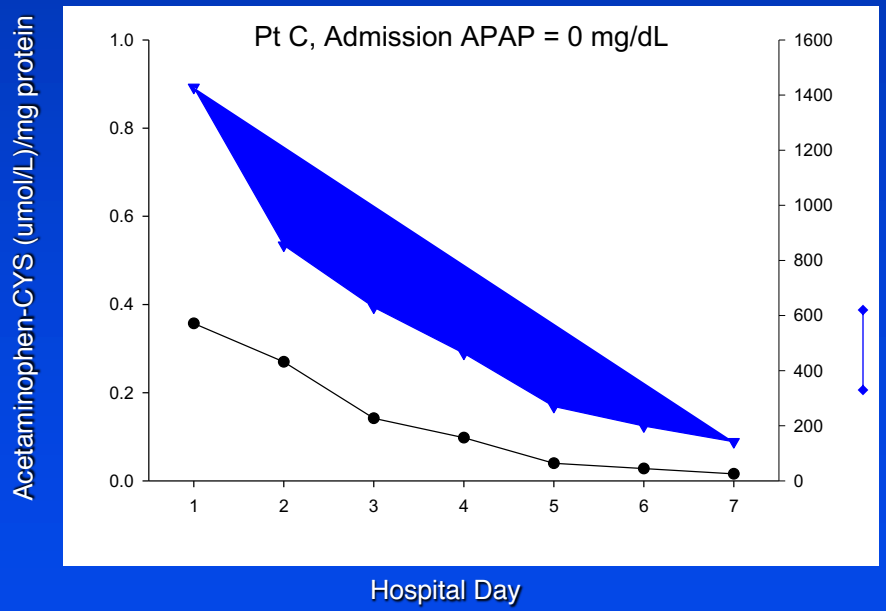
H
NCOCH3
Glucuronidation
Sulfation
H2O-Soluble
Conjugates
OH
Cytochrome
P450
N-acetyl-p-Benzoquinoneimine
(NAPQI)
NCOCH3
Glutathione
Conjugation
OH
covalent binding to
proteins at cysteine residues
Cellular
injury
H
NCOCH3
Protein
OH
Acetaminophen-protein
adduct
Release into
serum with
hepatocyte injury

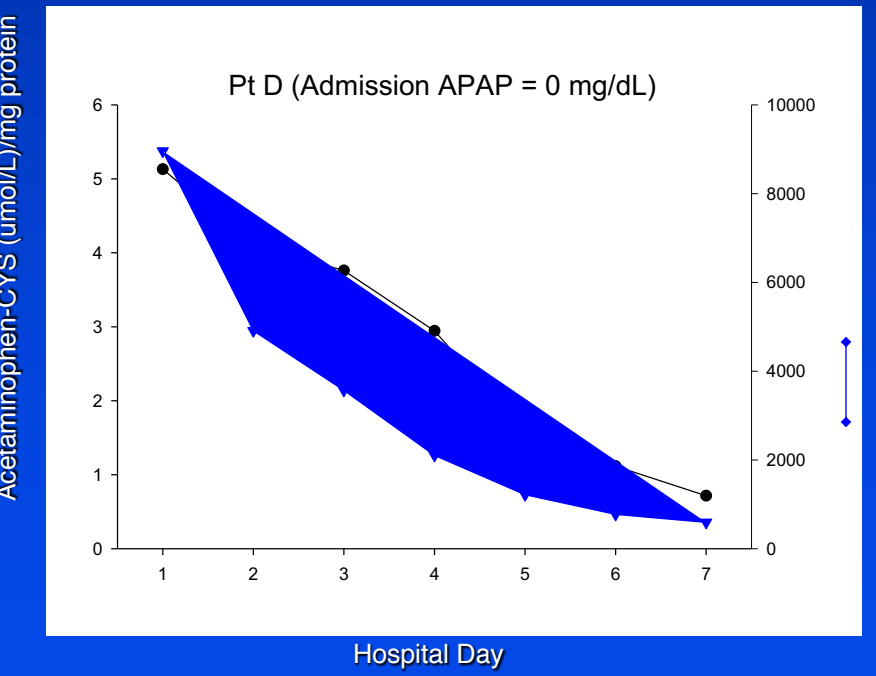


Gastroenterology 2006;130:687-94


Pt A, Admisssion APAP = 90 mg/dL
Acetaminophen-CYS (umol/L)/mg protein
ALT (IU/L)
Hospital Day


Pt B, Admission APAP = 105 mg/dL
Acetaminophen-CYS (umol/L)/mg protein
ALT (IU/L)
Hospital Day


Pt C, Admission APAP = 0 mg/dL
Acetaminophen-CYS (umol/L)/mg protein
ALT (IU/L)
Hospital Day


Pt D (Admission APAP = 0 mg/dL)
Acetaminophen-CYS (umol/L)/mg protein
ALT (IU/L)
Hospital Day

Acetaminophen Poisoning
"The Elephant in the Room"

- The most common cause of ALF in the US
- Increasing incidence over last 15 yrs?
- Many misconceptions:
  - "The acetaminophen level is zero so the patient's liver injury can not be from acetaminophen."
  - "It is too late to give NAC since the patient already has ALF"

"NAC is TPA for the Liver"

- Early administration of NAC is potentially life saving
- NAC should be given ASAP to patients with suspected APAP overdose
  - We always be suspicious
  - APAP levels are unreliable
- IV NAC is safe and more reliable than oral NAC in patients with ALF
- Treat patients with cryptogenic ALF and high aminotransferases with NAC
- Late administration of NAC appears to be ameliorate APAP toxicity

Acetaminophen Poisoning
"The Elephant in the Room"

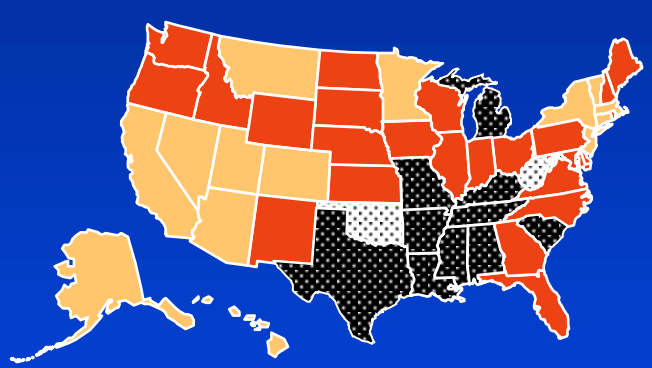
- **High risk patient groups:**
  - Chronic pain (APAP-Opiate combinations)
  - Depression
  - Prolonged fasting
  - Alcoholics
  - Bariatric surgery

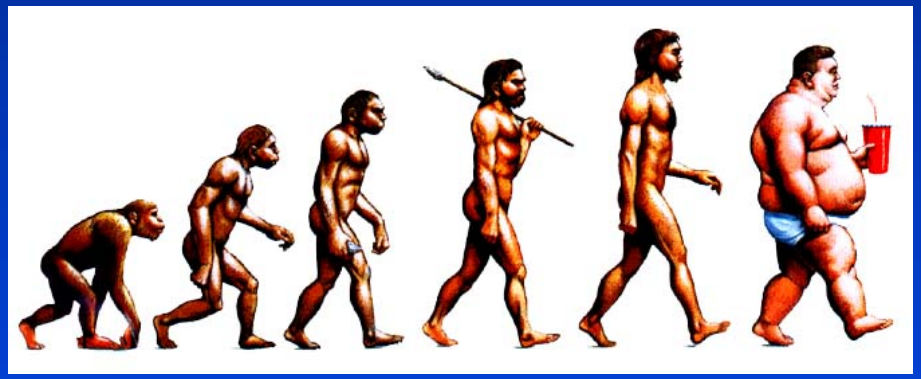
Acetaminophen Poisoning
"The Elephant in the Room"

- **High risk patient groups:**
  - Chronic pain (APAP-Opiate combinations)
  - Depression
  - Prolonged fasting
  - Alcoholics
  - Bariatric surgery

Background: Obesity

- In 2009-2010 35.7% of U.S. adults were obese (BMI ≥30 kg/m^2).

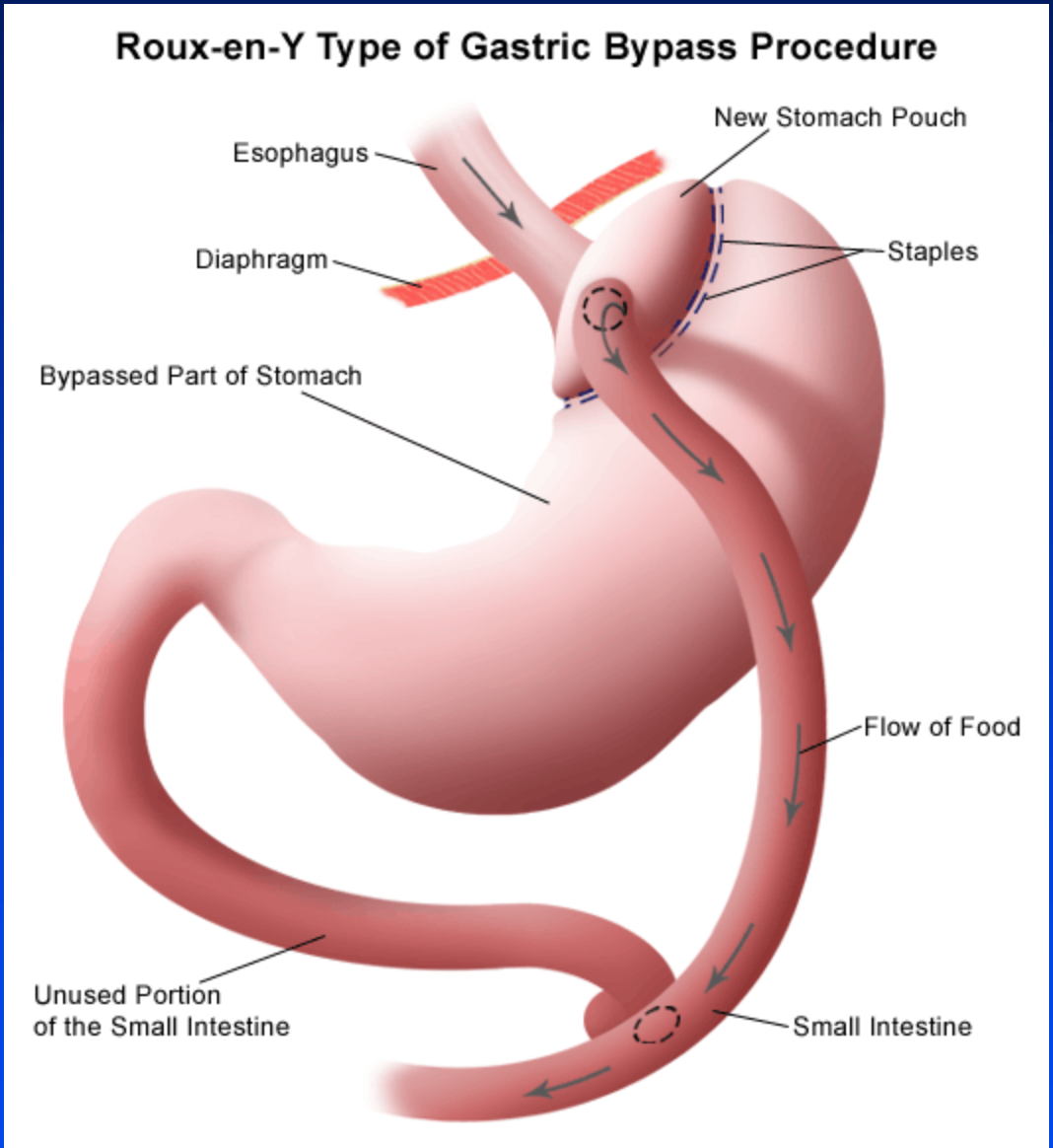




No Data <10% 10%–14% 15%–19% 20%–24% 25%–29% ≥30%

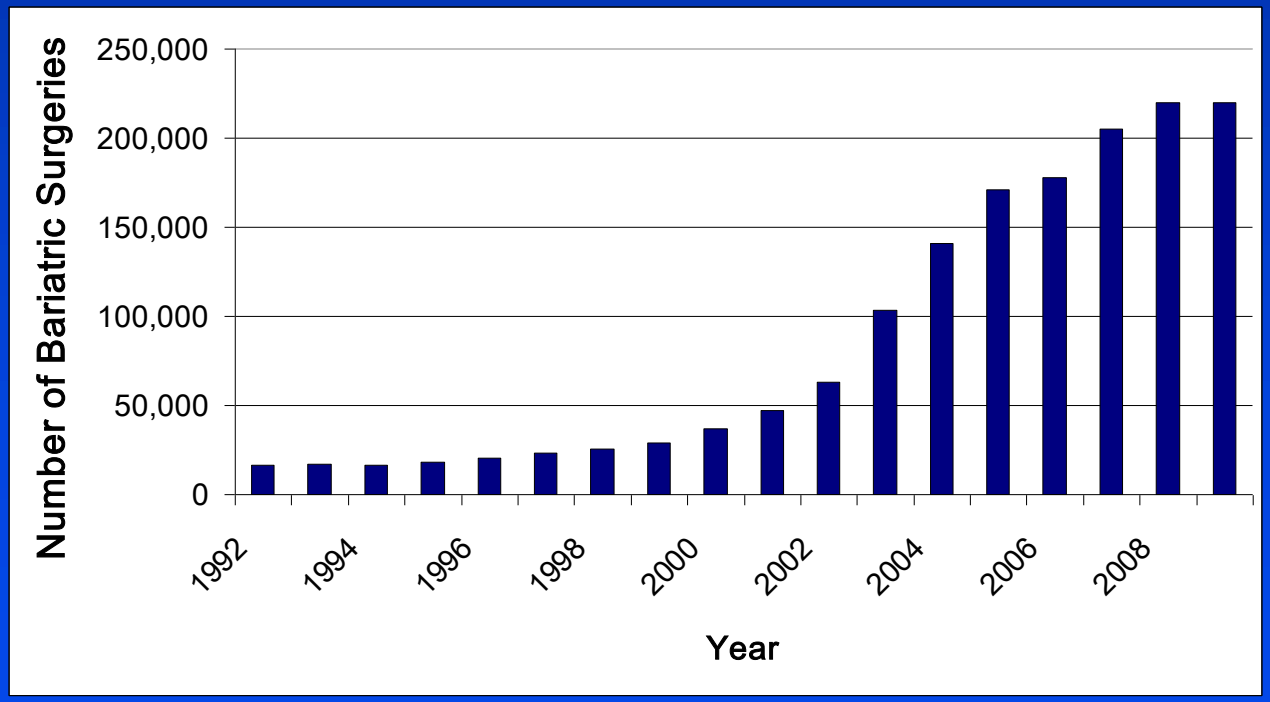
- Only bariatric surgery achieves significant and durable weight loss.

cdc.gov; Sjöström, *New Engl J Med* 2004


Roux-en-Y Type of Gastric Bypass Procedure
New Stomach Pouch
Esophagus
Diaphragm
Staples
Bypassed Part of Stomach
Flow of Food
Unused Portion
of the Small Intestine
Small Intestine

Background: Bariatric Surgery

- The prevalence of bariatric surgery in the US is ~ 1.5 million (0.5-1% of ~225,000,000 U.S. adults) and the incidence is increasing.



Acetaminophen Poisoning
"The Elephant in the Room"

- Gastric bypass appears to alter absorption and metabolism of APAP and may predispose to liver injury
- We studied 101 consecutive ALF pts presenting to our center between 1999-2011
- 54 APAP; 47 other causes
- 9/54 APAP-ALF and 0/47 non-APAP-ALF patients had prior bariatric surgery ($p = 0.003$)

Acetaminophen Poisoning
"The Elephant in the Room"

- The bariatric surgery group did NOT have higher rates of depression, alcohol abuse, or intent for self harm
- After adjusting for age, gender, race, depression and alcohol abuse, prior bariatric surgery remained independently associated w/ APAP-ALF (OR 10.8, p=0.015)
- The prevalence of bariatric surgery among APAP-ALF patients in our cohort (16.7%) is almost 25 times higher than the US population

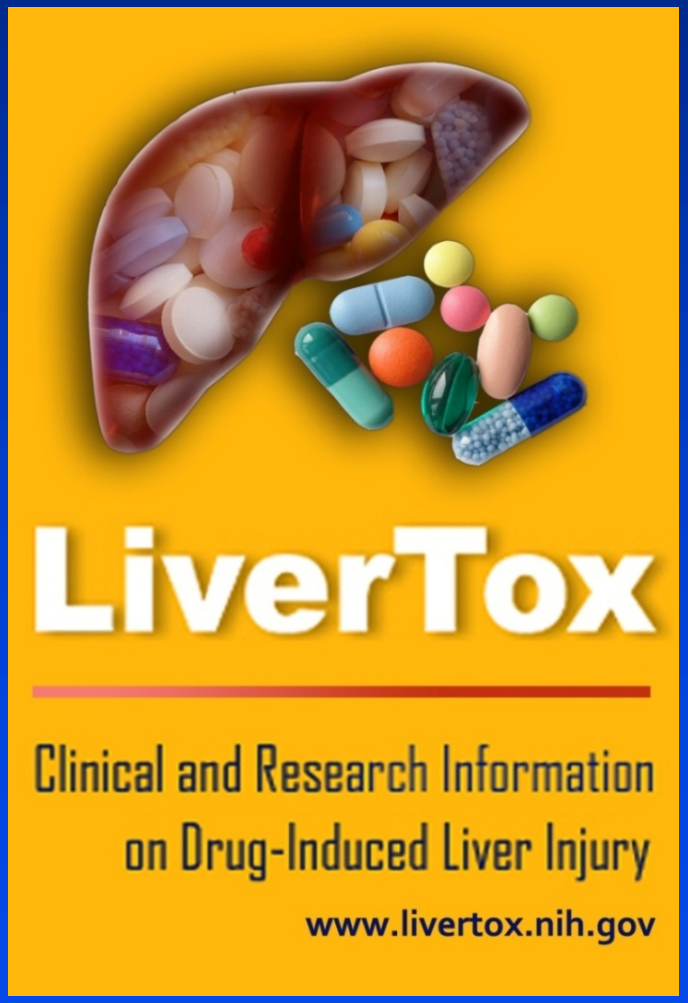
Acetaminophen Poisoning
"The Elephant in the Room"

- ***If these data are confirmed *, the label on all APAP-containing products should include a warning to use with caution in the setting of prior bariatric surgery***
  - **Such a warning already exists for heavy alcohol drinkers on APAP products, but we believe that prior bariatric surgery may be a much stronger risk factor for accidental acetaminophen poisoning based on our data.**

J Clin Gastroenterol. 2015 Oct;49(9):790-3.*

***These data have been largely reproduced/confirmed in an independent, multi-center US study - See AASLD meeting November 2015.**

LiverTox
"Virtual Hy"



- Collaboration between Liver Branch of NIDDK and NLM
- Up-to-date, comprehensive and unbiased information about DILI from prescription, OTC and CAM agents
- Guidance to clinicians on the Dx and Rx of DILI
- A “living textbook” that will be regularly updated and improved

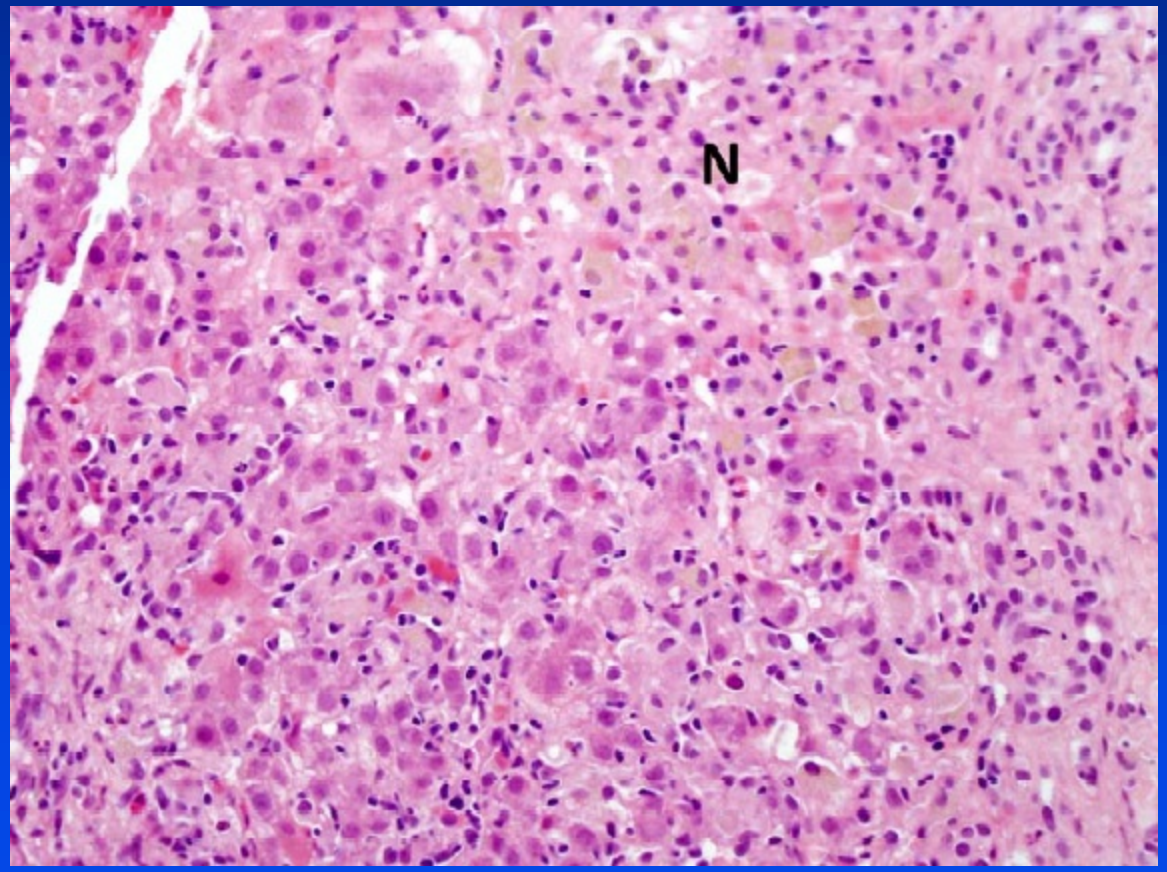
INH Hepatotoxicity
"Yellow Consumption"

- Used in rx of latent and overt TB
- Frequently causes of asymptomatic elevated liver tests (10-20%)
- Major cause of severe DILI (0.5-1%) and DILI-ALF
- Major risk factors – AGE , underlying liver disease (e.g., HBV), other drugs (rifampin, alcohol), race?, genetics?
- Latency 1-6 months

INH Hepatotoxicity
"Yellow Consumption"

- Clinically and histologically resembles viral hepatitis (hepatocellular injury)
- Hypersensitivity features rare, +/- ANA
- ALF more common in women, African Americans
- RX:
  - Stop drug ASAP (pt education)
  - NAC?
  - Steroids?
  - Think about liver transplant early
    - Remember to rx latent TB post-OLTx

INH Hepatotoxicity
"Yellow Consumption"



LiverTox

Augmetin Hepatotoxicity
"An Incredibly Intense Yellow Itch"

- Most common cause of clinically apparent DILI in US and Europe
- Clavulanate (not amoxicillin) responsible
- Risk factors: Age, prolonged course

Augmentin Hepatotoxicity
"An Incredibly Intense Yellow Itch"

- Latency typically ~ 3 weeks
- Presentation typically *after* completing course of antibiotic therapy
- Symptoms: fatigue, malaise, nausea, abdominal pain, pruritis and jaundice
- Biochemical pattern: cholestatic or mixed (hepatocellular in kids)
- Genetic risk factors: *HLA DRB1*1501*

211

Discovery of EARP Gene Expression as a Risk Factor for Drug-Induced Liver Injury Due to Amoxicillin-Clavulanic Acid

Paola Nicolette[1], Federico Innocent[2], Amy Etheridge[3], Naga P Chalasani[4], Robert J. Fontana[5], Yi-Ju Li[6], Joseph Odin[7], Jose Serrano[8], Andrew Stolz[9], Guruprasad P. Aithal[10], Ann K Daly[11], Paul B. Watkins [12], DILIN Investigators

- **ERAP2 – an enzyme that trims peptides so that they fit into the antigen binding site of HLA proteins**
  - **ERAPS polymorphisms associated with autoimmune dz**
- **444 AC cases; 10,397 population controls**
- **AC DILI was associated with a low ERAP2 liver expression - ? Alters presentation of AC-induced neoantigens on liver cells**

Augmetin Hepatotoxicity
"An Incredibly Intense Yellow Itch"

- Jaundice may be prolonged (4-24 months) and pruritis intense
- VBD syndrome has been described but is rare
- RX:
  - Stop drug
  - Urso
  - Cholestyramine
  - Steroids?

Nitrofurantoin Hepatotoxicity
"Autoimmune Mimic"

- Used for treatment of acute and prophylaxis of chronic/recurrent UTIs
- 5 million scripts per year under several names (Macrodantin, Macrobid, Furadantin, etc.)

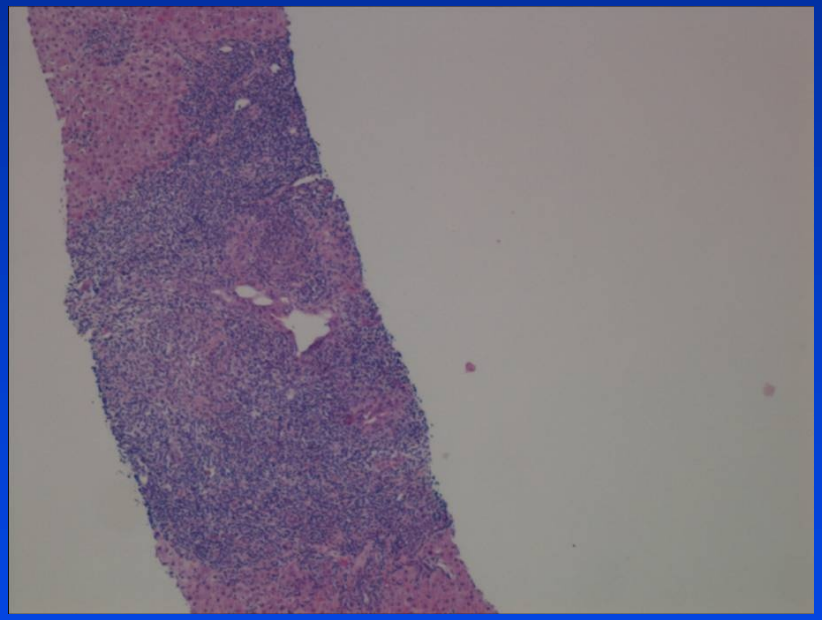
Nitrofurantoin Hepatotoxicity
"Autoimmune Mimic"

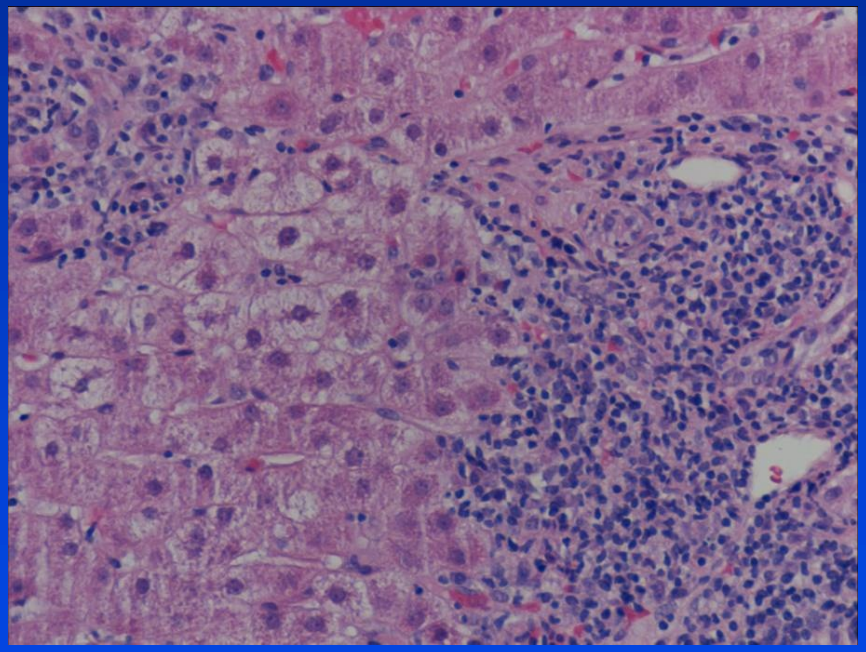
- Several significant side effects: interstitial pneumonitis, peripheral neuropathy, exfoliative dermatitis, hemolytic anemia, lupus-like syndrome, and DILI
- Two major forms of DILI:
  - Acute : less common; 1-3 weeks of Rx; hepatocellular; fever and rash common; + ANA uncommon
  - Chronic: more common; months to yrs of Rx; female gender and age are risk factors

Nitrofurantoin Hepatotoxicity
"Autoimmune Mimic"

- Autoimmune features are typically seen with the chronic form:
  - + ANA
  - + SMA
  - +/- hypergammaglobulinemia
  - HLA-DR6 and –DR2
- RX:
  - Drug withdrawal
  - Steroids (rapid taper with improvement)

Nitrofurantoin Hepatotoxicity
"Autoimmune Mimic"



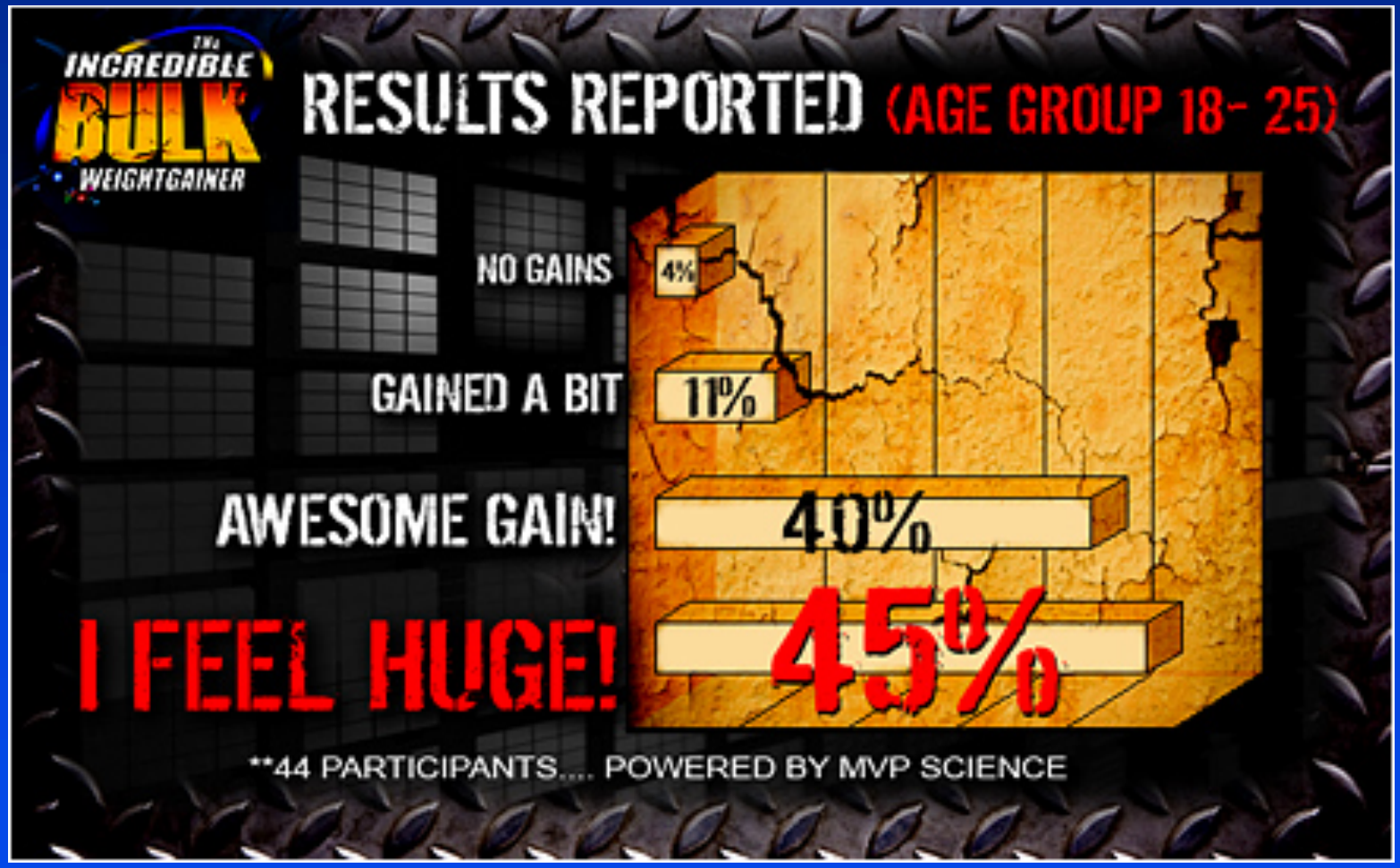


BJMP 2011;4(3):a429

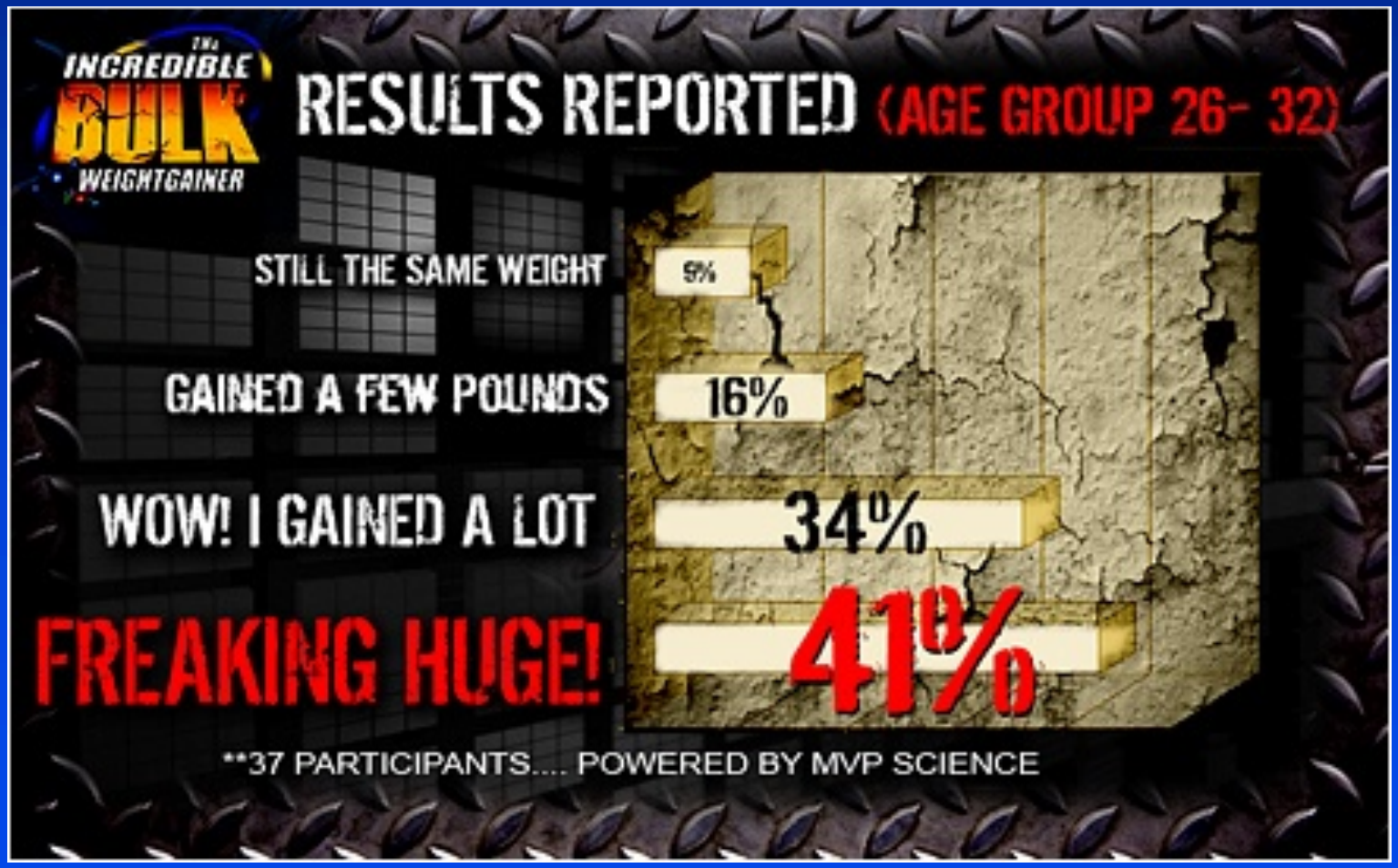
Anabolic Steroids Hepatotoxicity "Incredible Bulk"

- Alkylation of the C-17 position of testosterone allows for oral absorption and increased anabolic potency
- "The androgenic steroids are often used off label and illegally as a means of increasing lean muscle mass and athletic performance" - *LiverTox*
- Found in some nutritional supplements available OTC and on internet

Anabolic Steroids Hepatotoxicity "Incredible Bulk"



Anabolic Steroids
Hepatotoxicity
"Incredible Bulk"

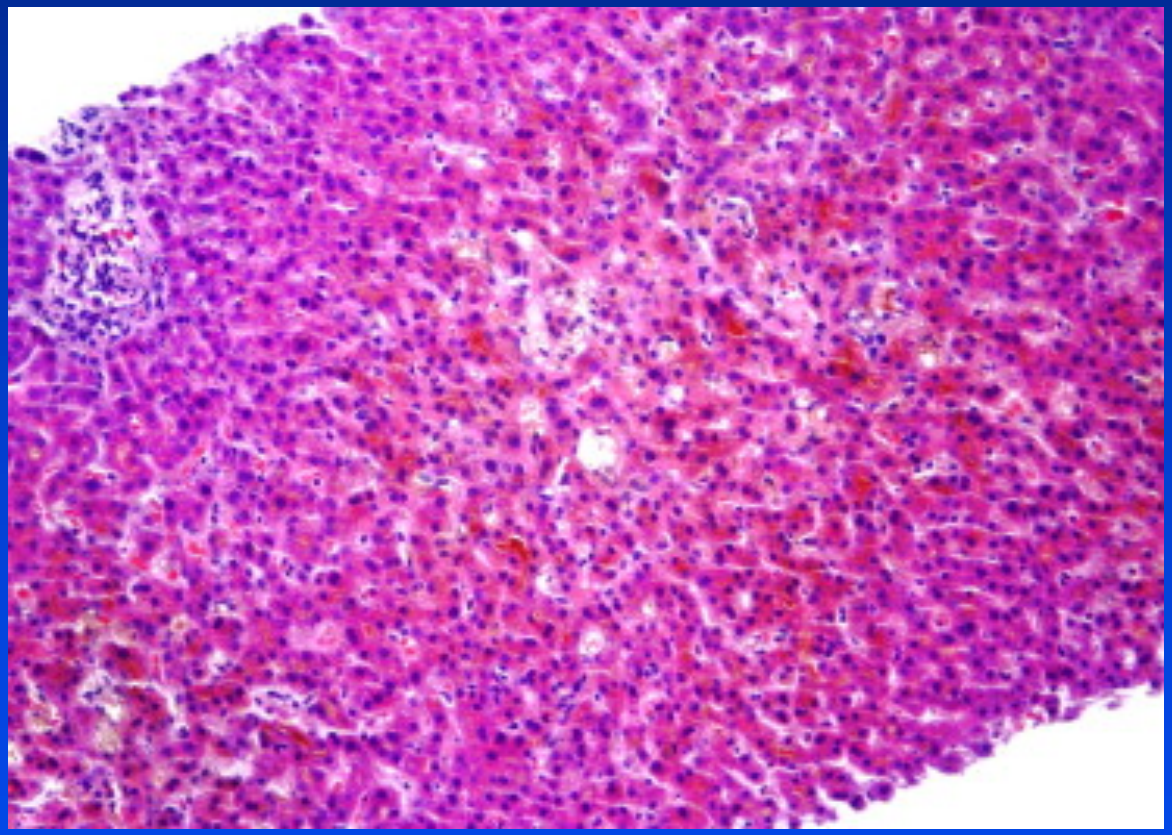


Anabolic Steroids
Hepatotoxicity
"Incredible Bulk"

Anabolic Steroids Hepatotoxicity "Incredible Bulk"

- DILI secondary to body building agents was commonly observed in DILIN registry
- The phenotype ("signature") observed with this class of CAM products is fairly easy to recognize – "bland cholestasis"
- Jaundice may be profound and long lasting; I have seen at least a few cases of ARF requiring HD in this setting
- ALF is very rare

Anabolic Steroids Hepatotoxicity "Incredible Bulk"



Clin Gastro Hep 2008;6:255–258

Anabolic Steroids Hepatotoxicity "Incredible Bulk"

- **Treatment:**
  - Stop juicing - "Unfortunately athletes and body builders may resist this recommendation" – *LiverTox*
  - Ursodiol
  - Cholestyramine
  - Nasobiliary tube?
  - No corticosteroids
  - No transplant
  - Hemodialysis for ARF

Weight Loss Agent Hepatotoxicity "OxyELITE Pro"

- Sept 2013: 7 initial cases of ALF associated with OEP in Hawaii; by October, 56 cases (43 in Hawaii) reported with at least one death and several transplants
- Phenotype: acute hepatocellular injury with jaundice
- Median latency ~ 60 days
- Responsible agent – "aegeline"

212

Increasing Episodes of Hepatotoxicity in the Drug Induced Liver Injury Network Associated with Kratom, a Botanical Product with Opioid-Like Activity

Victor J. Navarro [1], Joseph Odin[2], Jawad Ahmad[2], Paul H. Hayashi[3], Robert J. Fontana[4], Hari S. Conjeevaram[5], Bharathi Avula[6], Ikhlas Khan[7,8], Huiman Barnhart[9] (1) Digestive Diseases and Transplantation, Einstein Healthcare Network, (2) Icahn School of Medicine at Mount Sinai (ISMMS), (3) Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, (4) Internal Medicine, University of Michigan, (5) University of Michigan, (6) Pharmacy, University of Mississippi, (7) University of Mississippi, (8) School of Pharmacy, University of Mississippi, (9) Duke University

- **Herbal sedative/narcotic associated with 90 deaths**
- **7 cases of apparent Kratom DILI**
  - **6 M: 1 F**
  - **Latency 22 days**
  - **Mean ALT 326, AP 292, Tbili 9.5**
  - **All pts recovered**

Occult HEV Infection Masquerading as DILI

- First 300 cases enrolled in the DILIN Network were tested for anti-HEV
- 50 had IgG anti-HEV (16%)
- 9 were reactive for IgM anti-HEV (3%)
- 4 of 9 had HEV RNA, all were genotype 3
- 8 men, 1 woman; mean age 65 years
- None of the 9 had recent travel to endemic areas
- Think about HEV with cases of possible DILI particularly with hepatocellular injury and in older patients

Gastroenterology. 2011 Nov;141(5):1665-72

Statin DILI

- Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors
- Among the most commonly prescribed medications in the United States
- All 7 approved statins have been associated with mild to moderate ALT elevations that typically resolve even with ongoing rx
- All also associated with rare clinical DILI
- Mostly hepatocellular
- Variable latency – 6 months to years
- Some cases with autoimmune features

Statins and Cirrhosis

- Multiple (mostly retrospective) studies suggest statins not only safe but beneficial – reduced liver decompensation, HCC, nfection, and death
  - confounding by indication
- Statins appear to have anti-inflammatory and anti-fibrotic proprieties in multiple tissues
- The data available to date probably do not support wide-spread use of statins in patients with cirrhosis but no other indications
  - prospective studies needed

DILI – The Cardinal Rules

- Always think about DILI in the patient with liver injury
- Always think about acetaminophen poisoning
- Stop the culprit drug(s) ASAP
- Early and liberal use of NAC
- Monitor closely for evolution of liver injury
- Early referral for OLTx evaluation
- Consult *LiverTox* early and often

Finished!