



# More Lessons from Isoniazid

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***If research subjects show ALT >3xULN, or some other level of injury, stop drug, do not rechallenge ! ---- ???  
Does this waste possibly useful new drugs needlessly?***

Is this reasonable, or overkill based on selected emphasis on rare but very serious harmful events, ignoring the far more common negative rechallenge and liver adaptation that may not be reported?

*There is a major difference between rechallenge during clinical development, by sponsors with full resources and required reporting of results, and rechallenge by doctors in practice concerning approved drugs showing liver injury.*



I am not interested in “winning” this debate, but only in trying to reach consensus on the best way forward. Let us consider this a discussion rather than a debate, since we are all trying to do the same thing --- protect patients who will be prescribed the drug after approval.

It was intended that this discussion focus on NEW drugs under development, where adequate precautions can be taken and results fully reported.

**The critical issue is whether a new drug will do more good than harm in those exposed, i.e., good or harm in how many, how much, how soon, how likely.**



Despite thousands of papers on **benefit- risk *ratio*, *balance*, *profile*, or *difference***, we still do not have any valid, generally accepted measures for these important effects of drugs.

Patients differ in their responses to drugs, in both the intended beneficial and the unintended harmful effects. Simply averaging them does not solve the problem of balancing rare risks of serious harmful effects against the chances of frequent but modest beneficial effects.

... nobody said it was easy.

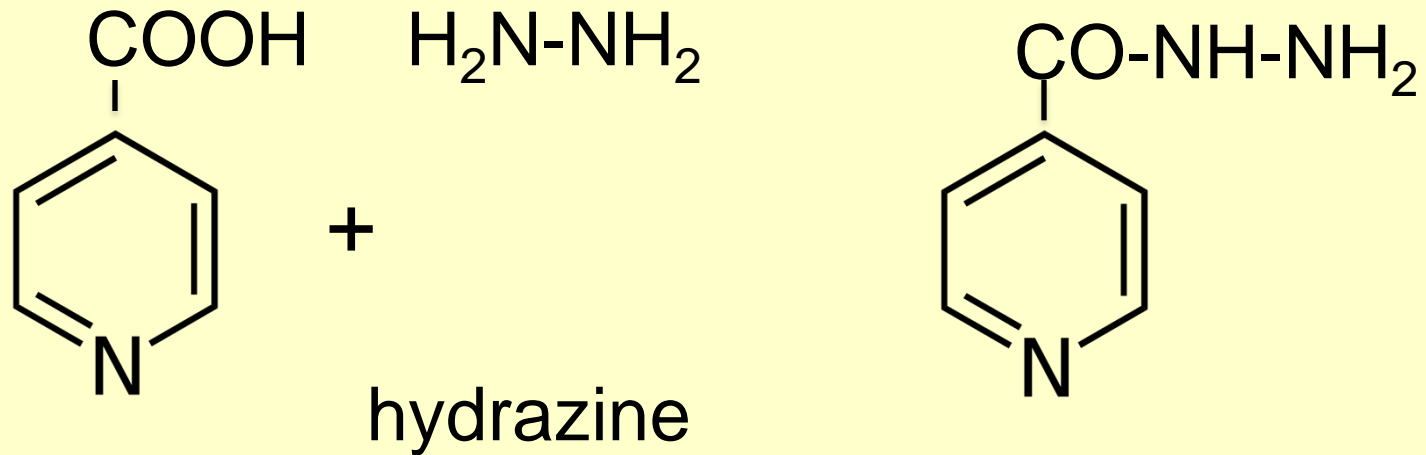


Therefore, I shall focus on **isoniazid**, to illustrate some key points that should be considered,

--- and ask this learned audience to think about the larger issues of how to measure and compare the beneficial vs. harmful effects of drugs.

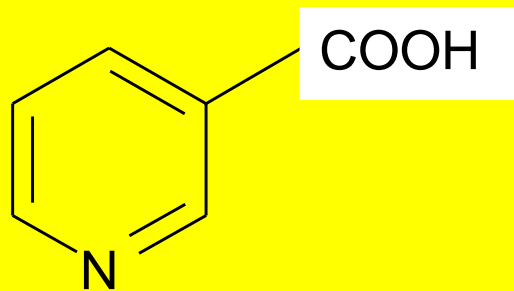
**Can we really figure out how to measure and compare good effects and bad effects of drugs?**

# What is isoniazid?

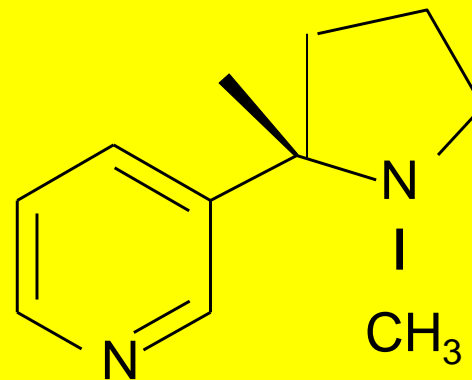


isonicotinic acid

isonicotinic acid hydrazine  
isonicotinyl hydrazine  
isoniazid  
INH



**nicotinic acid**  
**vitamin B<sub>3</sub>**  
**= niacin**



**nicotine**

# INH was very useful, valuable ...

It was found to prevent activation to full-blown lung infection by tuberculosis in people who had been exposed and were found to be infected (tuberculin-positive) ---

Bernstein J, Lott WA, Steinberg BA, Yale HL Chemotherapy of experimental tuberculosis.

V. Isonicotinic acid hydrazide (nydrazid) and related compounds. Am Rev Tuberc. 1952; 65:357-64.

Steenken W, Wolinsky E. Antituberculous properties of hydrazines of isonicotinic acid (Rimifon, Marsilid). Am Rev Tuberc. 1952; 65:365-75.

**--- but could also be hepatotoxic:**

Randolph H, Joseph S. Toxic hepatitis with jaundice occurring in a patient treated with isoniazid JAMA 1953; 152:38-40.

Sharar L, Smith JP. Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med. 1969; 71:1113-20.





## - INH could be dangerously hepatotoxic

In a large study of 18,383 patients at sites in 26 cities done in 1971-2 under US Public Health System auspices there were 87 probable cases of serious hepatotoxicity including 8 deaths, 7 out of 3,196 in Baltimore alone.

It took more than 20 years for Nolan et al. to figure out how to avoid serious toxicity without routine monitoring of all the patients treated, relying on patients' symptoms and prompt action to stop the drug --- with no deaths in 11,141 treated.

Black M, Mitchell JR , Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. *Gastroenterology* 1975; 69::289-302.

Kopanoff DE, Snider DE, Caras G. Isoniazid-related hepatitis. A U.S. Public Health Service Cooperative Surveillance Study. *Am Rev Resp Dis.* 1978; 117:991-1001.

Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associate with isoniazid preventative therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; 281:1014-8



# How did Nolan, Goldberg, and Buskin do it?

After >10 years of what seemed endless wrangling they ran a study from 1989 through 1995 at the Seattle-King County Department of Public Health Tuberculosis Clinic, treating 11,141 patients with single and multiple drug regimens and followed them monthly. They did NOT monitor them with serum transaminase measurements, but instructed them at the initial and all monthly visits to be on the alert for **signs or symptoms** (anorexia, nausea, vomiting, jaundice), stop taking the drugs, report immediately, and come for testing by laboratory tests. If AST >5xULN, no rechallenge was done. They found 11 patients showing hepatotoxicity from INH alone (1/1000), 4 more on combination therapy.

**All of the patients recovered and there were no deaths !**

# An important study . . .

Jerry Mitchell and his NIH colleagues were trying to understand the mechanism of INH-induced liver injury, especially whether acetylation of INH was a factor. They conducted a study in 1968-71 of 201 men in a Williamsburg VA mental hospital who were exposed to tuberculosis and were tuberculin-positive.

They arranged to have blood drawn q, 4 weeks to measure SGOT (AST) while the subjects were receiving 300 mg/day of INH for a year, freezing sera for batch analysis at CDC in Atlanta after the study end. Samples with SGOT >60 also had bilirubin concentration measured.

None of the patients showed clinical hepatitis or had to stop drug treatment, and none developed active tuberculosis,

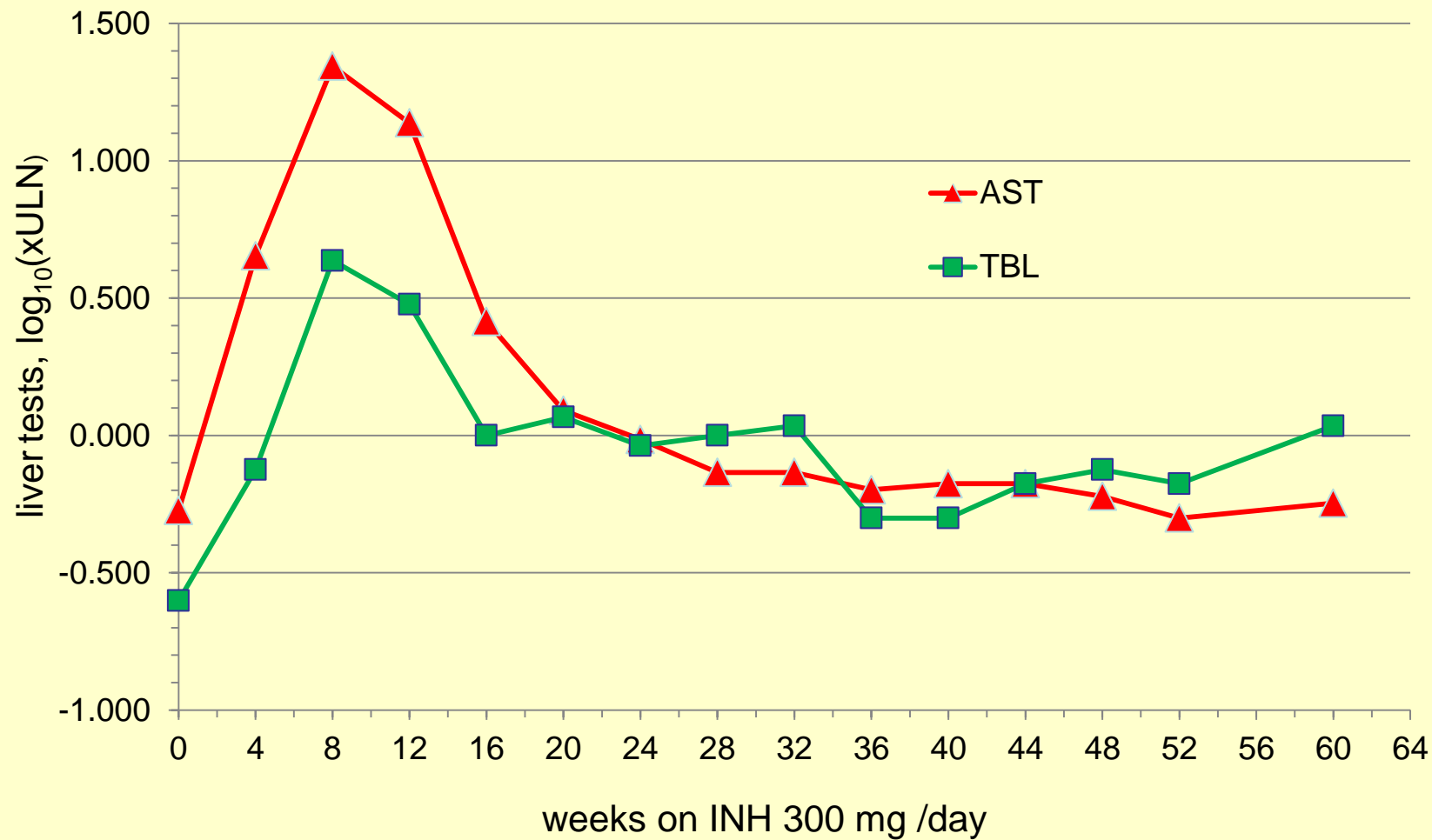
**--- but the results were remarkable !**

Mitchell JR, Long MA, Thorgeirsson UP, Jollow DJ. Acetylation rates and monthly liver function tests during one year of isoniazid preventative therapy. Chest 1975;68:181-90.



# Time Course on INH

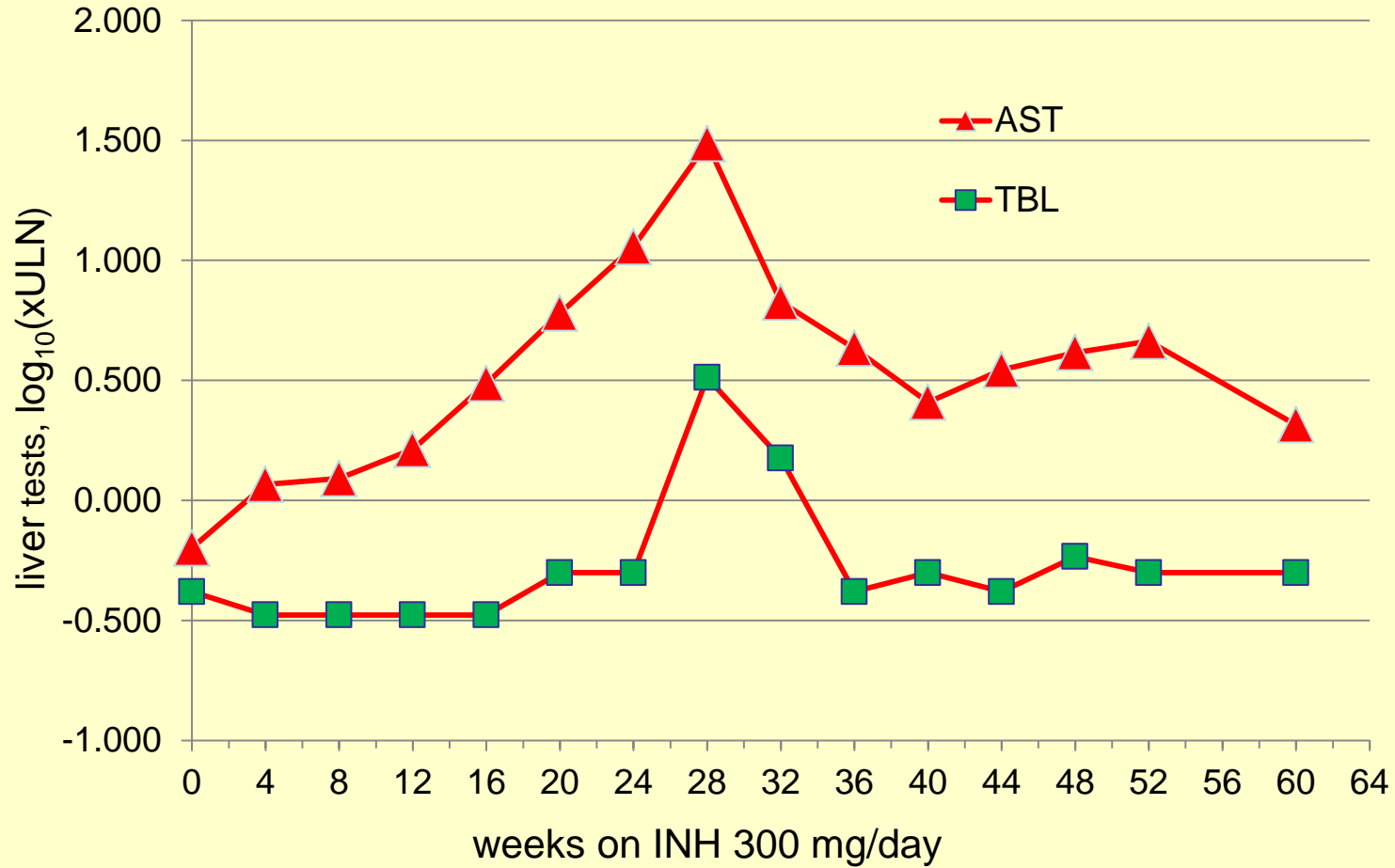
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# Time Course on INH

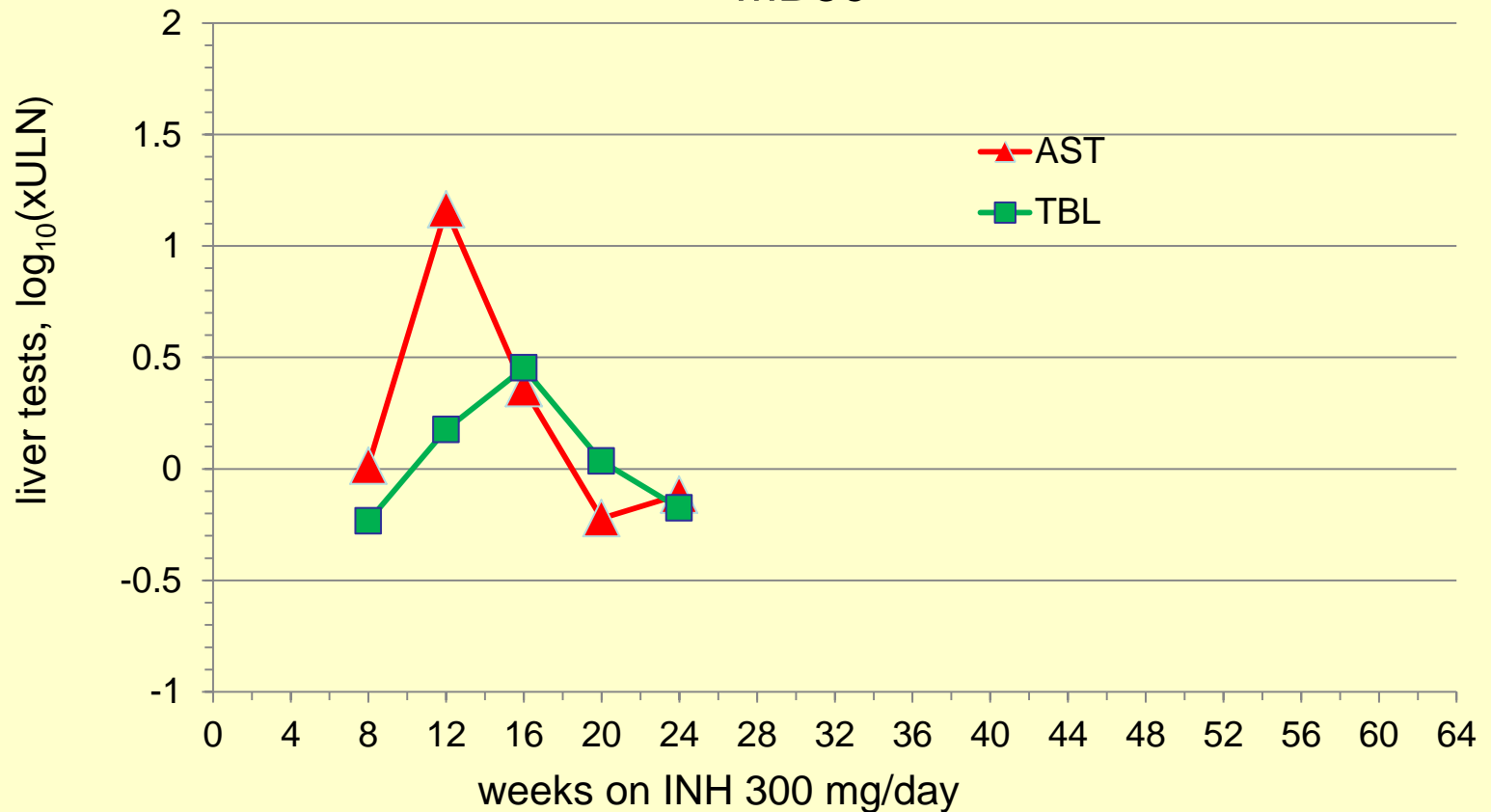
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# Time Course on INH

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--- INH is still with us, as part of combined therapy of active tuberculosis with ethambutol, rifampin, pyrazinamide ---

--- and tuberculosis is not going away, but infects about a third of the world population, mostly of the malnourished and poor of India, China, Africa, ---

--- and multidrug resistance *M.tb* is increasing ---




Back to the question of this debate ---

**Should rechallenge never be done for new drugs in development if they show serum transaminase elevations  $>3xULN$  in clinical trial subjects?**

Is it too dangerous?

I argue no, that's going too far, bending too far over backwards. Too many drugs will be lost.






# FDA Premarketing Liver Safety Guidance<sup>1</sup>

**“Generally, rechallenge of subjects with significant AT elevations (>5xULN) should not be attempted.** If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown:

- ***important benefit from the drug and***
- ***other options are not available or if***
- ***substantial accumulated data with the test drug do not show a potential for severe injury.***

***The subject should be made aware of the potential risk, and consent to the rechallenge, and the institutional review board consulted.”***



# FDA Premarketing Liver Safety Guidance<sup>1</sup>

“Possibly *liver-related deaths* and *liver-related treatment discontinuations*:


- These cases should be described and
- time-to-event analyses should be performed.
- Follow-up status also should be provided.
- ***There should be a description of*** any histologic and ***rechallenge data.***”



Have we not learned that the liver is able to change itself, adapt, become tolerant, besides its ability to regrow if hepatocytes are lost?

Have we not learned that every patient may differ in how they respond to a drug, well or badly? They are not all the same and should not be averaged.

Just because a very bad effect can rarely happen to some patient, it should not be assumed that it will occur to others, especially if you don't look at the negative rechallenges that might outnumber the positive rechallenges by 9 or 99 to 1.



## Back to the question of this discussion ---

--- it was proposed that this discussion be limited to **new** drugs in development, and I concede that rechallenge is indeed too dangerous to be carried out *in clinical practice* for drugs in patients who have shown serious hepatotoxicity probably attributable to the drug and not to disease or other cause.

***For new drugs under development it may be safe to carry out rechallenge , but carefully and only during well controlled studies by pharmaceutical companies.***

*Julie Papay has given examples of this.*

***We need more and better data from clinical trials!***

# Back-up Slides



As far as the question of this discussion ---

--- whether a **new drug in development** should be discarded or not may be an industry issue, not an FDA matter. The FDA only loosely supervises IND studies and does not look closely at data until NDAs are submitted.

***Should this issue be decided by industry, not FDA?***



There is need to think about the larger issues of drug safety mentioned previously, to find better ways to assure it to the public, for patients who will be taking the drugs and their prescribing physicians. Because of the rarity of serious drug hepatotoxicity (and other serious adverse effects, not just hepatic), it is not reasonable to expect that large enough trials be conducted long enough to provide probable safety assurances comparable to the efficacy findings from trials.

Reliance on voluntary reporting of adverse events after approval and marketing of a new drug is a failed concept. In the real world, doctors just don't report, and the required reports forwarded by industry lack sufficient information to draw any valid conclusions about causality, incidence, etc.



Under the Constitution of the United States, as amended, Congress has assigned responsibility to the FDA to ensure that new drugs approved are safe as well as effective, but that is a very difficult task. Much remains to achieve better assurances to the people that this is possible and true. We hope that these concerns will cause audience experts to think about what could/should be done, and speak up.

I, as a taxpayer but not as a federal employee, hope that legislators will think primarily about representing all of their constituents by enacting better laws to ensure drug safety.



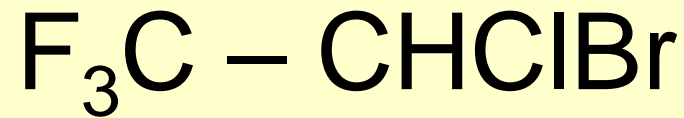


In the insightful words of Senator Pogo from the mythical State of Confusion . . .

“In our search for who’s responsible for the problems of drug safety and pricing, we have found the enemy -- and it is us.”



halothane



Wyeth-Ayerst, Fluothane<sup>R</sup>, 1958



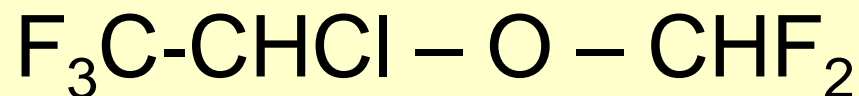
# The first anesthetics



diethyl ether

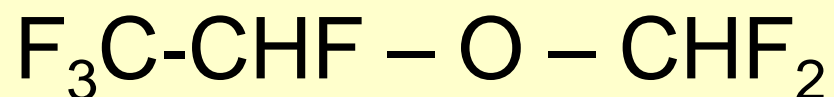


chloroform



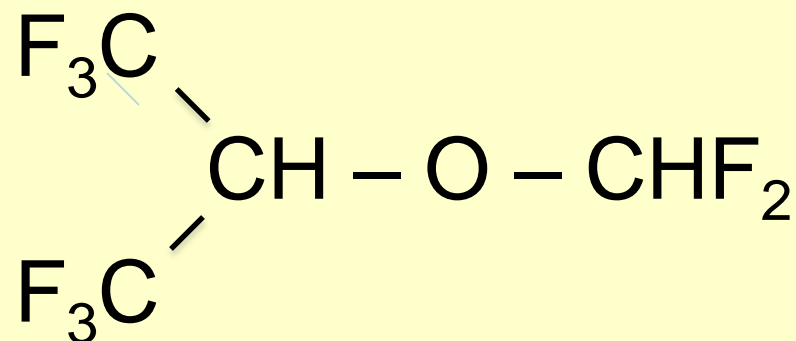
Baxter, Forane<sup>R</sup> 1979

isoflurane




Baxter, Suprane<sup>R</sup> 1992

desflurane



AbbVie, Ultane<sup>R</sup> 1995

sevoflurane



All the bad news about halothane was reported and well known long before the papers written by Chris and Julie in 2007-2012 --- but halothane was not removed from the market because of its rare but serious toxicity -- Wyeth just couldn't sell enough any more in competition with newer fluorinated ethers such as sevoflurane that were safer.

Julie and Chris probably are not allowed to say: how many new drugs in development were killed in the IND stage before NDA submission at GSK? At other companies?

The approach suggested by Chris and Julie in their first paper of 2007 on the topic was more reasonable ---

Hunt CM, Papay JI, Edwards RI, Dickens T, Alpers DA, Dollery C, DeBruin TW, Adkison KK, Sirnadel HA, Gibbs TG. Monitoring liver safety in drug development: The GSK experience. *Regul Toxicol Pharmacol.* 2007;49:90-100.

They proposed (Figure 2):

