Lessons from Isoniazid

Would it be approved today?

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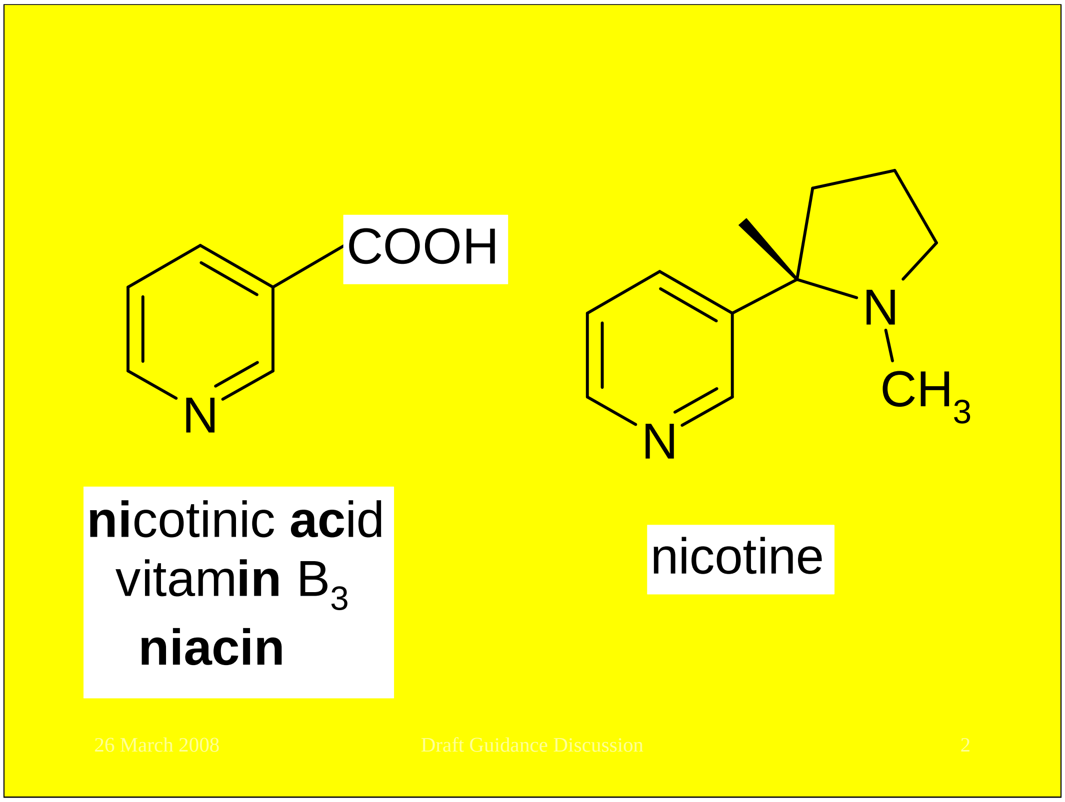
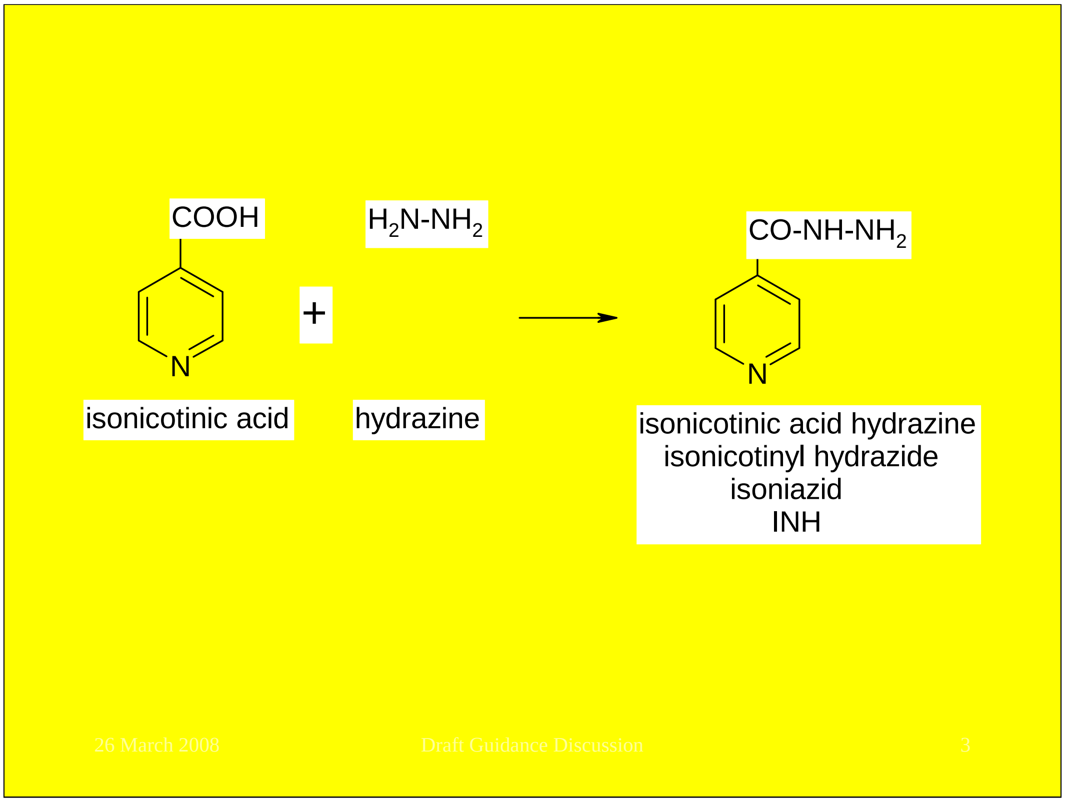
I'll start out with the disclaimer. I've been 12 1/2 years working for the FDA, but I had 20 years in academia and 16 years in industry plus 39 years in the Naval Reserve as a medical officer. That means I must be over 100. (Laughter.) But what I'm saying is my opinion and does not represent the position of the Agency or their policies.



We're going to start with nicotine. Nicotine, you see there on the right side of the slide, is an alkaloid, highly addictive. It's in tobacco but it's also in some other plants: egg plant, green pepper, tomato, potato, but more in tobacco. Nicotiana tobaciana was named for Jean Nicot, 1550, from tobacco leaves. Obviously well known, but very toxic. A lethal dose in a rat (50% LD level), is 50 milligrams per kilogram weight; in the mouse, 3; in the human, 0.5; a 100 times more toxic to humans than rats.

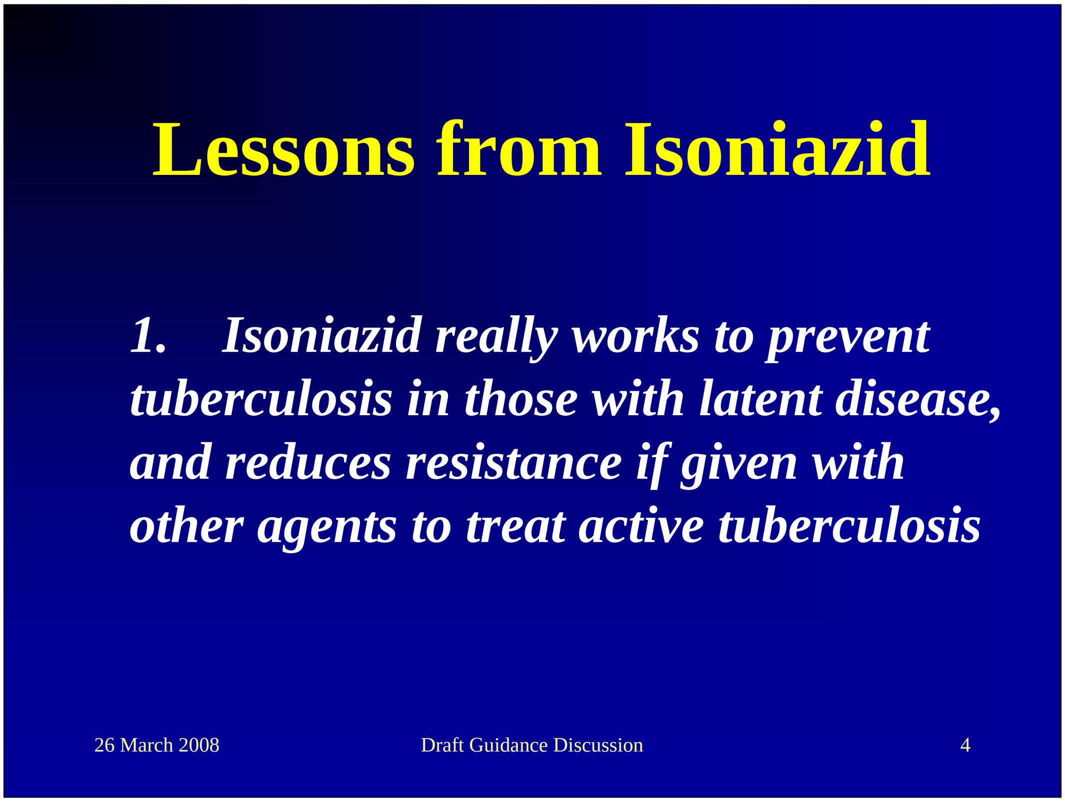
Now on the left side of the slide you see nicotinic acid. That was discovered by Conrad Elvahjem in 1937 as a vitamin, B3. It's anti-pellagra. Pellagra means rough skin, in Italian. Deficiency of vitamin B3 caused dermatitis, dementia, diarrhea, and death. So in order to distinguish the vitamin, the good stuff, from the bad stuff, nicotine, they said we'll call it niacin which is ni, nicotinic; acid, ac; vitamin, in; equals niacin, so we don't mix it up with nicotine.



Now we're going on to talk about isonicotinic acid. Here we've moved the carboxyl group around the pyridine ring to opposite the nitrogen. So it's an isomer of nicotinic acid. This was combined with hydrazine back in 1912 by a couple of chemistry Ph.D. students in Prague. They didn't have any idea what it was good for. They were just making a new compound, and it wasn't discovered until many years later, really by some work in Germany. Domagk, who was the first one who discovered the structure of sulfanilamide, made some compounds that were anti-tubercule and they were used to treat about 7,000 Germans for tuberculosis. Well, this was so interesting that Walsh McDermott from Cornell and Conrad Hinshaw from Stanford went to Germany after World War II to find out what's going on. What's this anti-tuberculosis thing?

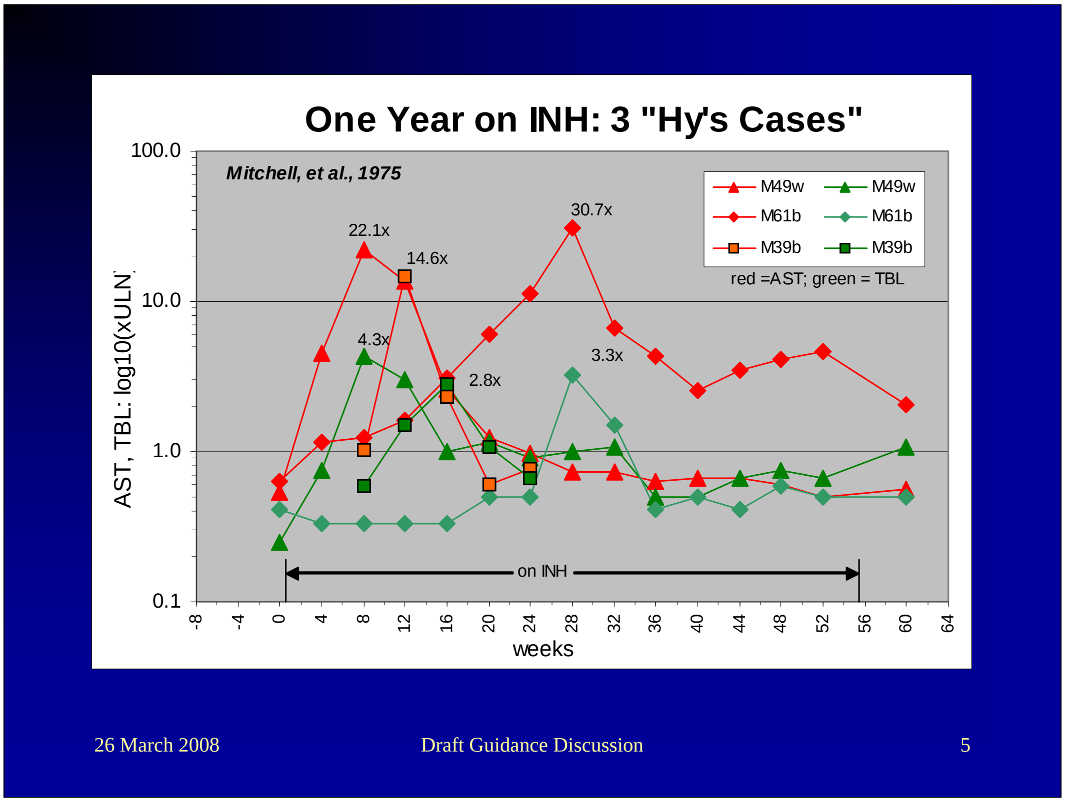
Well, they brought back the compound, Conteben, and they looked at it, and they made a lot of derivatives, ending up with isoniazid in 1951 They discovered both in Germany and the United States, independently, that isoniazid had very powerful anti-tuberculosis activity.

So in 1952, it was introduced into clinical practice. Now this was 10 years before the FDA required that drugs be shown to be efficacious, but it went on the market and it worked. Within two years, the sanitariums were closing. Trudeau closed Saranac Lake because there were no patients anymore. But although it was very effective, uht-oh, toxicity reared its ugly head. The first case was in 1953, a case report in JAMA, and I'll provide the reference for that on the website.



So what was the first lesson? Isoniazid works. They didn't know how it worked but it worked. It took another 50 years to find out how it worked.

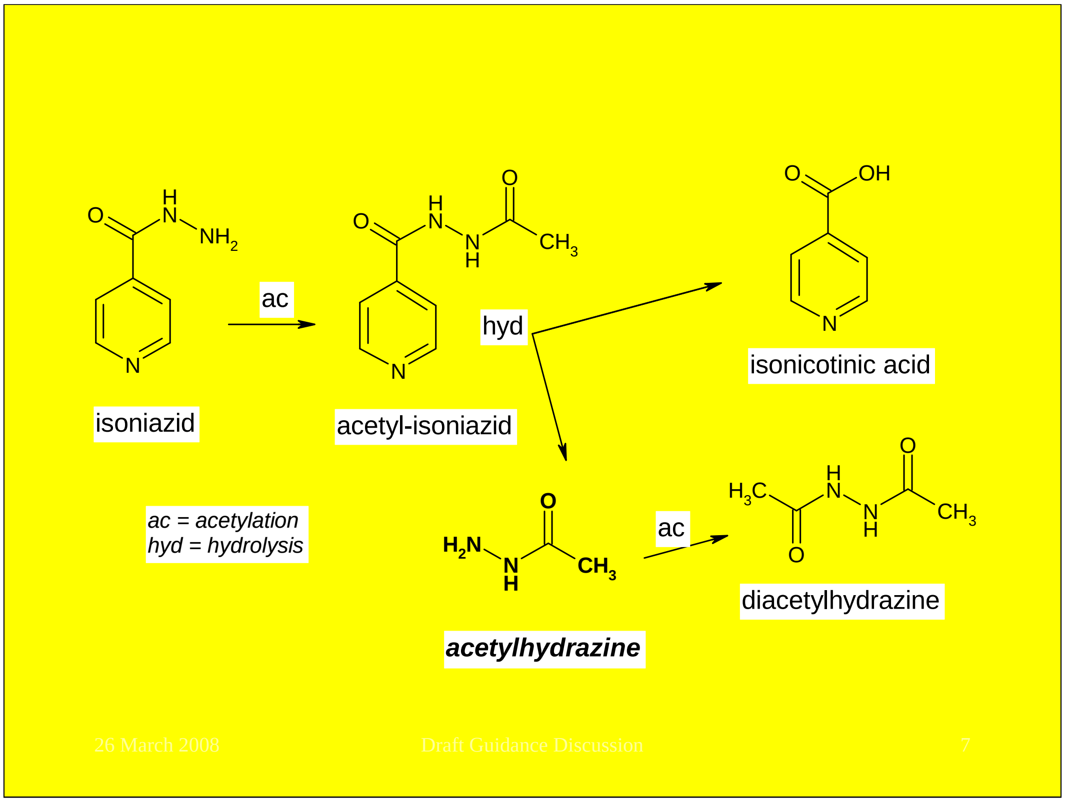
Okay. So they started using it, and hepatotoxicity was a concern. Next slide.



Now here is a study published by Mitchell in Chest, 1975. Look at these cases. These are 3 cases out of about 100 men treated with isoniazid only. They had presumably normal livers to start with even though they had no tests to rule out viral hepatitis then. These are all Hy's Law cases from a drug. Now if we encountered this today, that drug would be toast. (Laughter.) But they didn't know that. This was three years before Hy even mentioned his observation at the Fogarty Conference in 1978 at NIH. So they didn't know it. So they let these people continue taking the drug and what happened? It all went away. They didn't die.

So what about it? Well, Martin Black who was working with Mitchell, and with Hy Zimmerman and Kamal Ishak, reported 114 cases of isoniazid hepatitis in that same year, 1975. That group was taken from a large group of public health study of 13,000 patients, put on isoniazid prophylaxis. There were 13 deaths reported, maybe not all due to isoniazid. Maybe only eight of them were caused by isoniazid. We'll talk about them in a moment. But Mitchell really made a very penetrating observation. I think this was the first description I can find, Paul. I know you and Russo talked about this, but they said this raises the problem of adaptation. What was going on? These patients changed in some way. They became tolerant to a drug that had caused rather serious liver injury. However, they did not pursue this concept because they were on the track of something else. They were on the track of searching for a toxic intermediate which they thought was acetylhydrazine, the acetylated hydrazine liberated from acetylated isoniazid.

They also thought that people who got it were the fast acetylators.



On this slide isoniazid is on the left, the acetylated product. Then that gets hydrolyzed down to liberate isonicotinic acid, which is harmless, and acetylhydrazine. They thought that since fast acetylators made more acetylhydrazine, they were the people at increased risk. But if you acetylate it a second time to diacetylhydrazine, it's harmless. It inactivates the toxicity. So they turned out to be wrong, but at the moment, it was a good idea and it got people thinking.

Worrisome incidence of serious liver injury, with 92 cases and 8 deaths in 13,838 persons taking INH prophylaxis, monthly visits (Kopanoff et al., 1978).

A new study of 11,141 patients was done from 1989-1995 by (Nolan et al., JAMA 1999; 281:1014-8). No transaminase monitoring, but patients reminded to check daily and report any symptoms at once, stop INH, get checked. No deaths; only 11 (1:1000) had to stop INH permanently. Most adapted to INH. **Why? 1) younger patients 2) daily self-monitoring for symptoms and prompt stopping/interrupting**

I mentioned the study that Martin Black had reported, the 13,000 patients put on isoniazid. Well, the full study didn't get reported until 1978 by Kopanoff, et al., and there were eight deaths, showing that isoniazid could kill people from liver injury

But another study of about 11,000 patients by Charles Nolan and colleagues in Seattle, showed that it doesn't have to kill people. They decided to do treat patients a little differently. Instead of routine monitoring of enzymes every month or so, just told the patients to look at themselves in the mirror every morning and say, how do I feel? Do I have nausea? Do I have loss of appetite or anything else that might suggest liver injury? And if I do, I'm not going to take my isoniazid today. I'm going to call my doctor and get checked. Well, it worked. It worked like a charm. They found a lot of people with mild symptoms. They went to be checked and some of them had elevated enzymes, which they watched until the enzymes went away. Then they very carefully restarted isoniazid and most of the patients got away with it. They only had to stop isoniazid permanently in 11 out of 11,000. That's 1 per 1,000. And no deaths.

Isoniazid alone, as prophylaxis against tuberculosis, leads to high incidence of liver injury (serum ALT or AST elevations), more with older age recipients or with concomitant alcohol or other drugs.

Most people can tolerate isoniazid chronically, or adapt without progression to severe hepatotoxicity, but a few recipients are more susceptible or cannot recover from mild injury.

Is monitoring for ALT/AST elevations necessary for preventing serious liver injury? Will symptoms do?

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So Isoniazid didn't have to kill people. You could pick it up by symptoms and stop the drug in time to prevent serious injury.

So isoniazid is a very valuable drug. Most people can tolerate it or adapt to it, and monitoring is not such a good idea. So another lesson comes.

Lessons from Isoniazid

2. It is not necessary to monitor <u>all</u> of the patients taking INH monotherapy for prevention of tuberculosis by periodic ALT measurements

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It is not necessary to monitor with ALT measurements, which is very inefficient, very costly, very objectionable. Nobody likes it, and it doesn't work anyway.

So periodic measurement is not the way to go but self-monitoring for symptoms was learned by the tuberculosis treatment community to be an effective way to go. Next slide.

Drug-Induced Liver Injury (DILI)

Most people exposed to a new drug show no injury;

"tolerators"

Some people show transient injury, but adapt;

"adaptors"

A few fail to adapt and show serious toxicity !

"susceptibles"

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So now let's get back to our concept of adaptation. Now most people that start taking isoniazid showed no effect at all but 20 to 30 percent, depending on the age group and so forth that you work with, may show some enzyme elevations but nearly all of them can adapt to the drug and they do it fairly promptly. Even if you give the drug again, it doesn't cause any harm. Rechallenge is negative. But there are a few who can't adapt, who become susceptible to serious injury, liver failure and death if you keep giving it to them.

Levels of DILI Severity

5	Death/Tx
4	Acute Liver Failure
3	Serious DILI; Sick, Threatening
2	Detectable but Slight Functional Loss
1	Just Enzyme Elevations; Most People Adapt
0	Patients Tolerate Exposure - No Adverse Effects

We have the old iceberg, or pyramid. Level 0, no effect, down there in white. Level 1, mild injury, just transaminase elevation. Level 2, which we now call Hy's Rule, Hy's Law. You begin to see in addition to transaminase elevation, you see loss of liver function. Lebel 3, bilirubin goes up, patient gets sick, patient's in the hospital. Patient's at risk. Level 4, liver failure. Level 5, death or death of liver in transplantation.

So what's going on? What we do know is that the frequency of the injury falls off as the severity goes higher. Well, why is this happening? What's different about the people who adapt and those who don't? Well, that is the big question and that's what we have to chase, and we're going to do so I hope.

Why Are They Susceptible ?

"idio-sug-krasia" (Hippocrates, ~ 400 B.C.)

idios (ιδιος) - one's own, self
syn (συν) - together
crasis (κρασις) - mixing, mixture

therefore,

a person's own individual mixture of characteristics, factors; "nature and nurture," unique in the world

[it does NOT mean rare, unexpected, unexplained, not dose-related; although it may or may not be any or all of them]

So what is this idiosyncrasy and what it is not?

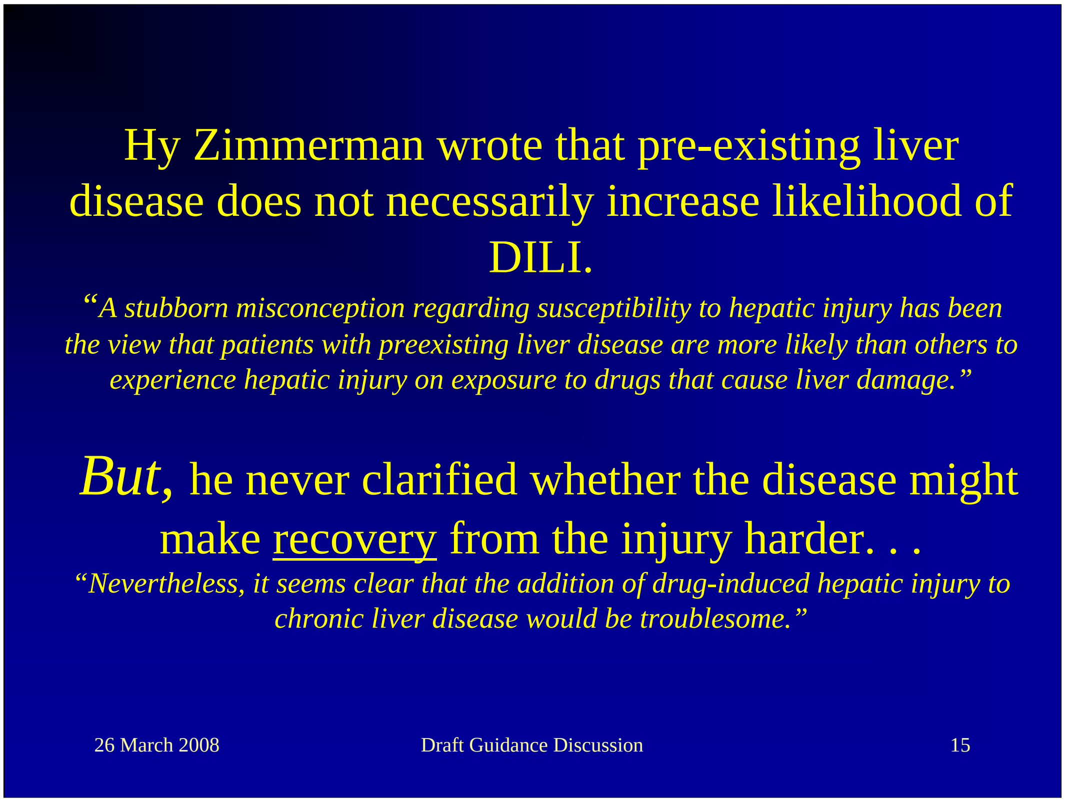
Idiosyncrasy is not a new idea. It's been around for 2400 years. Hippocrates noticed that all people were different. The word means "one's own mixing together" of factors or characteristics. They responded differently to the same thing, the same infection, the same drug, the same anything. It wasn't the stimulus; it was the recipient response that was different.

Factors in Idiosyncrasy

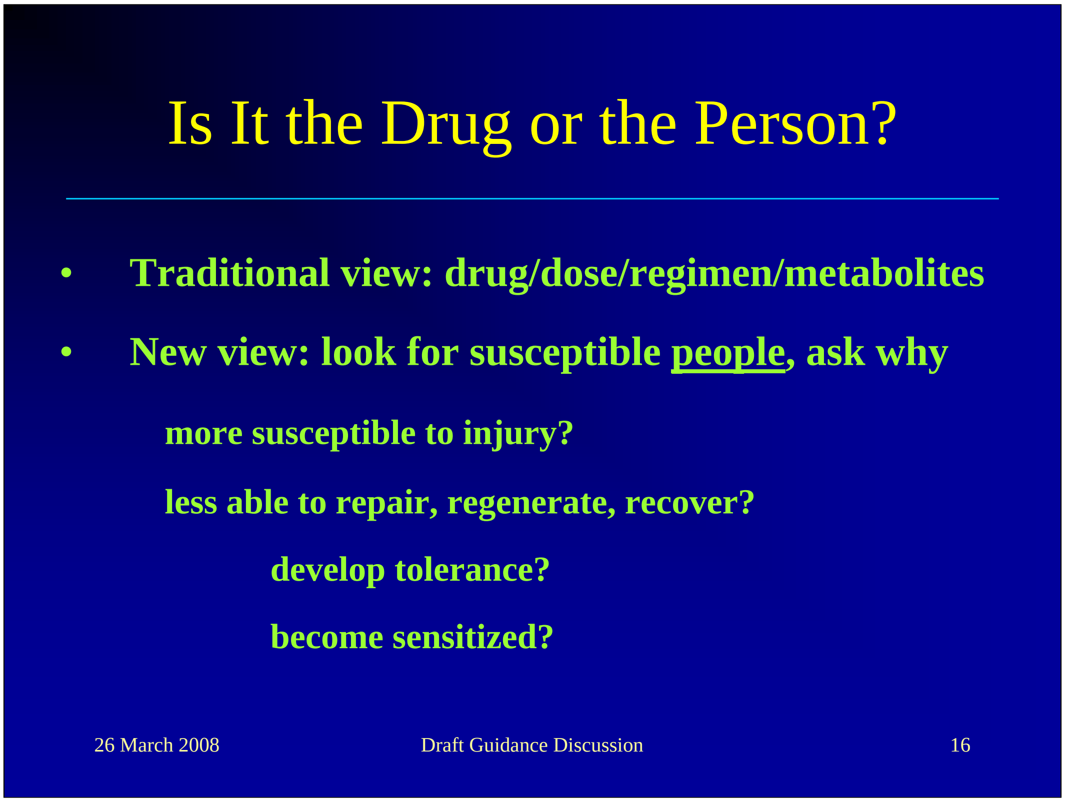
- **genetic, bestowed at conception**
  - –gender
  - –cytochromes, enzymes, transport systems
- **acquired in life since conception**
  - –age, activities, travels
  - –infections, immunities, diseases
  - –diet, obesity, dietary supplements
  - –other drugs, chemical exposures
  - –epigenetic responses; gene expression changes
- ***differences in resistance, repair, healing !!***

Maybe genetic. Maybe they had a different inherited set of genomes at conception. Maybe it was something they acquired along the way. Maybe it was all of that and maybe it was a difference in their ability to respond, to heal, to repair, to regenerate injured liver.

It's not just the injury, but the capacity to heal that may be critical, and we haven't been looking at that but we should.



Now Hy said in his book, in both '78 and '99 editions that you'll hear more about from Bob Temple and Will Lee and Arie Regev tomorrow. Hy thought that having preexisting liver disease didn't increase one's chances of getting an injury from a drug, and he may have been right. But he didn't say whether or not that might affect your ability to recover from the injury, which is a different idea.



So is it the drug or is it the person getting the drug? Paul Watkins and I have talked about this a lot. I think we need a shift in how we look at things. A new paradigm in toxicology. It’s not the drug, the dose, or the regimen. It's the patient who gets it, or the animal that gets it, who's different from the others.

Lessons from Isoniazid

3. On balance, isoniazid is doing more good than harm, and is essential to the world program to reduce the prevalence and incidence of active tuberculosis

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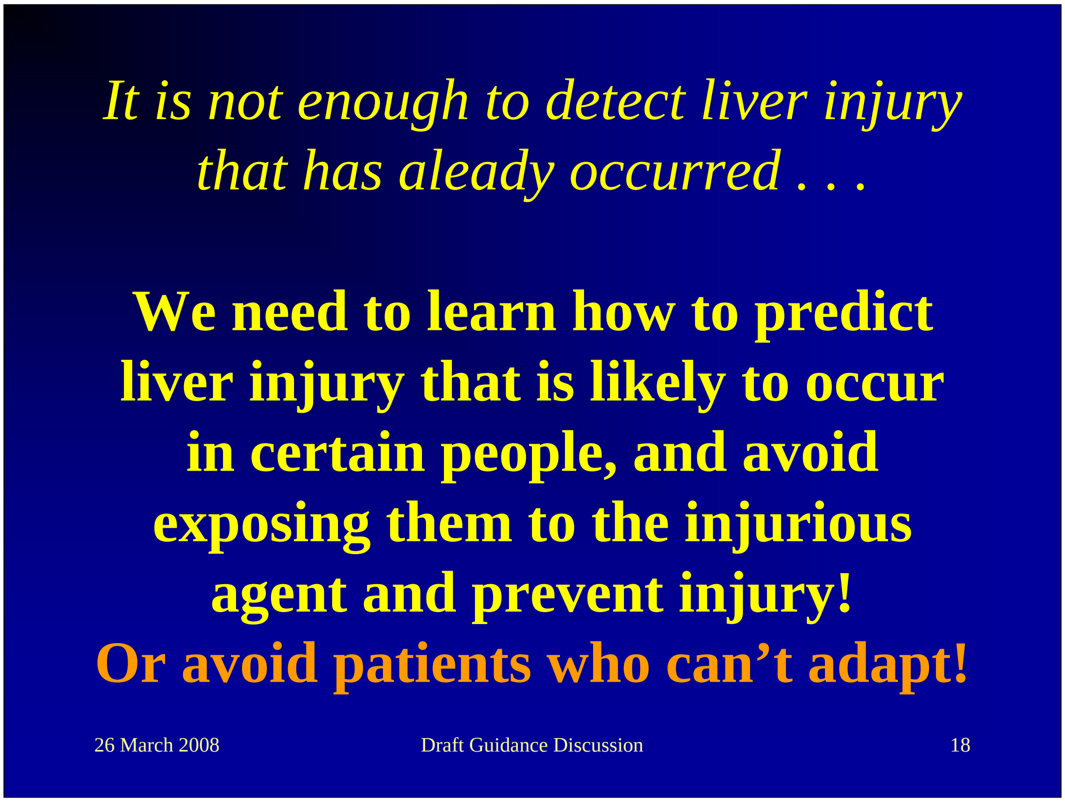
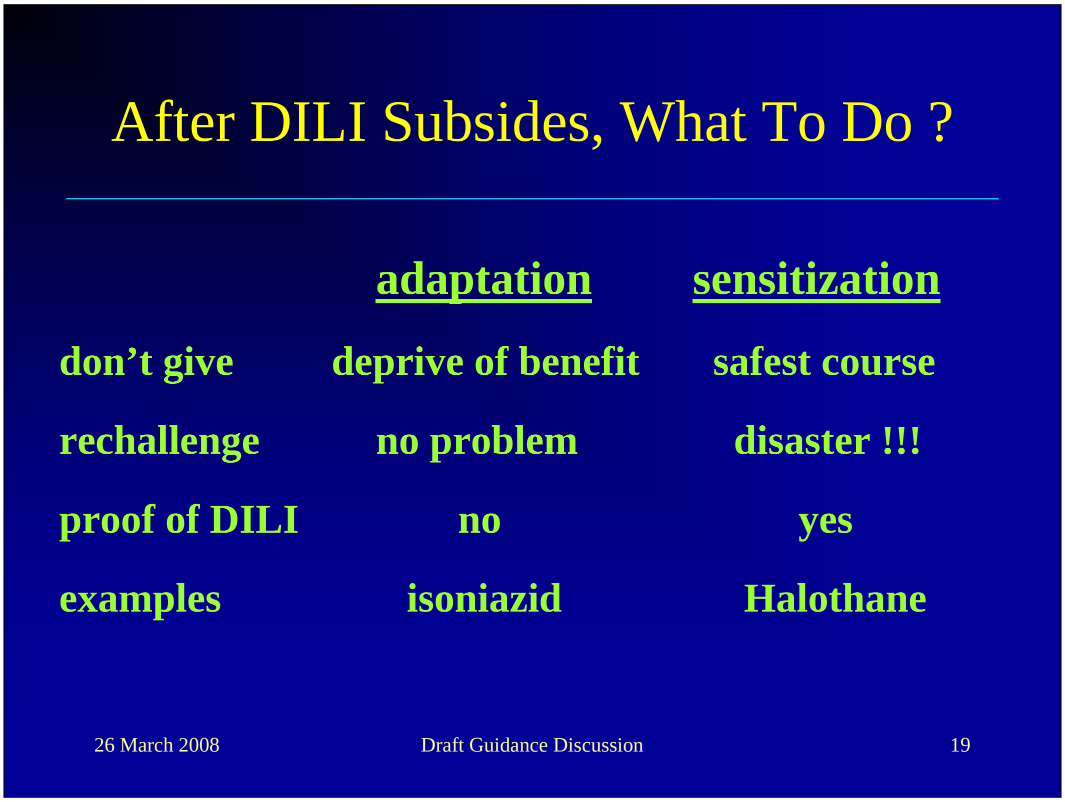
So we have another lesson. On balance, isoniazid is helping more people than it hurts, especially since we've learned that we don't have to kill people with isoniazid but we can use it as a very valuable drug to treat the most prevalent disease on the planet. Two billion people are estimated to be infected with tuberculosis, mostly in the poor populations of Asia and Africa. Nine million active cases are discovered every year, with one and a half to two million deaths from tuberculosis. Isoniazid is the mainstay of treatment, both for prevention in people who are exposed, and for treating the active disease that occurs, and when it's used in combination with pyrazinamide and rifampin and ethambutol and so forth.



We need to do something more. We need to find the Holy Grail. We need to chase it. You'll hear more of this tomorrow from Mark Avigan and Jack Bloom, but we need to find a marker, a predictive biomarker, next slide, not just a marker that's a more sensitive test of injury that's already occurred but a predictive test of what will occur if you give that drug.



With isoniazid, what do you do if you see a rise in serum aminotransferase activity? You stop the drug for a while. You watch the patient. Should you give the drug again? Jack Uetrecht and Leonard Seeff this afternoon and maybe Chris Hunt and Julie Papay will talk about rechallenge. It can be a disaster. Remember Halothane. You could take it once but take it again and bad news. We don't want that to happen. We can't afford to risk it but we also realize that rechallenge may not cause injury because adaptation has occurred. So we really need to think about what to do, and we'll talk about that more.

Safety Biomarkers (Tests)

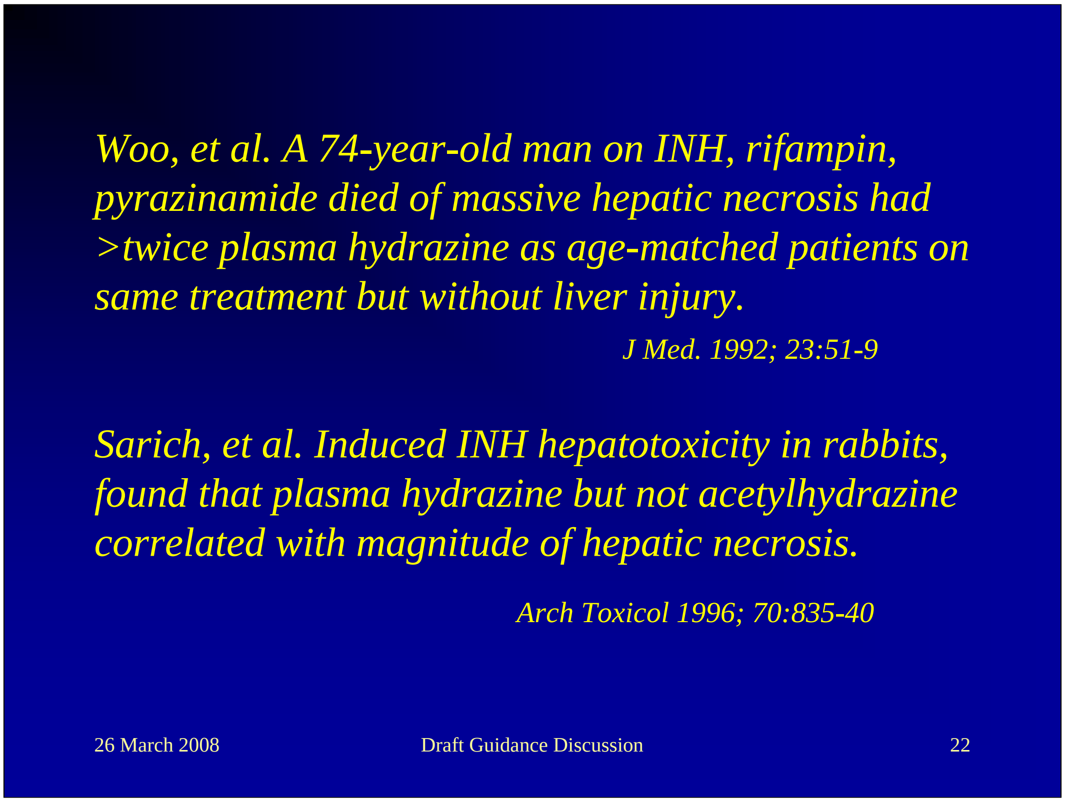
	detective	predictive
when	retrospective	prospective
damage	already started	not yet done
testing	repeated monitoring	once, before
if +	stop drug	don't give
if -	continue drug	may give drug
need	very high specificity	high sensitivity

So that for these safety biomarkers which we're going to discuss tomorrow, we want to make a clear distinction between predictive and detective biomarkers. Are you detecting something that's already occurred, a drug injury that's already occurred, and what you're hoping to do is avoid worse injury. Or are you really predicting what will occur even before you've given the drug? That's a distinction, another lesson.

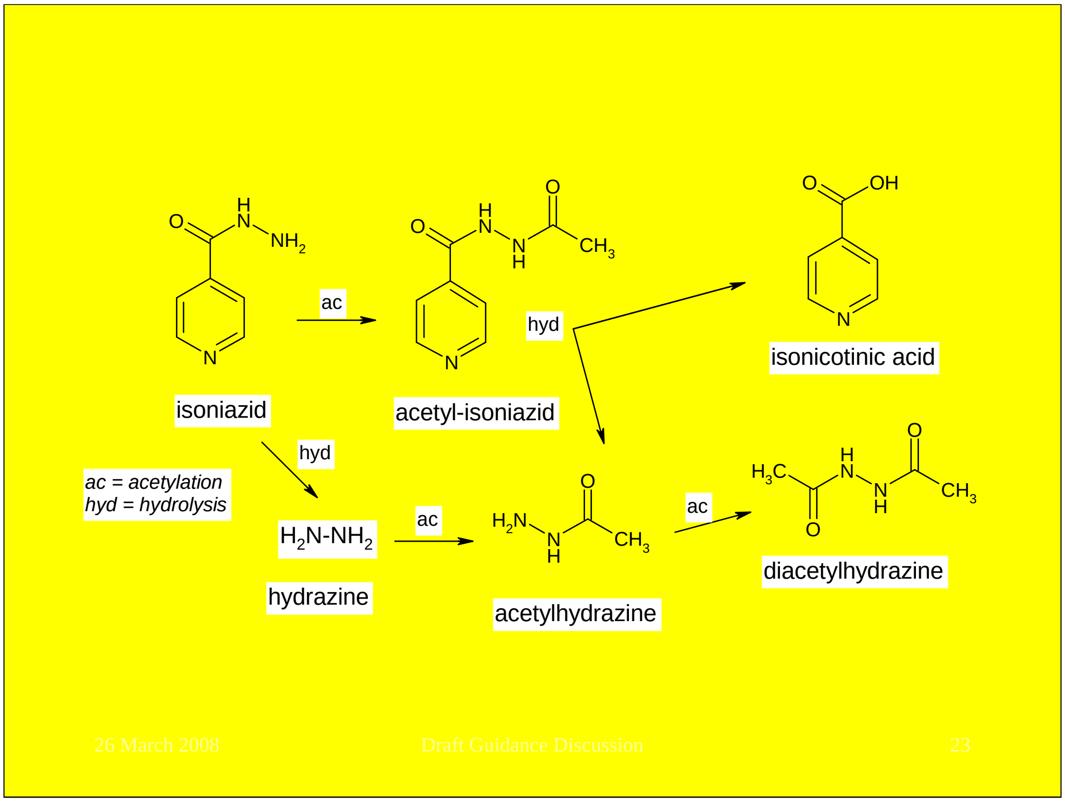
Lessons from Isoniazid

4. It has taken over 55 years to have even an inkling of how isoniazid works to kill tubercle bacilli, and we still have no firm clue as to exactly how it may be causing hepatocellular injury in many or in a few people progression to severe liver failure and death

It's taken a long time to have even an idea of how this marvelous isoniazid works. We still don't know exactly how it may be causing injury in certain people. I want to refer you to the excellent review of the mechanism. It's in that reference by Vilcheze and Jacobs, and that will be published in full on the internet if the copyright will allow it afterwards.



Something new happened, and it wasn't much noticed, next slide, in Hong Kong. It was a report by Woo way back in 1992, that a patient died of massive hepatic necrosis induced by isoniazid and they found that what was elevated in the blood was hydrazine,. This was confirmed by Sarich in animal studies, where he showed it was not acetylhydrazine but hydrazine itself that was probably the most toxic intermediate.

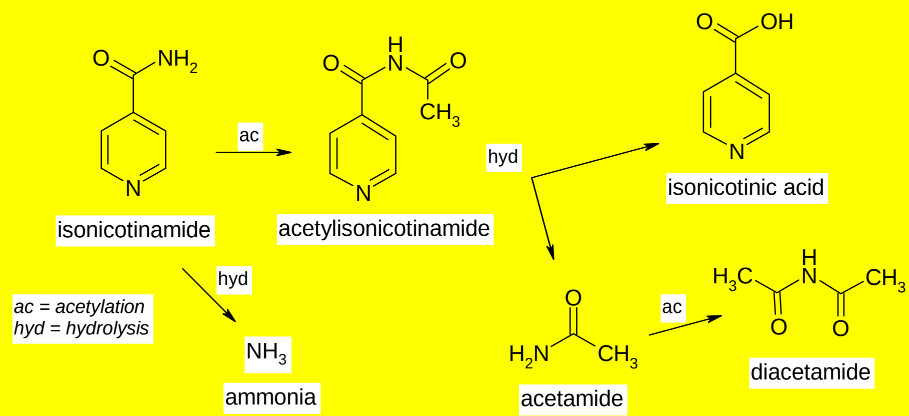


Now let's look at that possibility. While on the left here you see isoniazid which if hydrolyzed produces harmless isonicotinic acid, and hydrazine. Now that hydrazine can be acetylated to acetylhydrazine and acetylated again to harmless diacetylhydrazine.

So what do we know about hydrazine? Well, that stuff is really toxic. It's a caustic, fuming, unstable liquid, strongly alkaline, strong reducing agent. It was used by the Germans in World War II to fuel the first rocket fighter, the Messerschmitt 163B, the fastest plane in the world but their manufacturing capacity didn't allow it to be made. We kept bombing their plants. It's now used as rocket fuel for space rockets. It's very, very toxic.

Now how toxic is it if it's liberated inside a liver cell? I don't know but I think it could be very bad. Now could a safe probe be found?

Could a safe probe be found ?



Could we find a predictive biomarker? Now I'm suggesting here on the left isonicotinamide, not hydrazide, but amide, similar in compound. It could be hydrolyzed and would liberate fairly harmless ammonia or it could be acetylated and maybe if we found people who had increased ability to hydrolyze and decreased ability to acetylate, we might find a combination that leads to special sensitivity.

I think we need a large prospective study of isoniazid. Paul and I have been talking about this. We hope to put together a real proposal and get some funding to do this. It could be expensive. It could be a large study but I think we have a lot to learn.

Lessons from Isoniazid

Can isoniazid teach us still more about what makes certain people different and more susceptible to INH-hepatotoxicity?

Can it show us the way to find the truly predictive biomarker or procedure that will predict accurately who should <u>not</u> be treated with INH?

We have learned a lot from isoniazid. I think we can learn more. It is a valuable drug. We don't want to give it up. We know it can kill people but it doesn't have to.

Lessons from Isoniazid

We've learned much from isoniazid already.

It's a very valuable drug, but dangerous to a few people. We think we know how to use it safely.

From it can we learn how new drugs that hurt a few people can be studied so they may be identified and not treated, so that others may benefit?

Let's do the necessary studies and find out!

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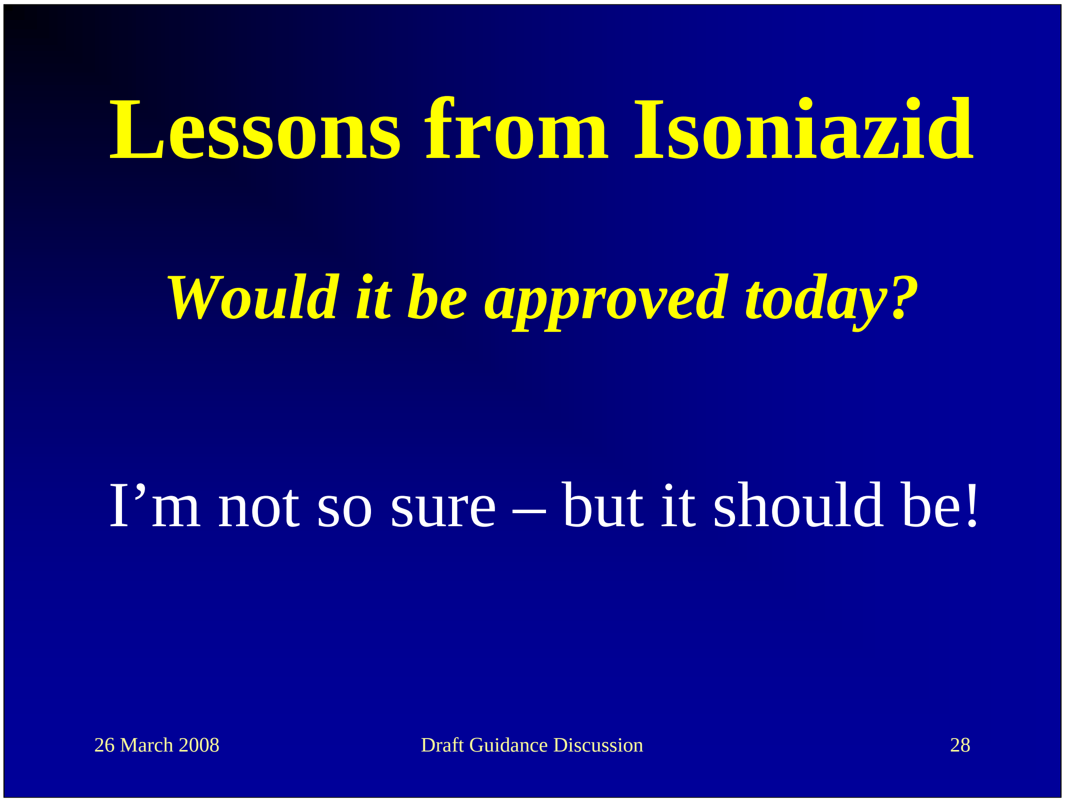
So I think we need to do some more study of isoniazid and learn some more lessons.



Would Isoniazid be approved today? I'm not so sure. The current climate might now allow it but I think it's one thing that this conference is intended to think about. This is a very valuable drug. Just because there's one or two or three cases of Hy's Rule occurring, doesn't mean we should throw the baby out with the bath water. Thank you.