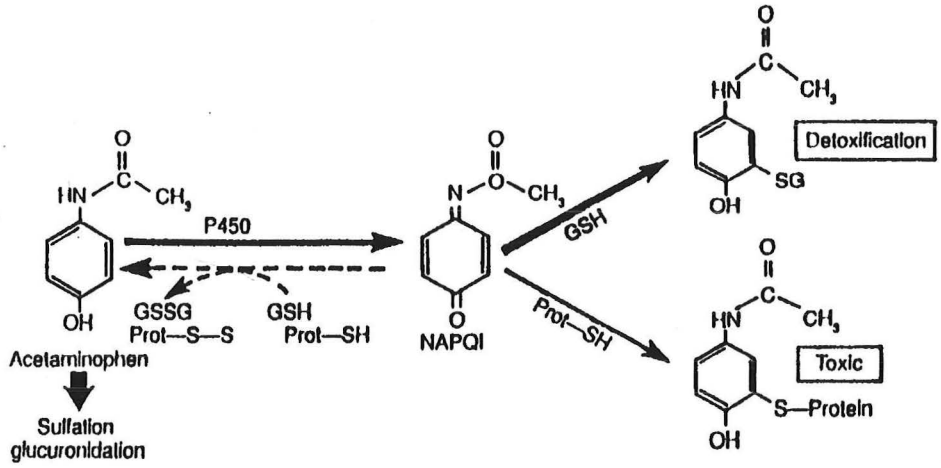
Drug-induced Hepatotoxicity



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Introduction

Grand Rounds take various shapes: narrow and deep or broad and expansive (some might say superficial), depending on the topic chosen. Drug-induced hepatotoxicity is one of the latter, a wide-ranging topic which is relatively unwieldy, but nevertheless important for a general medical audience, since liver damage is a potential outcome with almost every prescription we write. The liver is central to the metabolic disposition of virtually all drugs and xenobiotics (foreign substances).[1-5] For the most part, this process is accomplished without injury to the liver itself or to other organs. A few compounds such as acetaminophen, CCl_4 and the toxin responsible for mushroom poisoning are toxic themselves or produce metabolites which cause liver injury in a uniform, dose-dependent fashion.[6-10] By contrast, most drugs form a sufficiently toxic byproduct to cause liver injury only rarely, and under special circumstances. Generation of a toxic metabolite within the hepatocyte may produce direct cell injury with disruption of intracellular function and membrane integrity, or may cause indirect injury by immune-mediated membrane damage. Factors promoting the accumulation of toxins include genetic enzyme variants which allow greater formation of the harmful metabolite, induction of an isozyme species which produces more than the usual quantity of the toxin, interference with regular (non-toxic) metabolic pathways by substrate competition for enzyme, or depletion of required detoxifying substrates.

This review will provide the theoretical background to drug-induced hepatotoxicity, outline clinical examples of each of the most common forms of liver injury produced by drugs, and address some new issues in drug-induced hepatotoxicity, such as use of combination agents and complex multiple drug regimens, AIDS-related drugs, alternative health strategies (vitamins and herbal remedies) as well as cocaine-related hepatotoxicity. One overall message is that, as new compounds are issued, new opportunities for drug-induced hepatotoxicity arise. Until extensive experience with any new compound has evolved, it is best to maintain a healthy paranoia concerning the safety of newer drugs--there are very few totally safe agents.

Background

Most drugs and xenobiotic compounds enter via the gastrointestinal tract, with a minority being absorbed directly through the lungs or skin, or via a parenteral route. Each foreign compound must either be eliminated unchanged, metabolized by enzymes, undergo spontaneous chemical transformation or simply not be eliminated. To enter the GI tract and the hepatocyte, compounds typically are in lipophilic form in order to cross membrane barriers. Thus, most therapeutic agents begin as relatively lipophilic compounds. Metabolism of drugs within the liver (biotransformation) is the process by which lipophilic compounds are rendered water soluble. Once compounds become hydrophilic, they are filtered by the glomerulus or can be excreted in bile via hepatocyte membrane receptors which recognize highly polar groups. Typically, the conversion from a non-polar to a polar compound takes place in several steps, grouped as phase I and phase II reactions. In the phase I reaction, oxidation or demethylation occurs which typically results in a hydroxyl group being placed on a carbon-hydrogen

skeleton. Oxidation is mediated by the cytochromes P-450, a super-family each member of which employs NADPH for electron transfer.

In a typical phase II reaction, a larger water soluble polar group is attached to the hydroxyl oxygen by esterification or by formation of an ether linkage. This occurs primarily by glucuronidation or sulfation. Phase II reactions may occur as the sole step in hepatic metabolism, or be preceded or followed by the phase I process described, as is seen with acetaminophen. The main groups involved in biotransformation are listed below.

Table 1. Important enzyme families

Enzyme family	Cofactor	Location	Phase
Cytochrome P-450	NADPH, O_2	ER	I
Glucuronyl transferases	UDP-glucuronate	ER	II
Sulfotransferases	PAPS	Cytosol	II
GSH S-transferases	GSH	Cytosol/ER	Neither

Adapted from Kaplowitz, ref 2

Many other enzymes such as alcohol dehyrogenase and mono-amine oxidase are important in metabolizing individual compounds, but the majority of reactions involved in biotransformation stem from those listed above. More than 60% of drugs are metabolized by the P-450 family of enzymes, so it is important to consider P-450 in some detail.

Cytochrome P-450

A variety of oxidative reactions are performed by the super-family of enzymes which make up the P-450 system.[11-15] These include aliphatic and aromatic hydroxylation, O-, N- or S-dealkylation, and dehalogenation. Virtually all of these generate a hydroxyl group which can then participate in the phase II reactions.

There are a remarkable number of cytochromes P-450, at least 300 of which have been cloned and sequenced. Most are located in the microsomal membrane, although some reside in nuclear and cytoplasmic membranes as well. P-450's are composed of a unique apoprotein and a heme prosthetic group, with a total molecular weight of approximately 50 kd. Each cytochrome has limited substrate specificity, although many enzymes subspecies are involved in the metabolism of several different compounds. Although more than one isozyme may be involved in the metabolism of each xenobiotic, one species predominates as the primary metabolic pathway for a given pharmacologic agent in a given individual. Groups of isozymes with similar sequence homology which function in similar fashion are considered as a single family with subfamilies and genes within each subfamily. For examples, cytochromes P-450III is a family which contains an 'A' subfamily and several genes, numbered 1,2, etc. The primary enzyme for the metabolism of erythromycin in humans is P-450IIIA4, sometimes abbreviated 3A4. Enzymes may be induced by drugs or alcohol or inhibited by agents which utilize the same iso-enzyme.[16,17] The typical reactions for P-450 are shown below.

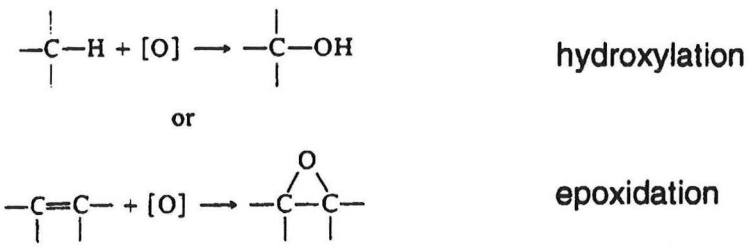

Figure 1. Typical P-450 reactions.

The heart of P-450 is the heme ring with an iron center coordinately covalently linked to a thiolate ligand, which is capable of the electron transfers required.

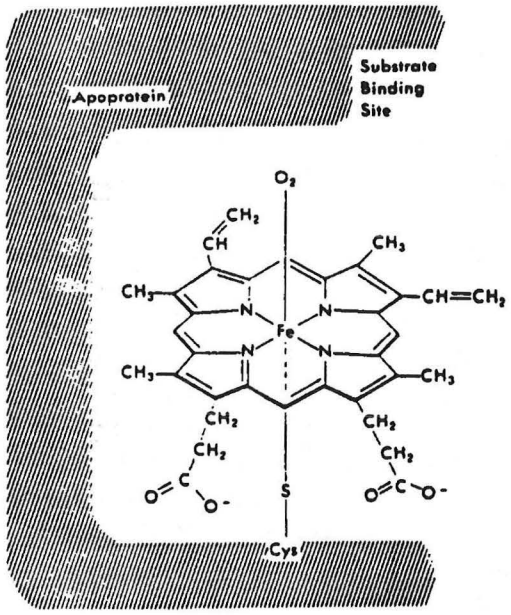

Figure 2. Proposed strucure of P-450
From Vessey DA, ref 2

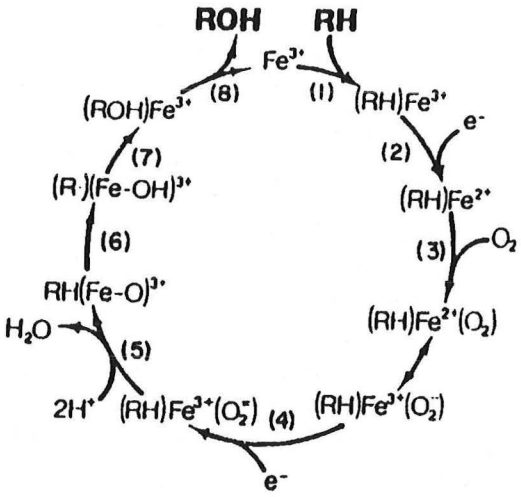

Figure 3. Oxygenation mechanism of P-450.
From DM Ziegler, ref 3

In the process of the typical hydroxylation reaction, reactive oxygen species including O^- and H_2O_2 are created, and these must be dealt with for the most part by superoxide dismutase and other protective mechanisms (see below). In addition to liver, P-450 systems are also found in kidney, brain, intestine and steroidogenic tissues.

Glucuronidation and sulfation

Most compounds require further metabolism beyond a phase I reaction to be eliminated. The phase II reactions of glucuronidation and sulfation utilize hydroxyl groups to render compounds fully water soluble. Hundreds of compounds undergo glucuronidation by formation of ester or ether linkages with

UDP glucuronide as shown below. Compounds requiring glucuronidation include acetaminophen, morphine, furosemide and bilirubin. A typical gluronidation is shown below.

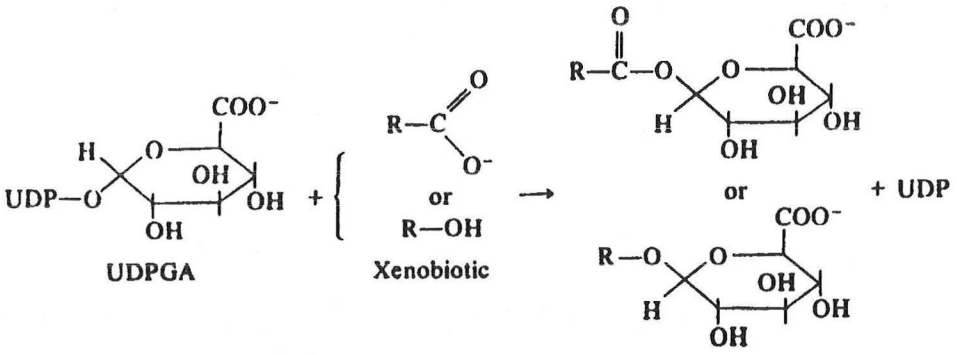

Figure 4. Typical reaction of glucuronyl transferase

The number of glucuronidation enzymes in human liver is much smaller than that observed in the P-450 system, and one species may metabolize a large number of compounds. Enzyme induction occurs with glucuronyl transferases as with most enzymes, and allows us to see how generalized induction works. Induction is the process by which the presence of a xenobiotic substrate increases the level of enzyme in the hepatocyte, to further aid in its own metabolism. Indirectly, it alters the metabolism of other compounds. The most common induction agents observed clinically are ethanol, phenobarbital and phenytoin, but cigarette smoke is also a potent inducer of certain P-450's. For example, phenobarbital induces glucuronyl transferase and in doing so aids in the metabolism of bilirubin. We take advantage of phenobarbital induction in patients with cholestatic liver disease to augment their faulty bilirubin excretion process. Induction involves the generation of increased cellular mRNA encoding the appropriate enzyme, but the mechanism by which enzyme induction occurs is poorly understood. For example, no phenobarbital receptor capable of mRNA has been identified. Studies in humans are limited for ethical reasons but recent use of hepatocytes in culture has permitted more extensive analysis of the induction process.

Sulfation is a less frequent but equally important mechanism of solubilization for non-polar compounds, and is particularly involved in the metabolism of steroid compounds and bile acids.

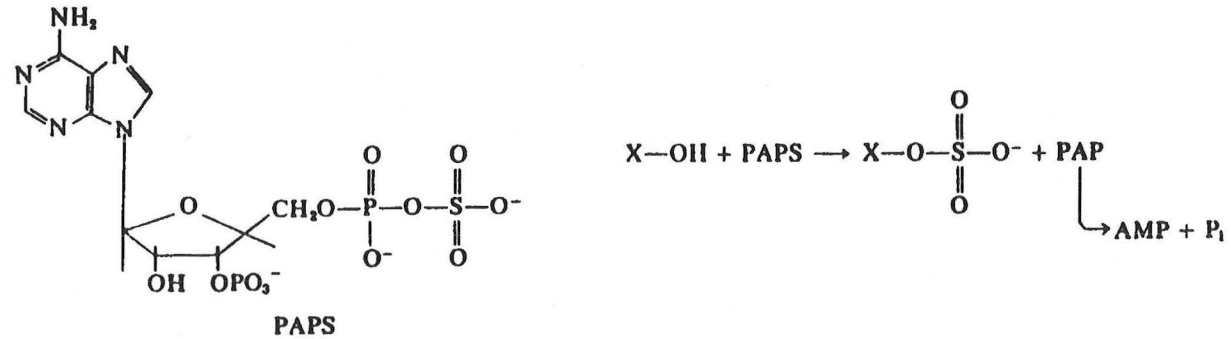

Figure 5. Structure of PAPS and a typical sulfation reaction.

As with P-450, there are several species of sulfotransferases with overlapping specificities. All employ 3'-phosphoadenosine-5-phosphosulfate (PAPS), which is synthesized from ATP and sulfate ions, produced from degradation of hepatic or dietary cysteine. Glucuronidation and sulfation may occur simultaneously using the same substrate, depending on the K_m and V_{max} of each system and availability of co-factors.

Glutathione S-transferase

Glutathione is the tri-peptide γ-glutamyl-cysteinyl-glycine, the free thiol group of which is capable of binding to electrophilic compounds and serves to detoxify a number of reactions. Glutathione substrate is depleted in the process, and must be repleted by sulfhydryl compounds from the diet, or by cysteine containing drugs such as N-acetylcysteine (see below). As such, the glutathione S-transferase reaction is central to detoxification of a number of compounds including acetaminophen. This family of enzymes is smaller than P-450 but includes at least 13 isoforms, many of which have overlapping substrate specificities. The typical reaction is shown in the acetaminophen diagram below.

Pathogenesis of toxic reactions

Most drug reactions result in hepatocyte necrosis, since the hepatocyte is the main metabolic engine of the liver. The most common reaction leading to cell necrosis is the formation of covalent bonds between a reactive metabolite of the parent compound and cell proteins or DNA. Many of the mechanisms of liver toxicity are poorly understood. The best understanding we have is that oxidative reactions may go awry if either a reactive electrophilic compound is formed, or if oxygen intermediates (such as superoxide or free radicals) are formed which can then react with cellular components. The four classes of direct (non-allergic) toxic reactions are shown below:

Table 2. Classes of toxic reactions.

	Class A	Class B	Class C	Class D
Protein alkylation	++++	++++	++++	0
Necrosis inc by GSH depletion	0	++++	0	++
Necrosis dec by GSH precursors	0	++++	0	++
Necrosis inc by Vit E deficiency	--	--	+	++++

Adapted from Smith CV, in ref 3

Reactive electrophilic compounds typically bind by a disulfide linkage as is observed with acetaminophen.

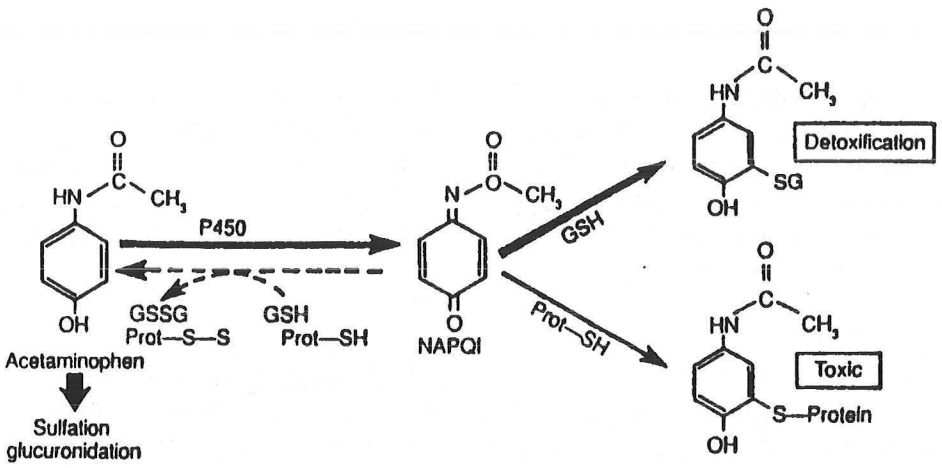

Figure 6. Acetaminophen metabolic pathway.

Acetaminophen metabolism has become the paradigm for virtually all our understanding of drug metabolism by the liver, and will be covered in detail. Although used universally for non-narcotic pain relief, acetaminophen has a predictable toxic effect if taken in doses in excess of the package recommendations. The metabolic pathway for acetaminophen involves both phase I and phase II reactions, glutathione detoxification, and the formation of reactive intermediates disrupting cell macromolecules. According to the schema listed above, acetaminophen is a class B reaction in that it is sensitive to glutathione depletion and restoration of glutathione stores. Acetaminophen causes centrilobular necrosis, occurring in the area with the least oxygen tension within the hepatic lobule.

In therapeutic doses, acetaminophen, already bearing a hydroxyl group, is non-toxic by virtue of the great excess of glucuronyl transferase and sulfotransferase available.[6] As a general rule, glucuronidation capability is in great excess of typical daily needs--even patients with far-advanced liver disease continue to have excellent glucuronidation capability. These phase II reactions (glucuronidation and sulfation) predominate when therapeutic doses of acetaminophen are given, with only a small fraction of acetaminophen being metabolized directly by cytochrome P-450. However, if the dose of acetaminophen is such that the capacity of both sulfation and glucuronidation is exceeded, an electrophilic compound, N-acetyl-p-benzoquinoneimine (NAPQI), is formed which is capable of binding covalently to cell macromolecules as described above, to disrupt mitochondrial and nuclear function.[6] The formation of covalent bonds is prevented if NAPQI can be rapidly detoxified by conjugation via glutathione-S-transferase to form mercapturic acid, a harmless water-soluble product, which is then excreted by the kidney.

Liver damage occurs when depletion of glutathione lowers this last defense against the formation of NAPQI-related intracellular compounds. Thus, any situation which leads to depletion of glutathione will increase toxicity while an increase in available glutathione stores will diminish this effect. Starvation and alcohol deplete glutathione, while N-acetylcysteine replenishes glutathione stores and protects against acetaminophen-induced injury.[16-24] In similar fashion, the P-450 isozyme (P-450IIE1) which is responsible for acetaminophen conversion to

NAPQI is induced by ethanol and blocked by cimetidine.[23-25] Thus, ethanol at an earlier metabolic step may be responsible for increased toxicity, while cimetidine serves as a possible antidote.[25-28]

Carbon tetrachloride (CCl_4) a lipid peroxidator

Other examples of toxic mechanisms which are partly understood include that associated with CCl_4. Certain halogenated hydrocarbons such as CCl_4 cause centrilobular necrosis in a dose-dependent fashion similar histologically to the effect observed with acetaminophen, however the mechanism is entirely different.

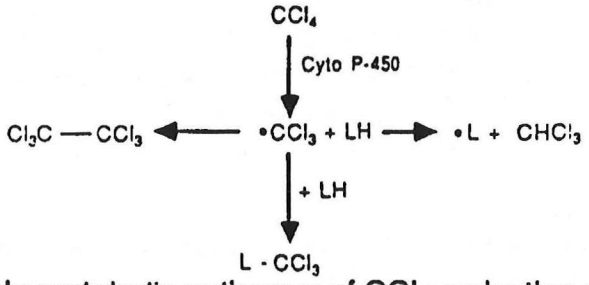

Figure 7. Possible metabolic pathways of CCl_4 reductive reaction.

The formation of $\bullet CCl_3$ is an example of an organic free radical by cytochrome P-450 or a class C reaction of Smith. The resulting lipid peroxidation can be ameliorated by antioxidants, and it is thought that lipid peroxidation itself leads to membrane damage particularly involving P-450. This explanation does not account for the centrilobular location of the damage, since oxygen tension should not play a role in lipid peroxidation. Clinically, this has been observed to be the cause of liver (and kidney) damage in glue sniffers and those ingesting halogenated alkanes.[7,8] Time does not permit a further examination of the details of drug-related pathogenetic mechanisms. Suffice it to say that the mechanism of toxicity of many compounds which are directly toxic, such as galactosamine has not been elucidated. No reactive species binding to cell proteins or macromolecules has been identified.

Enzyme polymorphism

Both acetaminophen and CCl_4 are examples of drugs with predictable toxicity. However, most drugs do not cause a predictable toxic reaction, with injury occurring only in one in 10,000 individuals. Explanations for these rare events involve understanding that genetic variants of P-450 isozymes certainly exist and may contribute either to lack of metabolism of a given compound or excess formation of a toxic substance. Evidence for polymorphisms present in a fraction of the population have been accumulated: these include fast and slow acetylators of isoniazid, and the debrisoquine polymorphism.

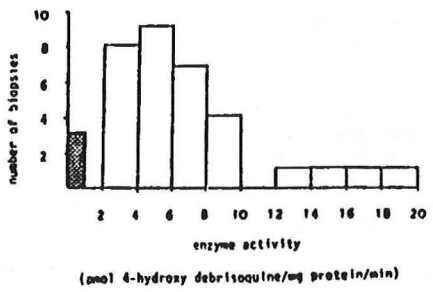

Figure 8. Frequency distribution of debrisoquine hydroxylase activity.

Debrisoquine is an anti-hypertensive compound unknown in the US, but marketed in Europe, and studied extensively, since analysis can be conducted of its urinary metabolites. Debrisoquine is hydroxylated by P-450 IID6, as is propranolol, quinidine and desipramine to name a few. In population studies, 10 percent of the population lack detectable IID6. Thus, any of the drugs mentioned if metabolized primarily by IID6 will have greatly prolonged half-lives. Similar defects in population groups have been demonstrated for mephenytoin and nifedipine. These defects are inherited as autosomal recessive traits, and involve lack of normal mRNA production, so that the appropriate apoprotein is not made.[11,12] These studies provide a plausible explanation for the occasional and isolated example of a substance which virtually everyone can metabolize being toxic for one individual. Allergic reactions play into this system but represent a separate step beyond formation of a toxic compound.

Mechanism of cell damage

What happens after covalent binding of substrate or lipid peroxidation occurs is mostly a matter of conjecture but recent evidence suggests that the net effect of the process is an increase in levels of intracellular calcium. Calcium is important for regulation of a number of cell functions including maintenance of the cytoskeleton and membrane integrity. For example, actin depolymerization and polymerization are dependent on Ca^{++} fluxes within the cytosol. Intracellular Ca^{++} concentration is maintained at low levels under normal circumstances by compartmentalization in the ER and mitochondria and by active extrusion from the cell via membrane transporters. Studies in isolated hepatocytes suggest that alterations in Ca^{++} homeostasis occurs with influx into the cytosol. NAPQI, for example, can be shown to lead to release of mitochondrial Ca^{++} in isolated cells. Whether this is the cause or the result of disordered membrane transport is unclear. Altered membrane permeability is a key feature, combined with blebbing. Blebbing is the result of disordered actin polymerization in the cortical cytoskeleton, those filaments which sit just below the plasma membrane.

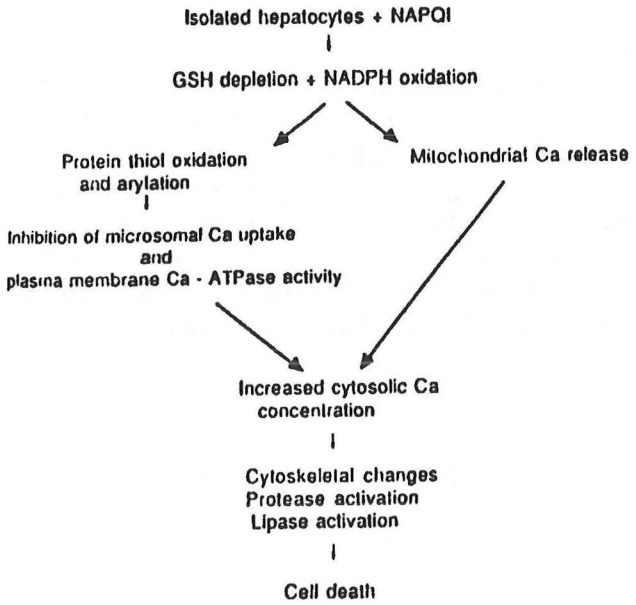

Figure 9. Pathway of cell damage involving increased cytosolic Ca^{++}.

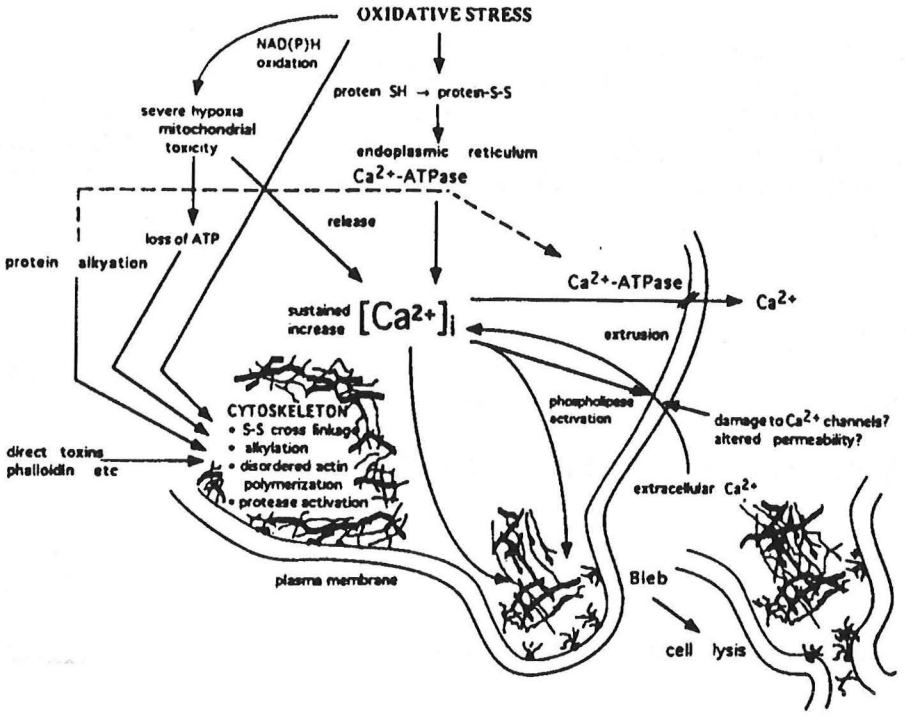

Figure 10. Disordered cytoskeleton due to increased cytosolic Ca^{++}

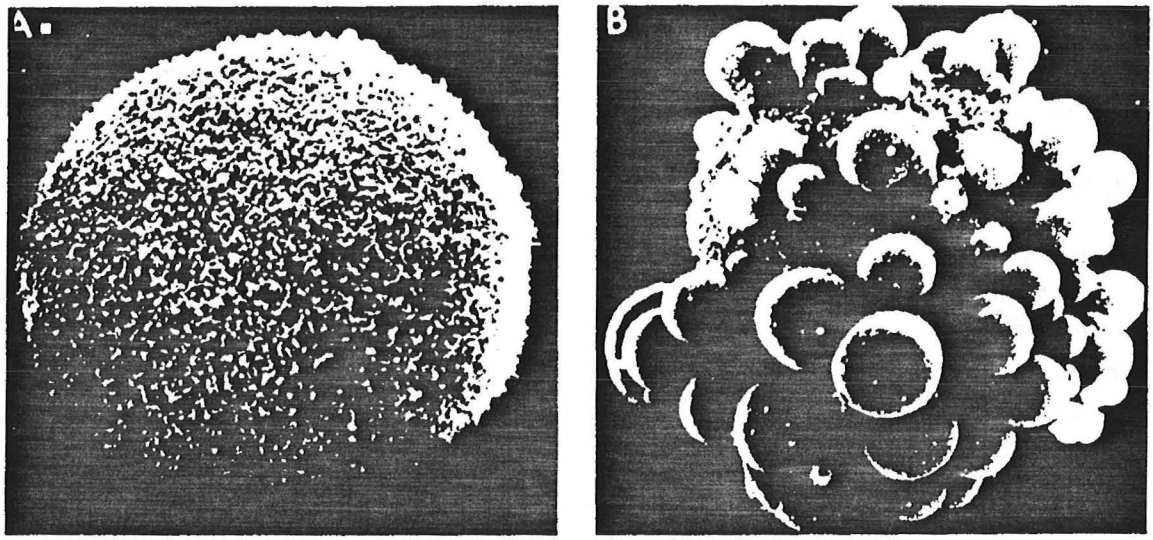

Figure 11. Scanning EM of normal and 'blebbed' hepatocyte.

In addition to producing direct toxicity, the formation of reactive intermediates may lead to allergic reactions, such as is observed with halothane anesthesia. Antibodies to P-450 enzyme species are observed in certain hepatotoxic/allergic reactions. Anti-liver kidney microsomal antibodies have been recognized in auto-immune chronic hepatitis without evidence of drug

involvement, but are also observed in drug related injuries. Nevertheless, even though anti-LKM may be directed against a P-450 species, and have been shown in vitro to inhibit activity of specific isozymes, there is no evidence that these antibodies are reactive in vivo. In addition to disrupting hepatocyte integrity, reactive metabolites may lead to toxicity in other organs such as the lung, or be carcinogenic or teratogenic.

Role of physiologic factors

There should be little doubt that the metabolic fate of any compound is a complex process. Table 3 outlines the variables other than the genetics and the compound itself which may be at play in determining metabolic outcome.[29]

Table 3. Variables determining metabolic outcome

Age[30,31]
Gender[31]
Diet
- micronutrients Ca, Fe, Mg, Cu, Zn
- caffeine
- vegetable enzyme inducers
- lipid[32]
- ethanol[16,17]

Pregnancy

Diabetes[33]

Hepatic disease

Renal disease[34]

Immune stimuli
- Interferon[35]
- IL-1[36]

Genetics
- a summation of multiple alleles[37]

Drug-drug interactions

Age appears to play a role in that metabolic rates are decreased and half-lives of many drugs prolonged in the elderly. Conflicting evidence makes it unclear whether rates of P-450 metabolism are decreased or whether liver blood flow is the determining factor. All things being equal, age is relatively unimportant compared to other factors. Although there are differences in metabolism of certain compounds depending on gender, and sex steroids may induce certain P-450 species, gender is also not an overwhelming factor in relation to drug hepatotoxicity, with the possible exception of ethanol. Availability of micronutrients is essential to metabolic functioning of the hepatocyte. In addition, a number of nutrients are capable of inducing P-450, from grapefruit juice to

caffeine. Diabetes alters hepatic P450 metabolism, by modulation of P-450 by insulin as well as induction of of certain species such as IIE1 by ketone bodies. Careful diabetic control restores normal P-450 functioning. Vitamin A itself plays a regulatory role in its own retinoid 4-hydroxylase, of possible importance in vitamin A hepatotoxicity. Pregnancy changes plasma proteins as carriers of xenobiotics, but whether significant changes occur in drug metabolism remains to be seen. Significant hepatic disease alters the half-life of most xenobiotics, but it is unclear in most instances that P-450 metabolic rates are decreased on a weight basis. The major effects may be caused by altered blood flow with decrease in hepatic first pass extraction due to this. Renal disease alters excretion of water soluble metabolites but also alters P-450 metabolism, and may be important in increasing the concentration of toxic metabolites in some instances. Although exogenous interferon has been implicated as the cause of hepatotoxicity in at least one instance, endogenous interferon levels undoubtedly produce direct effects on drug metabolism, as does IL-1. Finally, the most important factor is the genetic composition of ones P-450 alleles, in combination with the other drugs and diseases extant at the time of drug ingestion. In many instances, drug-drug interactions explain the presence of a toxic metabolite, either by blocking the normal detoxification pathway, or by induction.

Types of drug reactions

As has been mentioned, the leading cause of hepatotoxicity is hepatocyte toxicity, that is, reactions involving death of liver cells. However, some drugs injure bile ducts or canaliculi causing cholestasis without significant hepatocyte damage. Other chemotherapeutic agents affect sinusoidal or endothelial cells (producing venocclusive disease, or fibrosis) or Ito cells (vitamin A toxicity which leads to fibrosis) or present a particular pattern of liver injury affecting multiple cell types (for example, amiodarone). In a rough way, drug reactions can be grouped as hepatitic, cholestatic or mixed, but these are only very general terms and do not apply to all circumstances. Other ways of organizing drug reactions are listed below:

Table 4. Ways of organizing drug reactions

timing: fulminant, acute, chronic

histology: hepatitic, cholestatic, chronic active hepatitis, granulomatous, etc.

frequency/type of reaction: idiosyncratic, predictable, allergic

use of drug: anesthetic, antibiotic, non-steroidal, psychotropic

The most effective way of organizing drug reactions is by the "type" of reaction resulting, which includes histology as well as nature of the reaction itself. Note that this grouping crosses boundaries. It is well also to remember that some drugs may never cause hepatotoxicity while others are more frequently implicated.

Idiosyncratic vs. direct, predictable reactions

Few agents are directly toxic to the liver, probably because we don't often allow ourselves to take poisons, that is, drugs with a low therapeutic index. Nevertheless, there are several agents which cause hepatotoxicity in a dose-dependent fashion to which humans are exposed, the classic being acetaminophen. Virtually all other drugs cause hepatotoxicity only rarely, the result of the formation of a toxic metabolite from a normally non-toxic substrate. These reactions occur at an overall incidence of from 1:100 to 1:100,000. How does this happen? The best conjectures have been developed as a result of the background information given above. Each individual has a unique family of P-450's and may lead to a toxic metabolite when a bizarre genetically altered subspecies is present. These reactions can be enhanced by other factors such as age, pregnancy and other drugs. Finally, idiosyncratic reactions frequently have an allergic flavor. Presence of rash or eosinophils as well as an anamnestic response are evidence of the role the immune system may play. Some drugs are capable of causing a variety of reactions. Phenytoin, for example, may cause severe fulminant hepatitis, granulomatous hepatitis or hepatitis with a fever, rash and lymphadenopathy. It also uniformly induces gamma glutamyl transpeptidase, resulting in elevated serum enzyme levels in virtually all patients taking the drug.

It is important to realize also that although nearly every drug has been implicated once in causing hepatic damage, there are bad drugs and those which never seem to be implicated. The clinician must know the relative likelihood of a given drug being involved in a given reaction. For the remainder of this review, we will consider each type of drug reaction, give a clinical example and make appropriate teaching points about each.

Table 5. Categories of drugs in the liver, with examples.

Direct toxic reactions: acetaminophen, CCl_4, mushrooms, phosphorus

Idiosyncratic reactions: isoniazid, disulfiram, propylthiouracil, hundreds of others

Idiosyncratic/allergic: halothane, augmentin, sulfonamides, phenytoin

Cholestatic: erythromycin estolate, estrogen, captopril, sulfonamides

Granulomatous: diltiazem, quinidine, diphenylhydantoin, procainamide

Alcoholic-hepatitis-like: amiodarone, perhexiline maleate, valproate

Microvesicular fat: tetracyclines, aspirin, fialuridine, ddI

Fibrosis only: methotrexate, vitamin A

Chronic hepatitis: nitrofurantoin, alpha methyl dopa, isoniazid

Venocclusive disease: cytoxan, herbal teas, other chemotherapeutic agents

Vasodilation/shock-like state: cocaine, nicotinic acid

Acetaminophen: a direct toxin

Several clinical scenarios for acetaminophen hepatic necrosis are recognized. These include the intentional suicidal overdose, in which a large quantity of drug is consumed in a short period of time, such that the capacity of the glucuronidation and sulfation is exceeded, and the 'therapeutic misadventure,' in which an active alcoholic or binge drinker ingests acetaminophen in therapeutic or slightly excessive doses for pain relief, suffering enhanced toxicity due to the enzyme induction and/or glutathione depletion mechanisms outlined above.[25-28] The alcohol-acetaminophen syndrome may be the most common form of acute liver failure observed in the United States: when combined with acetaminophen overdoses, cases involving acetaminophen ingestion accounted for 65% of those admitted in the last two years for acute liver failure at Parkland Memorial Hospital in Dallas (unpublished observations). Acetaminophen has been implicated in causing chronic hepatitis in habitual acetaminophen abusers as well.[38]

Clinical case:

This 39 yr old alcoholic man was admitted to Parkland Memorial Hospital with altered mental status. He had a history of heavy alcohol intake (18-24 beers/day), and had been treated for a pancreatic pseudocyst 10 months earlier. He complained of chronic hangovers and had been taking acetaminophen, 3 extra strength tablets, every 4 hrs for the previous 72 hrs (total ca. 60 tablets).

On admission, he was tachycardic and tachypneic. Hepatic dullness was decreased. AST 14,400 IU/L, ALT 11,320 IU/L. Lactate level 5.5 mg/dl, T bili 12.4 mg/dl, prothrombin time 47 sec. The patient was resuscitated but never regained consciousness and died on the 8th hospital day.

This case represents a typical example of the alcohol-acetaminophen syndrome. Key features are excessive chronic alcohol intake (usually more than 6 drinks/day, plus excessive acetaminophen, but without suicidal intent. This is the "therapeutic misadventure." Usual features include both the alcohol ingestion, and the acetaminophen at doses approaching or exceeding the package recommendations. Diagnostic is the finding of extremely elevated transaminase values (mean ca 9,000 IU/L). High ALT values are also seen in suicidal acetaminophen ingestions. N-acetylcysteine is given by NG tube on admission, and for the ensuing 48 hrs, to provide glutathione substrate. Expected survival is approximately 80%.

Isoniazid: an idiosyncratic drug with potentiation by other drugs

By contrast, isoniazid represents an example of an unpredictable or idiosyncratic drug reaction: damage is not caused in a dose-related fashion, and no animal model of isoniazid toxicity is known. Since the 1960's, many examples of hepatotoxicity due to isoniazid have been noted. Fifteen to 20% of individuals receiving isoniazid as a single agent for tuberculosis prophylaxis may develop increased transaminases, but only around 1 percent develop hepatic necrosis necessitating withdrawal of the drug. During one study of isoniazid prophylaxis reported in 1972, a 1% fatality rate was reported, calling attention to the potential lethality of this agent.[39] Although most recent studies have shown a somewhat lower fatality rate than this, the risk-benefit ratio of widespread use of isoniazid prophylaxis is still an active issue at this point.[40-44]

Clinical case:

This 38 year old construction worker was found to have a positive PPD and was begun on isoniazid by his county health department. He was told not to consume alcohol. Over the first six months, he tolerated the drug well, continued to work and to consume 2-5 beers/night. At monthly visits, he was asymptomatic. His transaminase (ALT) level was noted to be 53 in July, and 273 in August. He missed his September appointment, but continued to take his isoniazid. In mid-October he developed flu-like symptoms, and was admitted with jaundice and early hepatic encephalopathy. Labs: AST 693 IU/L, ALT 817 IU/L, total bilirubin 23.6 mg/dl, prothrombin time 17.4 sec. Over the next four weeks, he remained lethargic and intermittently confused. Liver percussed to be small, and ascites became apparent. Liver biopsy could not be obtained. PT 23.6 sec, bilirubin 31 mg/dl, creatinine 2.7 mg/dl. A liver transplant was performed and the patient recovered uneventfully.

Several features explain the relatively common (albeit sporadic) toxicity observed. First, alcohol may be a co-factor in enhancement of toxicity, as is simultaneous use of rifampicin. Rapid acetylators of isoniazid have been said to have an increased likelihood of toxicity as well, although this remains controversial, with additional studies suggesting that 'slow acetylators' display more toxicity than 'fast acetylators'. In this light, we might say that these reactions which are called idiosyncratic are not really so, they are simply uncommon, and occur when a series of genetic and environmental influences on drug metabolism coincide to produce sufficient quantity of the toxic byproduct. No evidence of an allergic reaction is found in most patients with isoniazid toxicity.

Halothane: a toxic/allergic reaction

Halothane is now a rarely used anesthetic agent which was extremely popular for a number of years. Debate over the relation of halothane to post-operative jaundice flourished in the 1970's and early 1980's, with many anesthesiologists denying the possibility that this was a toxic agent. Reactions to halothane anesthesia are now well-documented and the pathogenesis is understood to be both a toxic and allergic reaction.[45-49]

Clinical case: This 29 yr old schoolteacher suffered an extensive fracture of her tibial plateau in a mountain climbing accident. She was seen in a local hospital and underwent open reduction and internal fixation. Five days later, she was febrile and slightly icteric (bilirubin 3.7 mg/dl). Wound infection was suspected and the wound was re-explored under anesthesia. Fever returned to 39° and she became more icteric, with bilirubin rising to 10.3. A second exploration of the wound was performed, and the following day the patient was comatose. Bilirubin, 32 mg/dl, PT 42 sec, eosinophils 12% on peripheral smear. Despite all supportive measures she died. The liver at autopsy weighed 650 grams and showed massive hepatic necrosis. Essentially no remaining hepatocytes were recognized. Halothane anesthesia had been used on all three occasions.

Like that occurring with isoniazid and other so-called idiosyncratic reactions, halothane hepatitis occurs only relatively rarely (1:10,000 anesthetics).

Most patients with this problem are seen on surgical subspecialty services such as gynecology, plastic surgery or orthopedics where several procedures are accomplished in a short period of time. Although there is usually no rash, halothane's clinical signature is reminiscent of an allergic reaction. The initial elevation in aminotransferases occurs at an interval of seven to ten days following initial exposure, while on re-exposure the interval between halothane exposure and symptoms shortens due to an anamnestic response. Thus, reactions to the second and third exposures occur more quickly and are typically more severe than the first. Also characteristic of the halothane toxicity picture is fever and eosinophilia, which increases in severity and duration with subsequent exposures. The initial episode often occurs after the patient has left the hospital and may be unrecognized or considered to be unrelated to the recent hospitalization. Only with subsequent more devastating episodes does the nature of the original episode become clear. Of course, the initial exposure may take place years before the second anesthetic. The reaction which causes the allergic response is the formation of electrophilic metabolites which bind to cell proteins. These protein adducts provide an initial toxic response, but also serve as a hapten for antibody formation. During subsequent exposures, antibody and cellular recognition of the halothane-protein adduct antigen on the hepatocyte surface leads to cell lysis.[47]

Phenytoin: an allergic hepatitis

Besides halothane, other drugs may be associated with reactions which are definitely allergic in nature. Signs of a systemic allergic reaction include fever, rash, lymphadenopathy, eosinophilia and the presence of eosinophils or granulomas on biopsy. Phenytoin (Dilantin) is a cause of this picture, and the clinical features include both hepatocyte necrosis and cholestasis.[50,51] The mechanisms responsible for the combined allergic and hepatotoxic reaction are unknown, but the slow resolution of the illness, suggests that the allergen remains actively present on the hepatocyte surface for weeks or months.

Clinical case: A 32 yr old woman underwent resection of an arteriovenous malformation of the right temporal-parietal region, and was placed on diphenyhydantoin as prophylaxis against possible siezures. She made an uneventful recovery, and was discharged to a rehabilitation facility two weeks later. Four weeks after her surgery, she developed fever, sore throat and lymphadenopathy. Liver function tests were noted to be elevated: aspartate aminotransferase (AST) 253 IU/L, total bilirubin 3.6 mg/dl, alkaline phosphatase 265 IU/L. Penicillin V was prescribed for presumed pharyngitis. Fever continued, the patient became jaundiced and developed a widespread rash; diphenylhydantoin was discontinued and phenobarbital substituted. The bilirubin level continued to rise and intravenous hydrocortisone was begun, 100 mg every six hours. On transfer to our hospital ten days later, the patient was febrile, deeply icteric, with a desquamating rash, including mucous membranes. Total bilirubin was 23.2 mg/dl, AST 74, alkaline phosphatase 874 IU/L. She required intensive care over the next two weeks, developing an episode of Streptococcal sepsis, and a further drug eruption attributed to phenobarbital. Over the next six weeks, she demonstrated slow improvement in her rash and liver enzyme abnormalities. By three months following the episode, her alkaline phosphatase

and aminotransferases were still mildly abnormal, although her bilirubin was within normal limits.

This case highlights some of the frequently observed components of the hypersensitivity hepatitis syndrome, or mononucleosis-like syndrome seen with phenytoin but also with other agents. First, the condition may be confused with other conditions such as viral illnesses or streptococcal pharyngitis. If this occurs, the offending agent may not be discontinued promptly, despite signs of developing hepatitis. Second, the condition represents a systemic illness with a "Stevens-Johnson" drug eruption and prolonged fever. Resolution occurs very slowly even with use of large dose corticosteroids. Third, a mixed cholestatic-hepatocellular picture was observed. Rapid recognition of the possibility of a toxic drug reaction and discontinuation of the agent is the most important feature in limiting hepatic damage. Allopurinol is another drug which causes this severe hypersensitivity syndrome. It is important to remember that features of an allergic reaction may (or may not) be obvious. Allergic features are not detected in the majority of the drug reactions grouped as idiosyncratic. In the absence of systemic signs of allergy, eosinophilia as well as granulomas still may be present on biopsy.

Cholestatic reactions

A number of drugs mainly affect bile flow and thus cause a cholestatic injury. The classic agent was chlorpromazine, which is rarely a problem nowadays, either because the drug is used less frequently or because a toxic byproduct which was the prominent cause of the cholestasis has been more carefully extracted during chlorpromazine production. Typically, jaundice is present early with associated pruritus but little alteration in general well-being. Liver biopsy reveals what one would expect: there is engorgement of the canaliculi with bile, but little evidence of hepatocellular injury. Eosinophils may be found in mildly inflamed portal tracts.

Clinical case:

This 57 yr old housewife was admitted for evaluation of pruritus and abnormal liver function tests. One months earlier, she had developed pruritus and sought medical attention on several occasions without relief; two forms of anti-histamines were given without success. Her gynecologist noted that she had abnormal lab values and referred her for evaluation. She denied alcohol or toxin exposure. There was no abdominal pain, nor had she been jaundiced. Stools had been normal to slightly loose, but she had had no weight loss. Meds: vitamins, Estrace (estradiol), numerous anti-histamines.
On physical exam: no spiders, trace icterus, no hepatosplenomegaly. Labs: T bili 3.2 mg/dl, AP 197 IU/L, AST 62 IU/L, LDH 210 IU/L, CBC normal except WBC 18,000/ cu mm, normal differential, and plt count.

Differential included pancreatic cancer, choledocholithiasis, as well as a possible drug reaction. USG: normal, ERCP: normal, liver biopsy: bland cholestasis. Discontinuation of Estrace resolved her symptoms and lab abnormalities over a four week period.

The list of drugs which cause pure cholestatic injury is relatively short, but includes estrogens, chlorpromazine,[52] trimethoprim-sulfamethoxazole, rifampin,

erythromycin estolate and captopril.[53] The patient had been treated with estrogens some years earlier for several years, and was withdrawn for unclear reasons, then restarted six months prior to onset of symptoms. The mechanism of cholestatic injury remains unclear. Estradiol and other estrogens have been shown to decrease bile flow, decrease Na^+-K^+ ATPase, change tight junctions, as well as alter hepatocyte membrane fluidity. An effect on microtubular function may also be important. Given the large number of women (and men) on estrogens, cholestasis is remarkably rare and implies an altered metabolic pathway.

Granulomatous reactions

Lesions resembling sarcoidosis in the liver are caused by a variety of drugs. The typical scenario is that of other forms of granulomatous hepatitis: low-grade fever, chronic fatigue. The list of possible agents is long.

Table 6: Drugs associated with granulomatous liver disease.

allopurinol	nitrofurantoin
aspirin	penicillin
carbamazepine	phenylbutazone
cephalexin	phenytoin
diazepam	procainamide
diltiazem	procarbazine
halothane	oxyphenbutazone
hydralazine	quinidine
isoniazid	sulfonamide
metahydrin	sulfonylureas
methyl dopa	
metolazone	

Adapted from Maddrey and Zimmerman, ref 1.

Clinical case[54]

This 68 yr old woman sustained a myocardial infarction and was placed on diltiazem 120 mg TID as well as aspirin 150 mg/day. Three weeks later, she was admitted with fever and generalized weakness. Exam was unrevealing but alkaline phosphatase was increased to 1331 IU/L, AST 94 IU/L. Total bilirubin and prothrombin time were normal. Blood cultures were negative. Liver biopsy revealed periportal granulomas. Diltiazem treatment was stopped and her aspirin continued. She defervesced and enzymes and sense of well-being continued to improve over a five week span, at which time her tests returned to normal.

Granulomatous hepatitis is often a mysterious illness. First symptoms include fever and malaise, while other signs of infection or systemic illness are absent. While the differential of granulomatous hepatitis is long, hypersensitivity reactions to drugs is a leading bet, and in this case proved to be the correct one.

Chronic hepatitis secondary to drugs:

A variety of agents have been found to cause a more indolent form of liver damage which closely resembles autoimmune chronic active hepatitis. Hyperglobulinemia and positive tests for anti-nuclear antibodies may be detected.

The classic agent here was oxyphenisatin, marketed as a laxative in the US (Dialose plus).[55] This agent has since been removed from the market but is still available in parts of Europe. While some drugs like oxyphenisatin have been withdrawn from the market, others continue to be available, in large part because the incidence of reactions remains quite low. Early identification of chronic drug-related hepatitis is not easy, and some patients may develop established cirrhosis prior to diagnosis. It is always difficult to implicate a drug or toxin as a cause of cirrhosis when other factors such as alcohol or unrecognized viral hepatitis may be present. Nevertheless, alpha methyldopa[56] nitrofurantoin,[57-61] isoniazid[40] and propylthiouracil have clearly been implicated. Because these drugs are taken chronically for relatively benign conditions, surveillance for untoward drug effects, and concern about multiple prescription renewals may not be stressed. This is particularly true for nitrofurantoin (Macrodantin, nitrofurantoin macrocrystals), which many people take chronically for control of recurrent urinary tract infections.

Clinical case:

This 34 yo mechanic presented with chronic fatigue and jaundice of several months' duration. He had no known toxin exposures, and denied risk factors for viral hepatitis. Over the past five years, he had been treated for recurrent prostatitis by his physician on numerous occasions, and in fact had a standing prescription for Macrodantin at the pharmacy. He denied alcohol intake. On exam, occasional spiders were noted, as well as jaundice, hepatosplenomegaly, ascites, and peripheral edema. T bili 13.6, AST 560 IU/L, ALT 760 IU/L, albumin 26 gm/L globulin 5.2 mg/dl, ANA + 1:320. Liver biopsy revealed florid chronic active hepatitis with early cirrhosis. The patient was treated with prednisone 40 mg/day and withdrawal of Macrodantin. Six months later, on 5 mg prednisone, his enzyme levels were normal, albumin level 3.7, and he felt well.

In many instances, the patient does not consider a urinary antibiotic a real drug and will not admit to its use, simply because it is used as needed, with a readily renewable prescription. This is the hallmark of most such cases. Alpha-methyl dopa was a commonly used anti-hypertensive now rarely prescribed. Both drugs may be a cause of cryptogenic cirrhosis without florid hepatitic features.

Fatty liver and alcoholic hepatitis-like syndromes

Fatty liver is ordinarily not a drug-induced problem, being most commonly related to obesity, diabetes, alcohol and only occasionally to steroid therapy. However, several drugs appear to cause the evolution of a picture similar to alcoholic hepatitis, sometimes termed steatonecrosis. One recent agent which has an unusual histologic and clinical profile is amiodarone. This potent anti-arrhythmic agent is used for life-threatening ventricular tachycardia, but has been shown to cause severe liver damage acutely or in a more chronic form,[62-65] as part of its multisystem toxicity. Many patients have aminotransferase elevations, and these patients will demonstrate the characteristic finding, a lesion which resembles very closely alcoholic hepatitis, and can proceed on to alcohol-like cirrhosis in as little as a few months' time. Electronmicroscopic studies show prominent lysosomal inclusions similar to those seen in the phospholipidoses

such as Niemann-Pick disease. Accumulation of phospholipid and the development of Mallory's hyaline and other alcohol-like features may not be linked directly, (except that both are part of the amiodarone toxicity picture).

Clinical case: A 30 yr old teetotaler with idiopathic cardiomyopathy was begun on amiodarone for recurrent ventricular arrhythmias. Holter monitor showed a marked decrease in ventricular irritability, and he was continued on medication for five months when it was discontinued because of weight loss, elevated thyroid function studies, and elevated AST levels (91 IU/L). Bilirubin and alkaline phosphatase levels were normal. Thyroid function returned to normal and his weight improved, but after ten months his liver function tests were unchanged. A liver biopsy revealed classic features of alcoholic hepatitis with steatosis, Mallory's hyaline, and a neutrophilic infiltrate throughout the biopsy. Features of early cirrhosis were present. Electronmicroscopic examination revealed lamellar lysosomal inclusions. Three hundred and five days after discontinuation of the drug, amiodarone was still present in plasma. Because the drug is very lipophilic and is stored in fat depots within the body, the plasma half-life is at least several weeks, and it clearly can remain in the body for extremely long periods of time.

Microvesicular fat: nucleoside hepatopathy in AIDS

Microvesicular fat within hepatocytes carries a different meaning from the presence of macrovesicular steatosis discussed above. Fine vesicles appearing within hepatocytes are associated with considerable cellular dysfunction without death of hepatocytes. This is the lesion of fatty liver of pregnancy, intravenous tetracyclines and Reyes syndrome (with aspirin implicated). Macrovesicular steatosis has been described recently in association with AIDS and use of zidovudine (AZT).66-68 Eight cases associated with zidovudine usage have recently been described, as well as at least one case related to didanosine (ddI).[69] These cases are of particular interest in light of the recent tragic experience of patients participating in a study of a new nucleoside analogue for treatment of hepatitis B infection, fialuridine (FIAU). After nearly eight weeks of therapy, several patients entered the hospital almost simultaneously with lactic acidosis, hepatic failure, and severe microvesicular steatosis; five of the nine patients died, despite prompt discontinuation of drug in all, and transplantation in most.[70,71] The previous ddI case had an identical picture, with profound and progressive lactic acidosis. Both FIAU and ddI (and AZT in certain cases) may produce uncoupling of mitochondrial oxidation leading to anaerobic metabolism. It is likely that some of these cases are under-diagnosed because it is difficult to be sure in patients with advanced AIDS, multiple infections, and multiple drugs which drug/virus/bacterium is responsible for the evolving toxic reaction. It will be necessary in the future to be aware of the possibility of nucleoside analogue-related mitochondrial dysfunction.

Silent fibrosis/cirrhosis

Several agents are capable of causing gradual evolution to cirrhosis, without manifesting any clinical illness in the process. Methotrexate is the most cited example. With this agent, which is used in patients with severe psoriasis or rheumatoid arthritis, toxicity develops over several years, without any evidence of hepatitis clinically or biochemically.[73,74] This poses a problem in surveillance of

these patients since even aminotransferase levels may be entirely normal while the disease develops. Liver biopsy represents the only sure way of diagnosing the condition. Psoriatic patients appear to have mild liver abnormalities on biopsy even prior to treatment with methotrexate and this has been attributed to recurrent bacteremia secondary to their skin disease. Occult alcoholism is also a factor when considering methotrexate use, since many psoriatic patients have severe psychosocial problems as well as difficulty sleeping due to their skin problem. Although guidelines vary, most clinicians with wide experience perform a biopsy after a total dose of approximately 2500 mgms, and perform a pre-treatment biopsy in anyone who has any degree of liver test abnormality or where there is any suspicion of excess alcohol intake. Perhexiline maleate, alpha methyl dopa[56] and vitamin A[75] have also been implicated as causes of a similar syndrome.

Clinical case:

This 76 yr old physician was referred for management of ascites. He had long-standing diabetes and was diagnosed in 1975 with prostate cancer. He underwent orchiectomy and, at a nutrition institute, began a high beta carotene diet consisting of vitamin A plus fresh carrot juice. For at least one year, his family reports that his skin was orange-yellow. He underwent coronary bypass surgery uneventfully in the late 1970's and developed signs and symptoms of cirrhosis over the last five years. Liver biopsy performed at the time of cholecystectomy in 1989 disclosed macronodular cirrhosis. All hepatitis serologies are negative including hepatitis A, B, and C. Alpha-1 antitrypsin level, ferritin and PSA level are all normal or negative. AST 26 IU/L, ALT 24 IU/L, T bili 1.2 mg/dl, albumin 23 gm/L.

In the absence of other apparent etiologies, this man is believed to have vitamin A toxicity as the cause of his cirrhosis. Management consisted of spironolactone therapy and, subsequently, sclerotherapy for variceal hemorrhage.

Alternative health agents

Over-the-counter preparations are assumed to be safer than prescription drugs, but this is not always the case. Dialose plus was one such example. Particular hazards reside in the health food store, where all agents are assumed, even if not effective, at least not to be toxic. Part of the problem resides in this implicit assumption of safety. Patients do not assume that any toxicity accrues from either cumulative doses or use of higher than recommended doses.

Clinical case:[76] This 33 yr old woman noted a breast lump and began, on the advice of a friend, to take Chaparral Leaf tablets, 15 per day. After three months, she developed nausea, anorexia and dark urine. She decreased the number of tablets to one/day, and noted some improvement After several weeks, she increased the dose to seven tablets/day, and once again noted fatigue, jaundice and increased abdominal girth. Liver function tests included a bilirubin of 12 mg/dl, alkaline phosphatase of 285 IU/L, and an aspartate aminotransferase of 1,285 IU/L. She discontinued the medication, and made a slow recovery over the next 11 months. Liver biopsy at the time of hospital discharge was consistent with subacute hepatic necrosis.

Note that the dose which she took was totally at her own discretion. The lack of adequate supervision of medications in the setting of alternative health strategies may be a real problem for the future. The list of alternative health agents implicated as a cause of toxicity besides vitamin A,[75,77] includes Jamaican bush tea, germander,[78,79] and comfrey.[80]

Safety profiles may change when apparently safe agents are reformulated. For example, a tried and true drug, nicotinic acid, demonstrated greatly increased hepatoxicity when repackaged in a sustained release form. Although hepatoxicity had been recognized with high dose therapy previously, no examples of severe toxicity had been observed in the usual therapeutic doses. However, the flushing reaction most patients experience on standard doses limits use of the drug for many individuals and inhibits excessive dosing. Once a sustained release formulation of nicotinic acid became available, reports of fulminant hepatitis and shock secondary to this agent began to appear.[81-83]

Combination agents with increased hepatotoxic potential

It should not be surprising that drugs interfere with each other's biotransformation. It is more remarkable that interference of drugs one with another does not occur more often. There are several circumstances where drug combinations come together. The first is when drugs are combined in a single agent such as trimethoprim-sulfamethoxazole[84] (Bactrim, Septra) and amoxicillin/clavulanic acid[85,86] (Augmentin). Numerous examples of hepatotoxicity have been reported with each of these combination agents, which exceed the sum of those associated with each agent's toxicity alone. The mechanism of injury here involves induction of P-450 by one agent, which then heightens the formation of a toxic metabolite by the other. A mixed hepatocellular-cholestatic hepatitis with fever, rash and eosinophilia ensues.

A different example is that observed with frequently-used single drug combinations, such as isoniazid and rifampicin as anti-tuberculous therapy.[87,88] Either agent alone can be the cause of an hepatotoxic reaction, although rifampicin usually causes primarily cholestasis. By inducing the P-450 isozyme responsible for isoniazid N-demethylation, rifampicin enhances isoniazid toxicity by formation of a toxic hydrazine. Many further examples will be observed when four and five drug regimens are instituted for resistant tuberculosis. Some reports of this have already appeared.[89-92]

Cocaine

The widespread illicit use of cocaine has become a national menace for reasons which are not directly relevant to its innate hepatotoxicity. Little has been written about hepatic injury with cocaine; nevertheless, this drug is a potent contributor to the death of certain patients who, after cocaine ingestion, develop shock, disseminated intravascular coagulation, and evidence of myonecrosis. In these instances, the liver toxicity is almost certainly ischemic in nature, the result of the systemic hypotension induced by coronary (and systemic arterial) vasospasm with congestive heart failure.[93] Sorting out more subtle forms of liver injury in drug abusers is complicated by concomitant alcohol use (which induces P450 and increases cocaine metabolism to toxic byproducts),[94] and the presence of other viral agents as causes of hepatitic symptoms and signs.[95,96]

General diagnostic and therapeutic measures

The diagnosis of drug-induced liver injury is often obscured by difficulty in reconstructing the timing of drug ingestion from the patient's history. Essential to the diagnosis is that the patient was not ill before the drug, became ill while on the drug, and in most cases, showed remarkable improvement with drug withdrawal. Since drug-related hepatitis is potentially fatal, it is vital to maintain a healthy respect for the possible severity of the hepatic reaction, and to stop any potentially offending medication if it temporally seems to be a possible culprit. Frequently, there are several possible villains. In this case, the best way to implicate the offending drug is to make a careful timeline of the agents and to eliminate those which have been taken for years, and those begun after the symptoms or laboratory abnormalities were noted. After that, one can usually suspect drugs which were begun in the previous two to three months as the most likely agents. With this short list, one can then usually consult a list of the more common offenders and find the perpetrator. This is the main reasons for lists of drugs such as those found in this protocol! Many drugs are virtually never implicated as causes of hepatotoxicity, but we just don't make a list of these. Some agents in this list would include digoxin, theophyllin, phenobarbital. Note that this group includes mostly old standard drugs which have withstood the test of time.

The mainstay of treatment for drug-induced hepatotoxicity is withdrawal of the offending agent followed by observation of the patient for the expected improvement. Improvement should follow within days, but often takes weeks or even months for the symptoms and liver enzyme pattern to fully resolve. Certain agents such as augmentin and phenytoin have been associated with a syndrome in which the condition actually worsened for several weeks after the drug was withdrawn and required months to resolve. If signs of hepatic failure are present (or there is laboratory evidence of this, such as elevated prothrombin time), then acute liver failure may be developing and hospitalization is mandatory.[97] The prognosis for drug-induced acute liver failure is dismal, with more than an 80% mortality rate in most series.[98] Steroid treatment may be used for prolonged symptoms, as it is in the phenytoin hypersensitivity syndrome, but controlled trials have not been performed to prove that there is any efficacy. Intentional overdoses must be treated as any poisoning with appropriate emergency measures. Suspected acetaminophen overdosage is treated with N-acetyl cysteine, even when the ingestion has occurred 36 hours or more previously. Hemodialysis or hemofiltration is rarely indicated.

New agents

Each year, dozens of new pharmacologic agents appear. The pressure from the public as well as the pharmaceutical industry to bring new agents to market is great, while cautionary tales of failed drugs whose toxicity was only recognized after they were marketed are often forgotten. Ticrynafen (tienilic acid) was just such a drug. Over the first nine months after its introduction, this diuretic and uricosuric agent was implicated in more than 25 instances of fatal hepatotoxicity, and the drug was withdrawn.[99] Although this agent was removed rapidly once the problem was recognized, its toxicity was only fully realized after FDA approval. Short of disastrous drugs such as Ticrynafen, how do physicians

become aware of drug-related toxicity? Many times the only means of instruction is via that much-maligned instrument, the case report. Even so, unless one reviews the Medline regularly it is impossible to keep up with such information. The proper stance with regard to new therapeutic agents is to consider any agent capable of a hepatotoxic response, and to withdraw the agent at the first sign of liver injury. Some of the frequently seen newer agents implicated in causing acute liver necrosis are listed in Table 7.

Table 7. Newer (and well-known) agents implicated in hepatotoxic reactions (partial list) with references.

allopurinol[100]
alpha interferon[101]
azathioprine[102]
carbamazepine[103]
cyproterone acetate[104,105]
cytoxan[106]
dapsone[107]
diclofenac[108,109]
disulfiram[110-112]
etoposide[113]
flutamide[114-116]
glyburide[117]
imipramine[118]
ketoconazole[119]
labetalol[120]
lisinopril[121]
lovastatin[122]
norfloxacin[123]
ofloxacin[124,125]
pentamidine[126]
piroxicam[127]
propylthiouracil[128]
rifampicin[129,130]
sulfamethoxazole[131]
valproic acid[132-135]

Although each agent approved by the Food and Drug Administration has been through rigorous clinical trials, there is no substitute for the scale of exposure which follows release of a new agent. As a prescribing physician, it is probably prudent to wait a year before embracing any new drug, particularly if it has no unique advantages over accepted formulations. Prescribing any xenobiotic carries with it the hazard of drug-induced hepatotoxicity. The physician should instill in his patient a healthy but not excessive degree of paranoia with regard to drug-induced liver injury. Many fatal drug reactions could be prevented if the drug were withdrawn at the first sign of an illness. Patients who believe in the complete safety of any product, or who don't think of drug-induced injury as a possibility, or who are encouraged to be compliant when signs of toxicity are beginning are at the highest risk for fatal drug reactions.

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