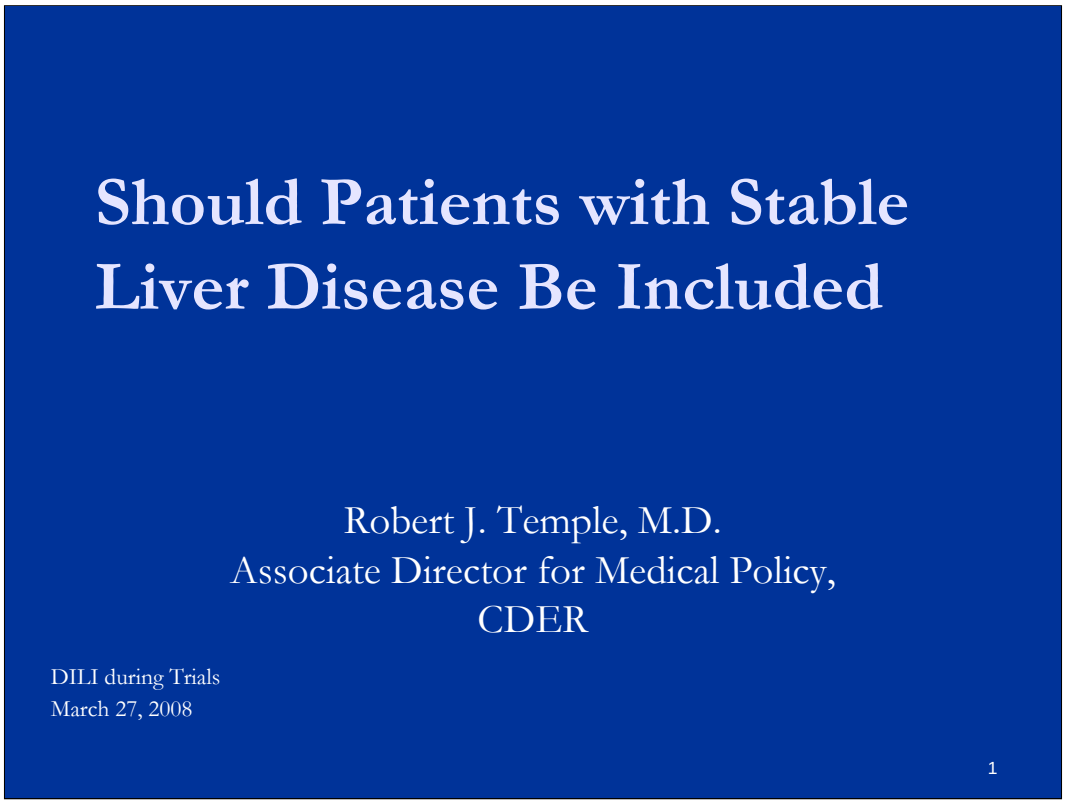
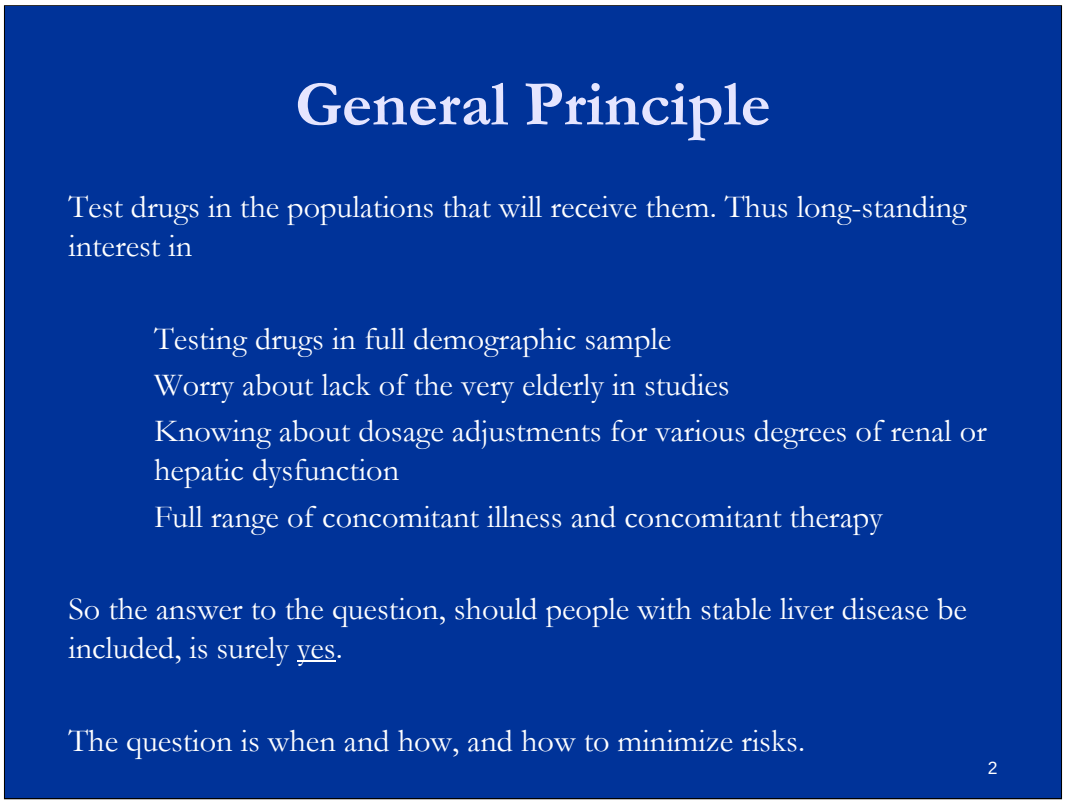


DR. PEARS: So without further adieu, Dr. Temple is our first speaker, and he's going to talk to us or give his view about whether patients with stable liver disease should be included.

DR. TEMPLE: Okay. I thought they had Egg McMuffins in the UK but they boiled them.

DR. PEARS: We do. We import them from you.

DR. TEMPLE: Yeah. Okay. My guess is that there was a complete discussion yesterday of everything I'm going to say, based on what Sara Goldkind presented. So I don't have many slides and we can get right onto the discussion.

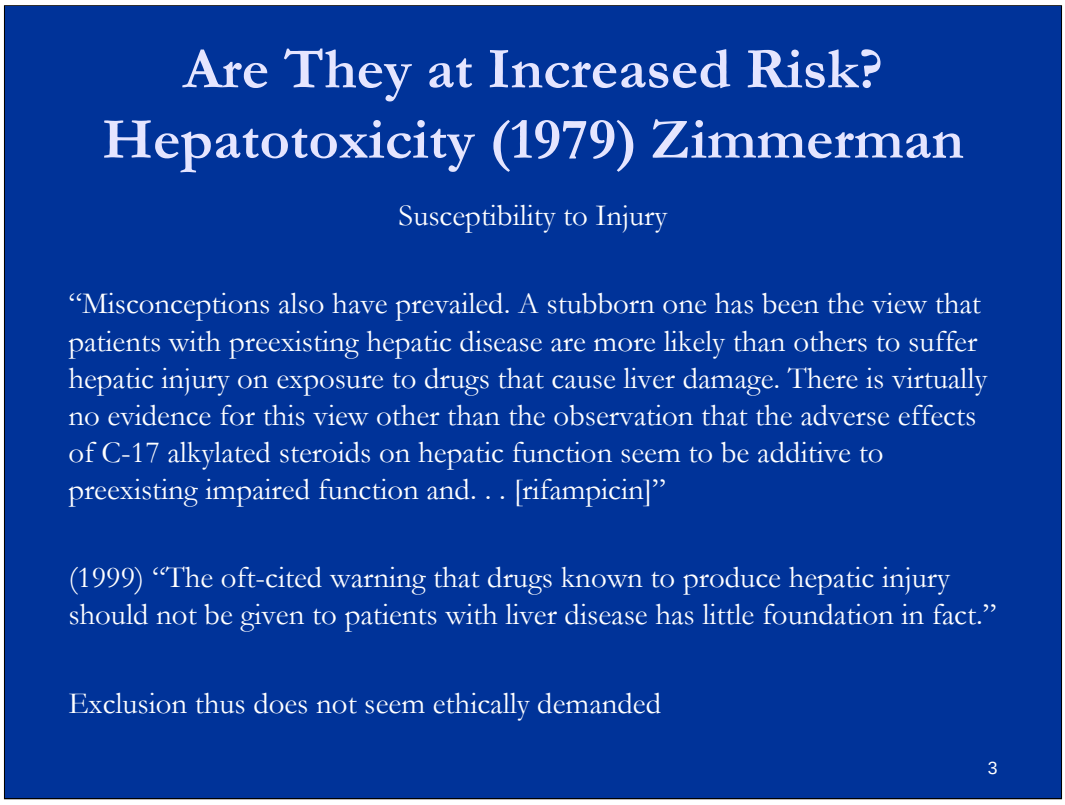


There is a general principle that we encourage, without always succeeding, that drugs are supposed to be tested in populations who will eventually receive them. And there has been longstanding criticism that they do not include very old patients and various other subgroups.

So we urge in various ways testing drugs in a full sample of the demographic population that will receive the drug. We worry a lot, for example, about the absence of the very elderly in the studies. In a document produced in 1989, we defined elderly as over 65, which is just totally ridiculous (laughter). John has pointed that out to me. But the fact is we're not very good at getting people over 75 or 85 into trials.

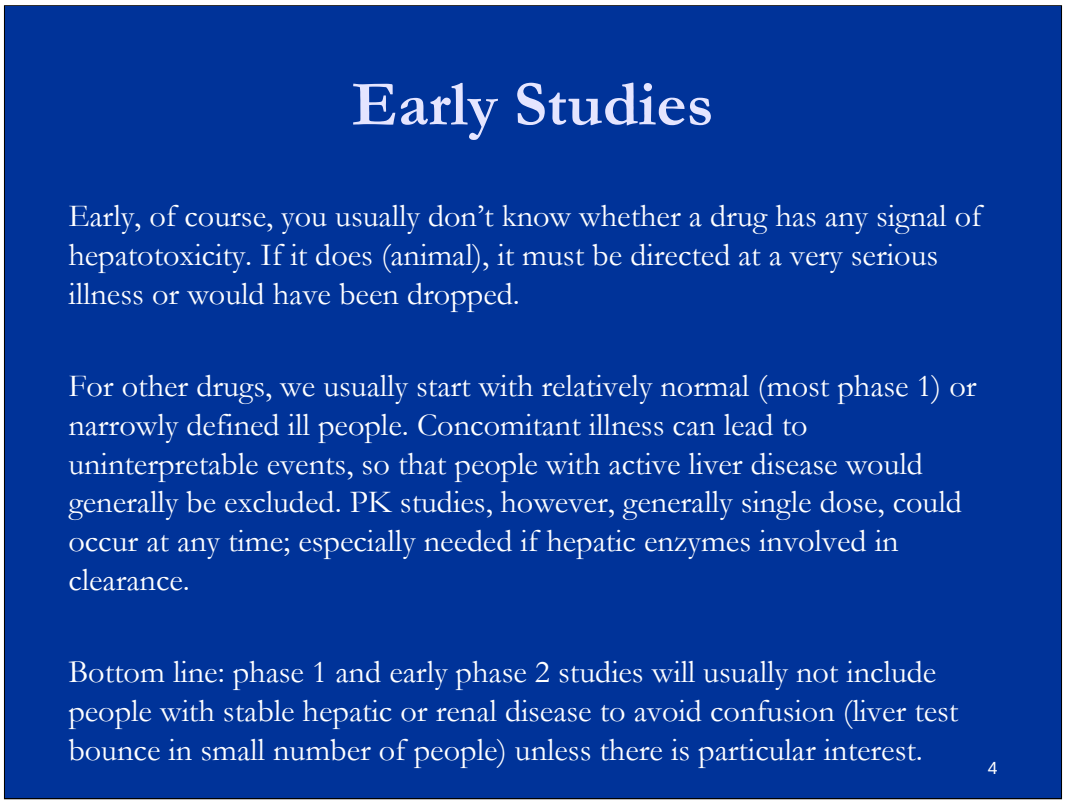
And we want to know about the needed dosage adjustments for various degrees of renal or hepatic dysfunction, depending a little bit on how we first metabolize the drug. And we like to be sure that people with concomitant illness and concomitant therapies are in trials so that we can see interactions.

The answer to the basic question : “should people with stable liver disease be included?” would therefore have to be yes, unless there's some reason not to do that, and we've got to think about how to minimize risk.



Are people with liver disease at particular risk from drugs that are hepatotoxic? Referring to a person I grew up with who knew more about liver disease than anybody else, Hy Zimmerman, he said repeatedly and wrote both in 1979 and 1999, that "Misconceptions also have prevailed. A stubborn one has been the view that patients with preexisting hepatic disease are more likely than others to suffer hepatic injury on exposure to drugs that cause liver disease." There is virtually no evidence for this view other than a few cases he cited where it might be true. He repeated this observation in 1999, saying that, "The oft-cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact."

Now I gather there're at least some people who feel there are some exceptions to this and, of course, there might be, but the idea that everybody with preexisting liver disease has to be left out of a study of a drug that increases aminotranaminases doesn't seem to be ethically required.

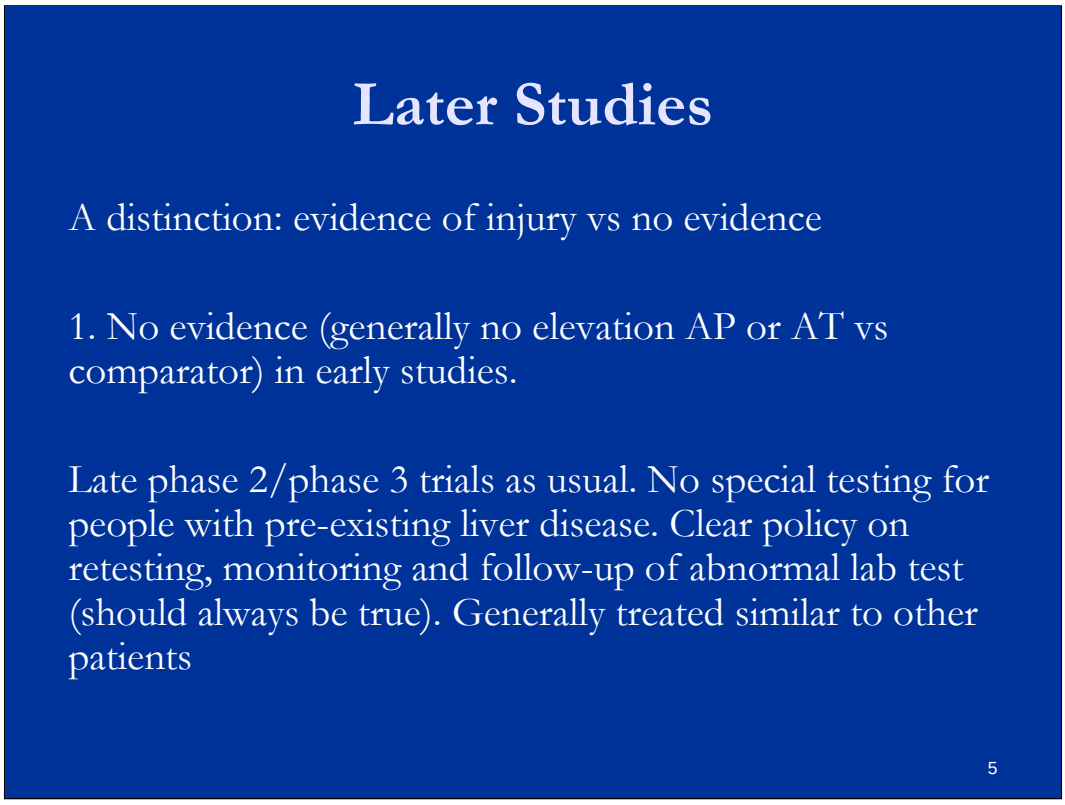


It's worth distinguishing between early studies and later studies. Early on, of course, you don't know whether a drug has a signal of hepatotoxicity. If you did have any animal evidence of toxicity, the drug would really have to be directed at quite a serious illness or it would have been dropped by then. You don't see it a whole lot of major hepatotoxins developed except for serious diseases.

For most other drugs, the dogma would usually be that you start with relatively normal people or narrowly defined ill people because you don't want to confuse the issue. You don't want someone with preexisting liver disease to have their serum transaminase go up through the roof among the first 20 people if the drug didn't cause it, because that finding might kill the drug. You wouldn't usually put someone with active liver disease into early trials, again unless the disease is a terrible disease.

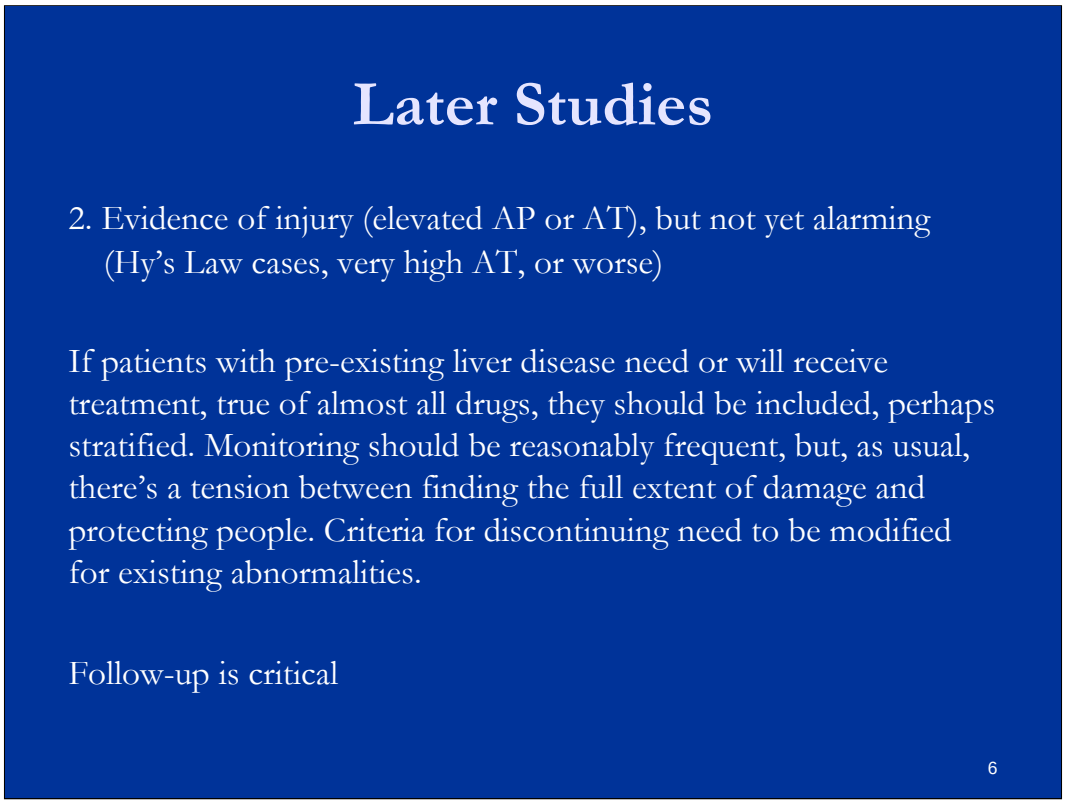
There would be no impediment to doing single dose case studies in people with preexisting liver disease however.

So in general, I would say as a rule, Phase 1 and early Phase 2 studies beyond single dose studies probably won't include people with known liver disease, mostly to avoid confusion of drug effect with the disease.



For later studies, we probably want to talk about the distinction between where there is some evidence of injury and where there isn't any evidence.

If there isn't any evidence from the early studies, i.e., nobody saw elevations of transaminases or alkaline phosphatase, it's hard to think of any reason not to include people with stable liver disease if it's important to know about how to treat them. There could be a difference between drugs for minor illnesses and drugs for more important illnesses. It is clear is that there needs to be a discussed policy on retesting, monitoring and follow-up of abnormal laboratory tests. Of course, that should be true all the time. In general, I would think people with liver disease would be treated similarly to other patients.



On the other hand, if the early data do suggest that the drug can cause serum enzyme elevations either of an obstructive or hepatocellular type, but it isn't really scary, you might still want to know what happens in people with underlying liver disease, but you're going to have to be very careful. You might want to stratify and you might want to increase the frequency of monitoring. Again, there's a tension between learning what happens, and monitoring so often that you keep from finding out. So that has to be resolved, not only for people with liver disease but for almost anybody. Certainly criteria for discontinuation need to be modified for the presence of an existing abnormality and close follow-up will be needed. From the point of view of evaluating the drug, if there is evidence of liver injury it is critical to follow-up to see whether people had an underlying abnormality or not.

Follow-Up

Any cases of apparent injury should be fully followed for

- Long term outcome; time course
- Viral studies, etc.

Re-challenge probably not a good idea

7

Any cases of apparent injury should be fully followed for long term outcome, and for the time course of worsening and resolution. Viral studies are critical.

There are varying views on rechallenge. Some hepatotoxic drugs on rechallenge have caused severe and life-threatening responses, so great care (low dose , daily follow-up) should be taken if done at all, e.g., for a critically needed drug.