

# Serious Drug Induced Liver Injury

**Lana L. Pauls, MPH**

**John R. Senior, MD**

Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research (CDER)

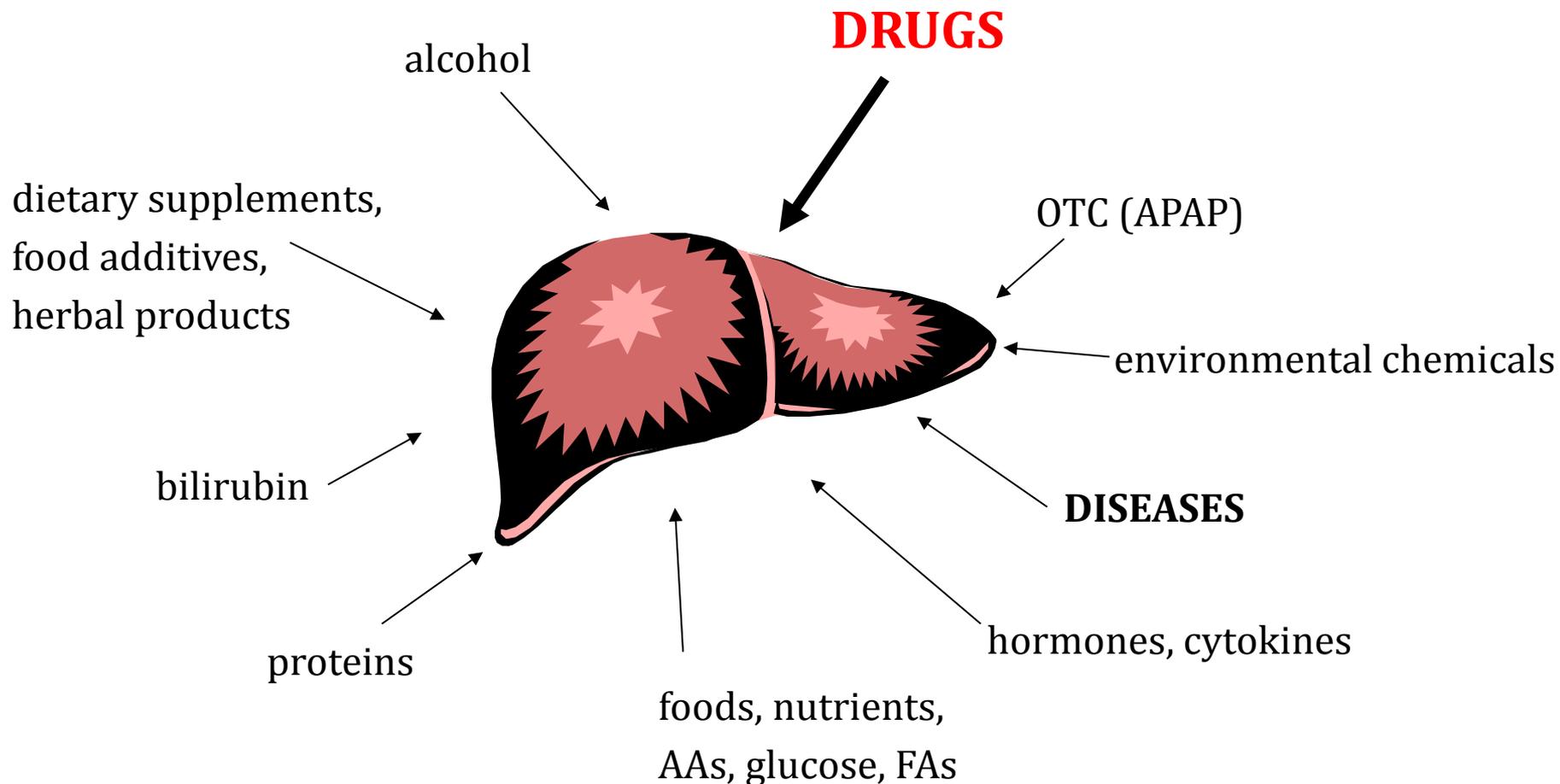
## Why Should We Care about DILI?

1. May cause serious or fatal liver injury in some patients
2. May result in disapproval of a new drug or its removal from the market
3. May be a troublesome problem for drug development, regulatory agencies, and patient care
4. It's not necessarily a dangerous drug, but may be an especially susceptible patient or subject
5. It's important to be able to identify susceptible people

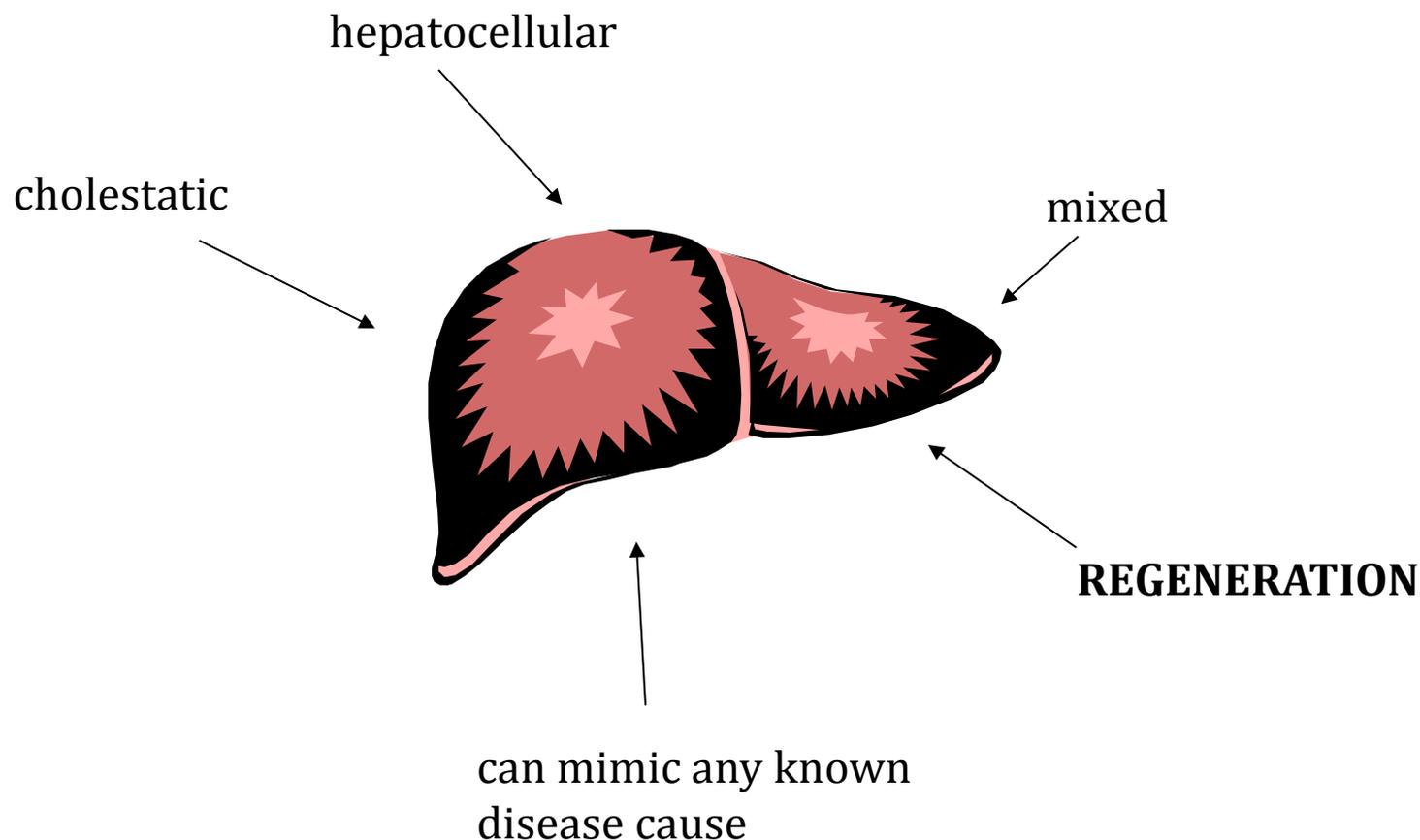
# What Does the Liver Do?

- Serves as the body's chemical engineering and control center
  - Regulates the metabolism of internal compounds
  - Copes with compounds coming in from the environment, such as DRUGS
- Has an astounding ability to:
  - adapt, change (regrows even if 2/3 resected)
  - alter activities of its enzymes and transporters
  - regenerate rapidly if cells are killed or removed

# The Liver: Many “Assaults”



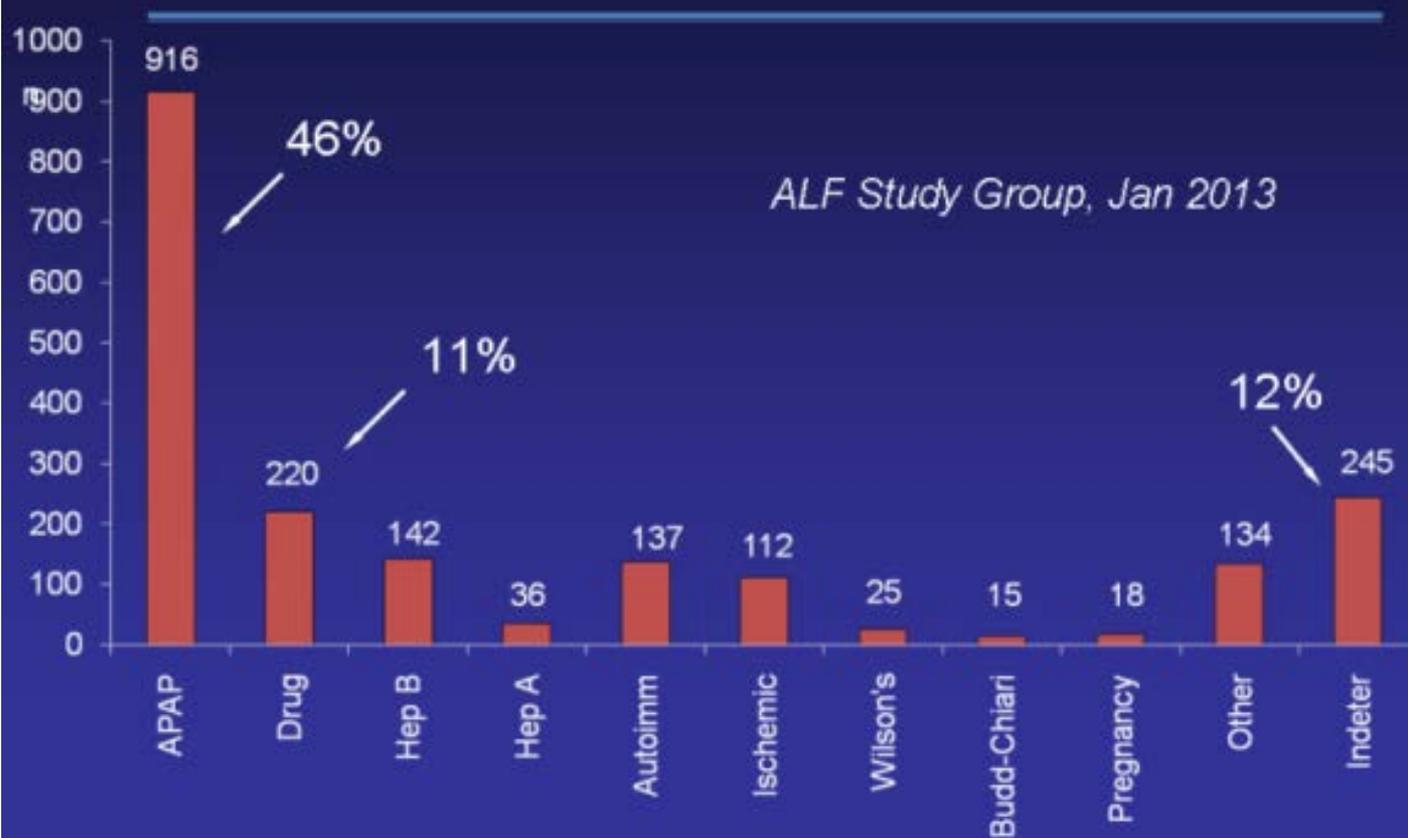
# The Liver: Many “Responses”



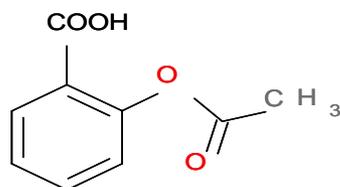
# Common Causes of Acute Liver Failure

- Approved drugs
- OTC products (APAP)
- Alcohol

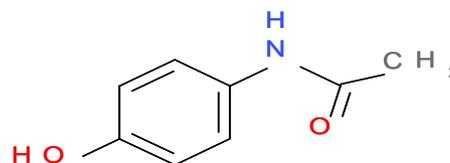
## Etiology of Acute Liver Failure in the USA Adult Registry (n = 2,000)



# Why So Much Trouble with Acetaminophen?



acetylsalicylic acid (ASA)  
Gerhardt 1853; Bayer 1879  
Dreser "aspirin" 1899



N-acetyl-p-aminophenol - "APAP"  
or acetaminophen (Tylenol)

- (a.k.a. "APAP" = N-acetyl-p-aminophenol {Lee}, paracetamol {England}, TYLENOL {trade})?
- More is not better – it can be dangerous!
- Often included in multiple medications without consumer knowledge

## What is a Hepatotoxic Drug?

- an oxymoron; if truly hepatotoxic, it is not, or should not, be an approved drug
- Admittedly some drugs are more likely to cause liver injury than other drugs -
  - some patients are more susceptible to the same drug and dose than are most people
- Drugs are not intended to cause harm, but may do so in some people

# Drugs that Cause DILI:

## Rates of mild transient liver injury and ALF

	Incidence	
	ALT > 3x ULN	ALF
isoniazid	~ 10 %	< 0.1 %
troglitazone	~ 2 %	< 0.05 %
ximelegatran	~ 8 %	< 0.05 %

# Regulatory Actions due to DILI Marketed Drugs: 1995 - 2012

Withdrawals	Warnings	
bromfenac	acetaminophen	leflunomide
troglitazone	nefazodone	nevirapine
pemoline	pyrazinamide/rifampin	terbinafine
ximelgatran **	valproic acid	zifirlukast
lumaricoxib **	atomoxetine	interferon 1b/1 <sup>a</sup>
	saquinavir	infliximab
<b>Special Use</b>	bosentan	telithromycin
trovofloxacin	erlotinib	natalizumab
felbamate	(kava)	(lipokinetix)
tolcapone		

**FDA has not approved any drug since 1998  
that has had to be removed from the  
market because of serious DILI!**

# Idiosyncratic DILI: Some Inciting Drugs

- ***Hepatocellular injury, immunoallergic:*** phenytoin, sulfonamides, allopurinol, halothane, diclofenac, quinolones, telithromycin,
- ***Hepatocellular injury, metabolic:*** INH, troglitazone, ximelagatran, bromfenac
- ***Cholestatic:*** estrogens, 17a androgens, chlorpromazine, clavulanic acid, piroxicam
- ***Bile duct injury:*** carbamazepine, chlorpromazine, chlorpropamide, cyproheptadine, thiabendazole, haloperidol
- ***Microvesicular steatosis:*** valproate, tetracycline, didanosine
- ***Phospholipidosis & pseudoalcoholic hepatitis:*** amiodarone, perhexiline maleate
- ***Chronic autoimmune-like hepatitis:*** dantrolene, methyldopa, nifurantoin, oxyphenisatin, propylthiouracil, tienilic acid

# What Do We Need to Know About DILI?

1. How clinically severe is it?
2. How probable is it that it was caused by the implicated drug?

Severity CANNOT be assessed by the level of serum enzyme elevation; it may indicate the rate of hepatocellular injury but does not measure the ability of the liver to function and support life.

The only true function tests often done are serum bilirubin and plasma prothrombin time.

Causality is another matter!

## Serum Enzymes are NOT Liver *Function* Tests !

- It is NOT a true function of the liver to regulate levels of enzyme activity in the plasma
- Elevated levels may reflect injury to liver cells, but **FUNCTION** must be measured by other tests
- The only tests commonly done that measure liver **FUNCTION** are:
  - Bilirubin concentration, BILI
  - Prothrombin time, or its INR derivative
- Should not be called “LFTs”, simply “LTs”

# Levels of DILI Severity

- 5** **Death or Tx**
- 4** **Acute Liver Failure**
- 3** **Serious: Disabled, Hospitalized**
- 2** **Hy's Case: Injury with Slight Functional Loss**
- 1** **Serum Enzyme Elevations Only; Many People Adapt**

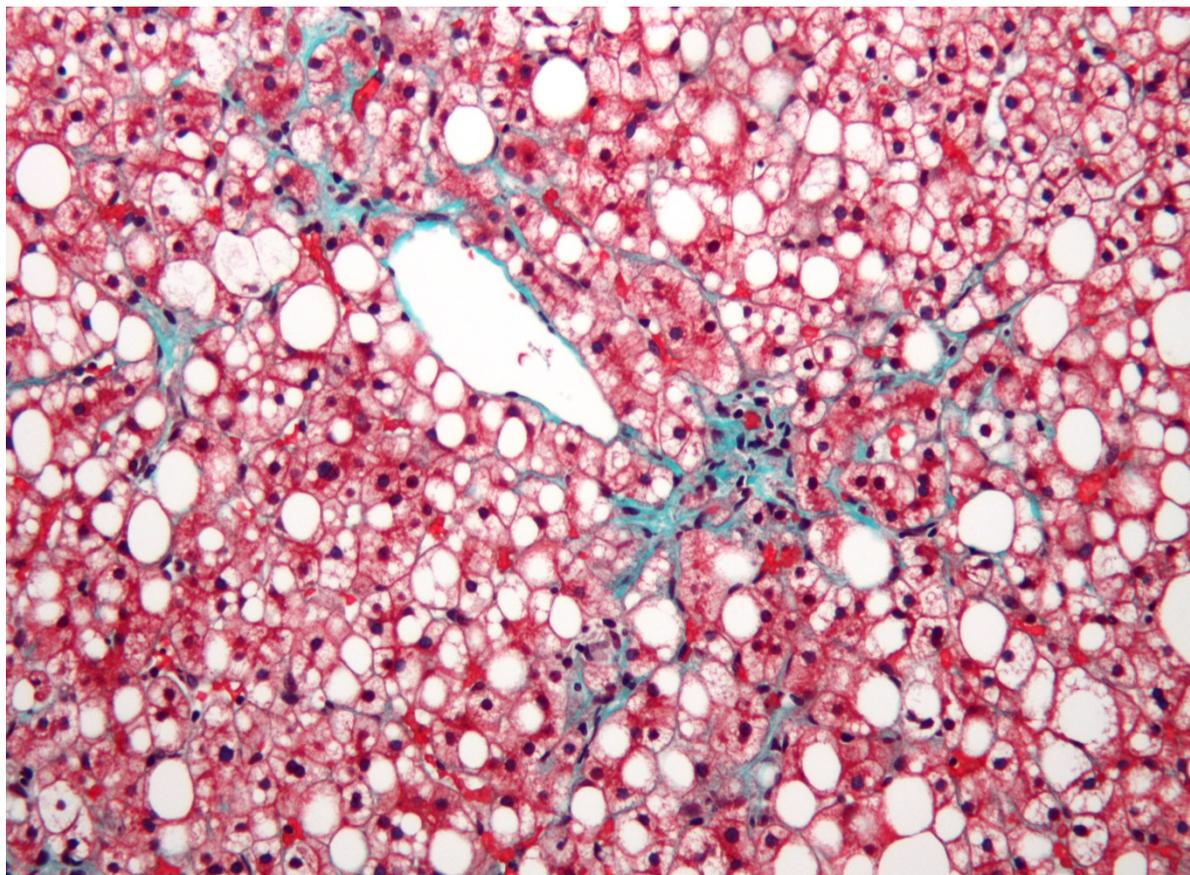
# Likelihood That the Liver Problem was Caused by DILI

NCI/ FDA			DILIN
1	5 to 25%	“unlikely”	5
2	>25 to 50%	“possible”	4
3	>50 to 75%	“probable”	3
4	>75 to 95%	“very likely”	2
5	>95%:	“certain, definite”	1

**Conversion: (6 - FDA/NCI) = DILIN**

## Clinical Importance (SEV-LIK score) for Individual Cases

DILI <u>Likelihood</u>	<u>Severity of Liver Dysfunction</u>					
	5 fatal or transplant	4 acute liver failure	3 serious	2 “Hy’s case”	1 enzyme rises only	0 none detectable
5: definite <i>&gt;95% likely</i>	<b>25</b>	<b>20</b>	<b>15</b>	<b>10</b>	<b>5</b>	
4: very likely <i>&gt;75 to 95% likely</i>	<b>20</b>	<b>16</b>	<b>12</b>	<b>8</b>	<b>4</b>	
3: probable <i>&gt;50 to 75% likely</i>	<b>15</b>	<b>12</b>	<b>9</b>	<b>6</b>	<b>3</b>	
2: possible <i>&gt;25 to 50% likely</i>	<b>10</b>	<b>8</b>	<b>6</b>	<b>4</b>	<b>2</b>	
1: unlikely <i>5 to 25% likely</i>	<b>5</b>	<b>4</b>	<b>3</b>	<b>2</b>	<b>1</b>	
0: certainly not <i>&lt;5% likely</i>						



**Hy Zimmerman  
(1916 - 1999)**



## What is “Hy’s Law”?

- Hy Zimmerman said, repeatedly:  
“**drug-induced hepatocellular jaundice** is a serious lesion, with mortality from 10 to 50%” ... *he did not say it was a law and didn't want it named for him*
- In 1999, Bob Temple articulated a modified form of this observation for use in controlled clinical trials as a screening threshold and dubbed it “Hy’s Law.”
  - {ALT or AST >3x upper limit of normal **AND** TBL > 2xULN}
  - Not primarily cholestatic; not caused by disease but by drug

***It was catchy then and now seems impossible to change !***

# What “Hy’s Law” is NOT!

- Not just abnormal serum chemistries:  $ALT > 3 \times ULN$  &  $TBL > 2 \times ULN$   
these are simply a signal to look closer
- Should not be initially cholestatic:  $ALT_x / ALP_x < 2$
- Must not be probably caused by other than drug --- find out
- Requires clinical adjudication (differential diagnosis) to determine probable cause
- Often misunderstood by sponsors, their staffs, and their consultants
- Important to find the probable cause of liver dysfunction

# Identifying a DILI Signal: *Clinical Trial Studies*

*Finding liver injury associated with exposure to a drug may indicate a higher risk to others exposed to the same drug*

*(note: “associated with” or “related to” does not prove “caused by”)*

1. Look for imbalance of liver injuries (enzyme rises) in randomized trials: more frequent and severe in those on drug, as suggestive indicators
2. Hy's case: ALT > 3 X ULN → bilirubin > 2 X ULN, not cholestatic and probably caused by drug: If present, predicts that serious idiosyncratic DILI cases **may be** more likely in post-marketing treatment population

# FDA Experience

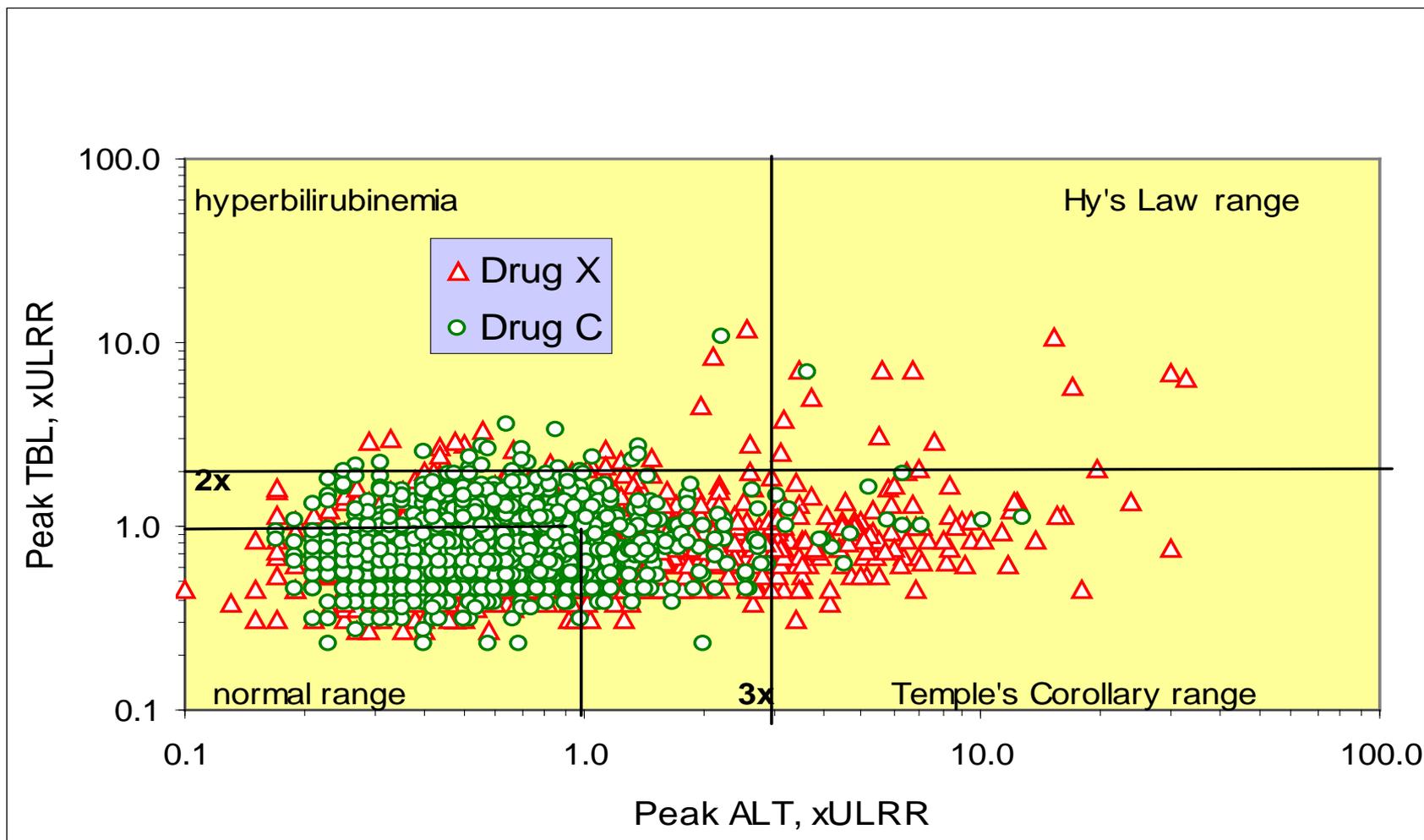
- Limitations of clinical trials
  - Subjects treated in a monitored setting
  - Have the disease being tested, nothing else
  - Selected participants, exclusion criteria
  - Limited numbers, limited time
- After product approval . . .
  - Often used off label, without monitoring, in patients different from those studied in the clinical trial, only voluntary reporting, burden on FDA to prove danger, huge numbers exposed
- Regardless of the above, it is still the largest, by far, database of clinical trial data, and best quality information in the world!

# The FDA Reviewers' Helper --- eDISH

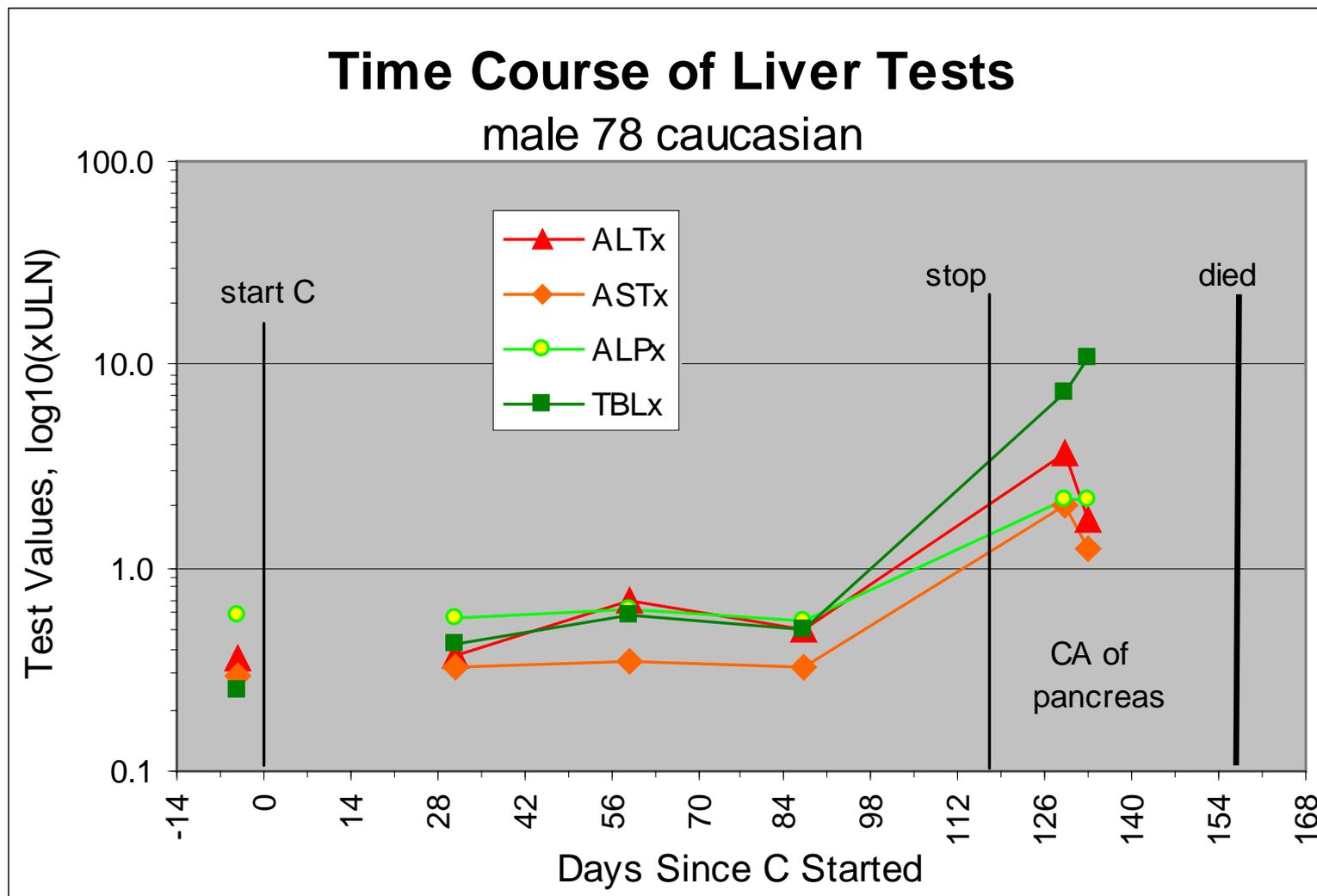
## - an analytical tool, software program

- (evaluation of Drug-Induced Serious Hepatotoxicity)
- to find quickly the “**needles in the haystack**” (rare subjects of special interest), out of large controlled clinical studies ... the few patients or subjects who need to be looked at more closely to determine if the case is clinically serious (disabling, hospitalized) or worse

# eDISH: Step 1



# eDISH: Step 2



## eDISH: Step 3

### Narrative:

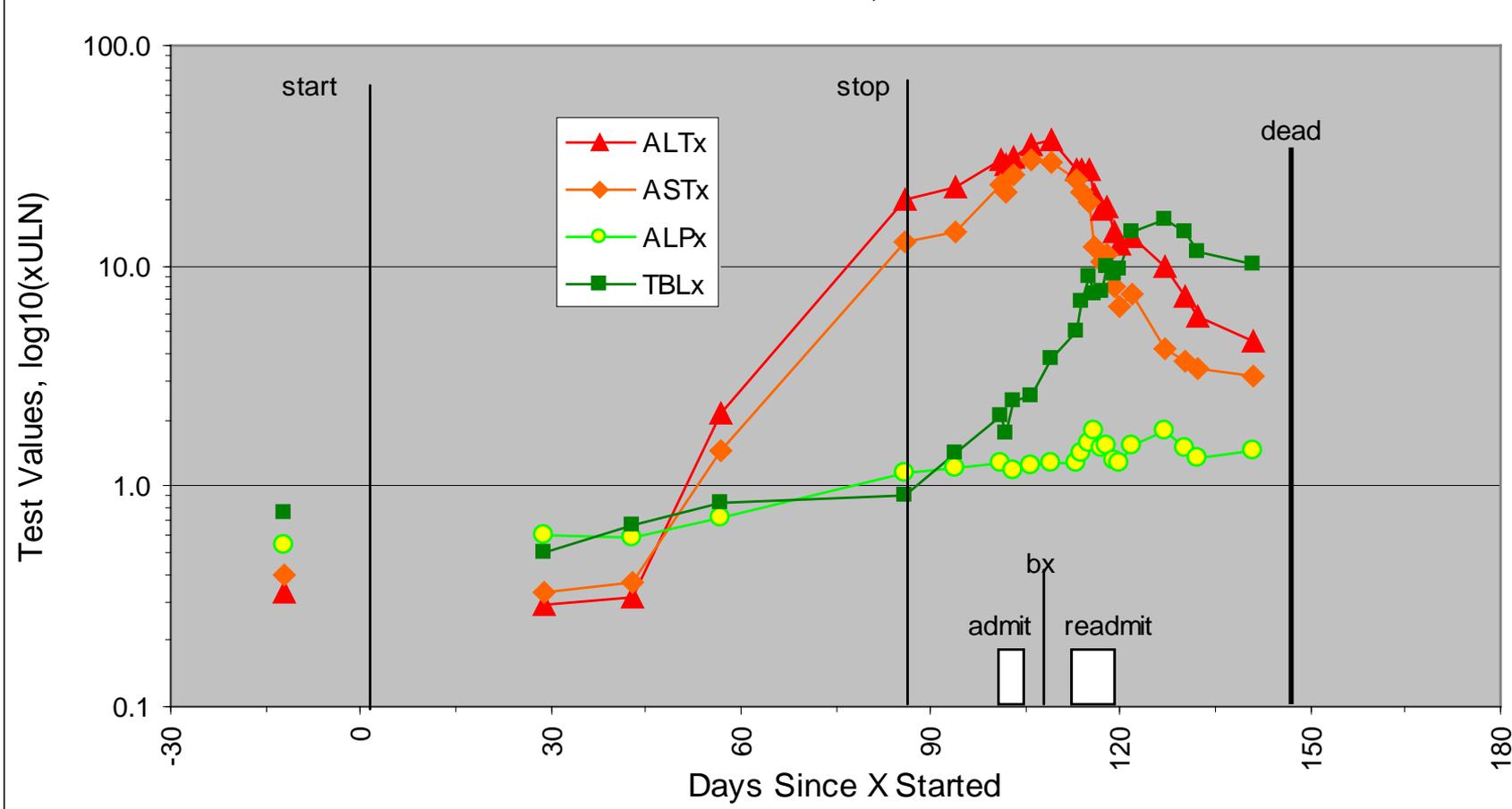
Subject #:8675, treatment: C, 78 yrs, white

78-year-old white male, history of cholecystectomy, atrial fibrillation, hypertension, hyperlipidemia, coronary heart disease, congestive failure. Taking digoxin, pravastatin. Started Coumadin 13 Nov 2001, all tests (ALT, AST, ALP, TBL) normal before and for 3 months, but TBL, ALP and slight transaminase elevations noted March 2002. Stopped Coumadin 20 March. Abdominal mass found on CT, common bile duct occluded by tumor; bx = **pancreatic carcinoma**, not considered resectable. Patient died in hospice on 19 April 2002.

*.... this was not a Hy's case, not caused by the drug*

# Time Course of Test Values

male 80, caucasian



## *eDISH*

1. In addition to the x-y log-log plot of peak ALT and TBL values for each person in the study, you then also need
  - The time course of all liver tests (ALT, AST, ALP, TBL) for patients or subjects of interest, and
  - The clinical narrative, for clues to probable cause and severity of the liver dysfunction; differential diagnosis and should be *written by a physician*

**Try to determine the probable cause!**

**Treat the cause if possible!**

**Interrupt the drug while the diagnosis is made!**

**If drug-induced, stop the drug!**

# Randomized Clinical Trials

- *Benefits*
  - Finding one or more true Hy's case(s) alerts to possible serious DILI in larger future exposure population post-marketing
- *Limitations*
  - Selected population sample for inclusion in study
  - Insufficient powering for rare serious DILI events
  - Short duration of treatment may limit risk of seeing DILI
  - Isolated ALT increases not predictive of serious DILI

# DILI Risk :

## Questions with Regulatory Impact

- Does a drug cause clinically significant DILI in the target treatment population?
- What is the clinical signature of injury associated with the drug?
- What ranges of dose & duration are associated with increased risk?
- What are the critical patient susceptibility factors?
- What incidences of mild & severe liver injury can be predicted in a large treatment population?

# When Should We Ask These Questions?

## **At all phases of the drug's life cycle!**

- Preclinical, before human exposure
- Clinical trials, leading to approval
- Post-marketing, after approval

# People Are All Different in Their Responses to Drugs

- No detected injury (**‘tolerators’**) - does not preclude micro-adaptive changes in liver cells
- Mild (transient & selective) injury (**‘adaptors’**) reflecting liver cell change followed by return to normal even if drug continued
- Clinically significant injury (**‘susceptibles’**) may be reversible when drug is withdrawn

# Pattern and Extent of DILI: *Patient 'Susceptibility' Factors*

- Pre-existing conditions or diseases
- Age & Gender
- Nutritional status
- Alcohol (chronic vs acute)
- Concomitant drugs
- Genetic variants
- Multiple DILI phenotypes

# Pattern and Extent of DILI: *Patient 'Susceptibility' Factors*

There are no “idiosyncratic drugs,” only idiosyncratic recipients (whether people or animals)!

*(idio = one's self + syn = together + crazy = mixing;*

A person's unique particular mixing together of inherited traits and life experiences that may make his/her responses different than that of most others

# Assessment of DILI Risk:

## *Ask and Find Out*

1. How many? population frequency
2. How much? severity of liver dysfunction
3. How soon? rapidity of onset, progression
4. How likely? probability of drug causation

# CIOMS Diagnostic Scale (*RUCAM*)

## *Roussel-Uclaf Causality Assessment Method\**

<u>Individual Criteria</u>	<u>Range of Scores</u>
Time from start of Rx until event	+1 to +2
Time from stop of Rx until event	0 to +1
Course after stop of Rx	-2 to +3
Age	0 to +1
Alcohol/Pregnancy	0 to +1
Concomitant Rx	-3 to 0
Non drug-related causes	-3 to +2
Previous drug information	0 to +2
Dechallenge/Rechallenge	-2 to +3

### Causality Assessment: Total Scores

If 8-10: highly probable: 6 or 7, probable; 3-5, possible; 1 or 2, unlikely.

\*Danan & Benichou, J. Clin. Epidemiol.; 1993

# The DILIN Network



# Registries

## **Geographically/academically defined site-specific networks of inpatient/outpatient referral systems**

- DILIN (US DILI); RRHSS (Spain DILI), SADRAC (Sweden DILI)
- ALFSG (US ALF network)
- UNOS (US liver transplant network)
- Vigibase (Europe)

### **•Benefits**

- Registries for serious outcomes both in US & Europe
- Structured clinical assessment of all patients referred for evaluation
- Useful sampling of 'what's out there'

### **•Limitations**

- Severe under-reporting
- Poor content quality of reports

# DILI Guidance (*July 2009*)

## *Evaluation & Management Steps in Clinical Trials*

- Characterization of baseline liver conditions/diseases
- Efficient detection of acute liver injury (early symptoms, systematic serum lab tests); confirmation with repeat testing
- Observation & workup of patients with liver injury
- Guideline study *stop rules*
  - ALT/AST > 8x ULN or ALT/AST remains > 5x ULN over 2 wks
  - ALT/AST > 3x ULN & T Bili > 2x ULN or INR > 1.5
  - ALT/AST > 3x ULN with symptoms (e.g. fatigue, N&V, RUQ pain, fever, rash) or eosinophilia
  - *rechallenge* generally should be avoided with ALT/AST > 5X ULN unless no other good therapeutic options, informed consent encouraged

# Drug Life-Cycle Data Streams

## *DILI Risk Assessment – Needs Improvement*

- Randomized clinical trials – best data; too small/short
- FAERS reports – usually inadequate data given
- Published case reports – spotty quality
- DILI in registries – often aimed at cost control
- Observational cohort studies – limited value
- Case-control studies – need confirmation

# Summary

- Individual idiosyncratic susceptibility factors determine if subjects or patients exposed to a new drug will be '*tolerators*', '*adaptors*' or '*susceptibles*'
- In pre-approval clinical studies, milder injury may be important especially if function disturbed
- Post-market DILI risk assessment is more difficult to evaluate for severity and cause, mainly because of poor information, as well as under-reporting
- Predictive biomarkers of DILI that identify *susceptible patients* are needed but do not yet exist

# DILI Best Practices

We all know there's a problem, *but what should we do about it?*

- but haven't been able to make ourselves well understood.
  - *we have found the enemy - it's us*
- We need to embrace the problem;
  - *use the KISS principle*

# How Should Liver Test Elevations be Handled?

- Sponsors of studies should make sure that their investigators know what to do, and report cases immediately
- They should confirm abnormalities promptly, in local laboratory as needed
- If confirmed, interrupt drug administration and follow ALT, AST, ALP, BILI serially and closely
- Serum enzyme activities do not measure liver functions; BILI and INR do
- Investigate clinically for probable or most likely cause
- Rule out as more likely causes: acute viral hepatitis; autoimmune/alcoholic hepatitis; other liver diseases; other drugs/chemicals, dietary supplements
- Liver biopsy, scans are rarely diagnostic; no pathognomonic test for DILI
- Request consultative help if needed to diagnose most likely cause
- Follow subject's course until resolution; record and report findings

## Questions about DILI?

- E-mail: [ana.pauls@fda.hhs.gov](mailto:ana.pauls@fda.hhs.gov)  
[john.senior@fda.hhs.gov](mailto:john.senior@fda.hhs.gov)
- <http://www.FDA.gov> enter “liver toxicity”
- March 19-20, 2014 Annual Meeting, co-sponsored by FDA/PhRMA, C-Path and AASLD