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SOME ASPECTS OF TOXIC HEPATITIS

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Traditionally hepatitis caused by chemical agents, including drugs, has been considered due either to a hypersensitivity reaction or to toxic effects of the agent or its metabolites. Hypersensitivity is usually implicated when: (1) Only a small fraction of exposed persons exhibit the injury and it cannot be reproduced in animals; (2) There is no close temporal relationship of the reaction to the beginning of exposure to the agent; (3) There is no relation between the severity of the reaction and the dose of the offending agent; and (4) There are extrahepatic manifestations of hypersensitivity such as fever, rash, and eosinophilia. Toxicity is implicated when: (1) All exposed persons exhibit the injury and it can be reproduced in animals; (2) The injury is manifest at a fixed, usually brief, interval following exposure to the agent; and (3) The severity of the injury is proportional to the dose of the agent.

Increased basic knowledge, especially in the area of drug metabolism, has provided a foundation for broadening this concept of toxic hepatitis. Some agents previously thought to cause hepatitis by hypersensitivity are now suspected to be hepatotoxins. As a result, the above criteria can no longer be considered completely reliable in separating hypersensitivity from toxic injury. We will review some of the basic information that has led to this reappraisal of toxic hepatitis and then discuss several important hepatotoxins which illustrate specific points.

An important basic question is: Why do some agents produce hepatotoxicity with less or no injury to other organs? One obvious consideration is the portal circulation. Absorbed toxins will pass through the liver before entering the systemic circulation. The liver may extract a large amount of the toxin from the blood and thus protect other organs at its own expense. This may account for the frequent dominance of hepatotoxicity in cases of poisoning by phosphorus which is a non-discriminating protoplasm poison.

There are many agents, however, which rather selectively produce liver damage whether they are administered enterally, parenterally, or by inhalation. The hepatotoxicity of these agents can usually be traced to their biotransformation by the liver. This biotransformation or metabolic activation, as it is sometimes called, is frequently carried out by the hepatic microsomal cytochrome P-450 system.*

The P-450 system consists of a flavoprotein reductase known as NADPH-cytochrome c reductase and a terminal oxidase, the P-450 hemoprotein. Both of these proteins

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* As used herein, P-450 system refers only to the liver system containing this hemoprotein. It is also known as the hepatic microsomal drug metabolizing system and the mixed function oxidase system.

are bound to the microsomal membrane. Present evidence indicates that there is only one reductase (1) but that multiple forms of P-450 exist (2,3). The P-450 binds the substrate and therefore is the major determinant of substrate specificity (3,4).

The P-450 system can consume a significant proportion of the O_2 taken up by the liver. It is a monooxygenase or mixed function oxidase system because one atom of the O_2 ends up in a product and one ends up in water (5). Various types of oxidative reactions are catalyzed by this system but hydroxylation and oxidative demethylation are perhaps the ones most often mentioned.

The activity of the reductase and the amount of the specific forms of P-450 present are highly variable. There are tremendous species and strain differences (6,7). Nutritional (8) and hormonal (9) factors also modify the system. Administration of drugs and other xenobiotics can alter selectively one or more components of the system leading to enhancement of some of its functions and diminution of others. Fig. 1 illustrates this.

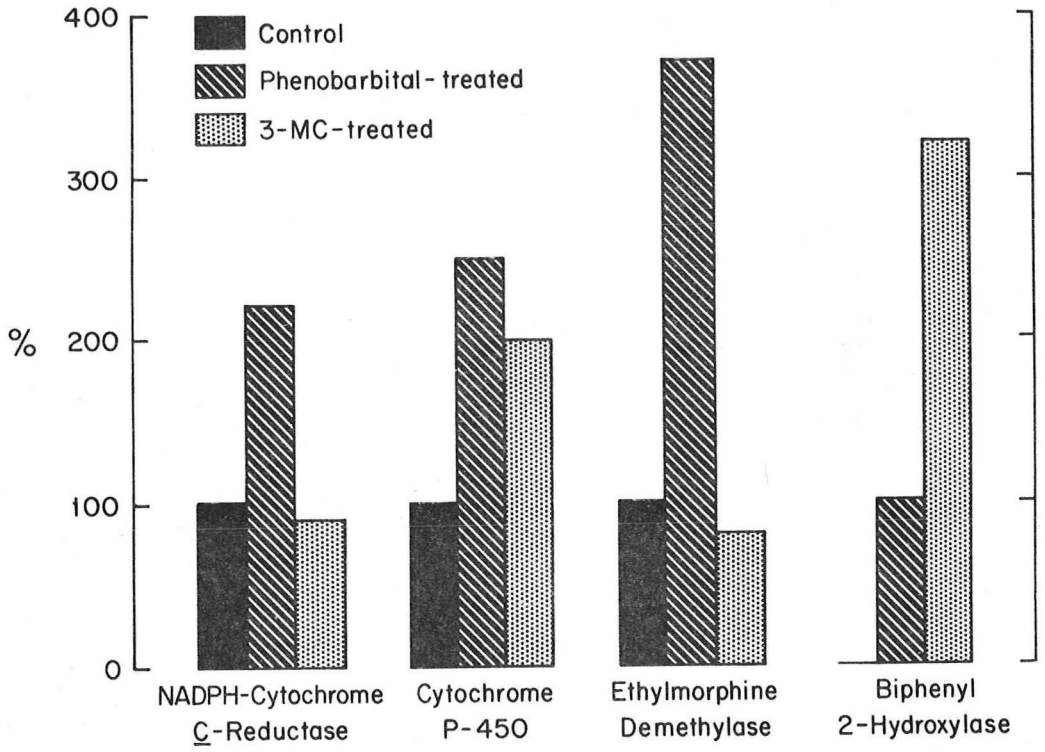

Figure 1. Effect of phenobarbital and 3-methylcholanthrene on constituents and activities of the hepatic microsomal cytochrome P-450 system. Animals were given the agents for 4 days before assays were performed. Control animals are shown as 100% except for biphenyl 2-hydroxylase which was undetectable in controls. Data from ref. 10.

Although it metabolizes certain endogenous compounds, the P-450 system is best known as a xenobiotic (or drug) metabolizing system. Its relative lack of specificity and its selective inducibility enable it to modify a wide variety of compounds so as to increase their water solubility or susceptibility to conjugation. Its action usually produces a biologically less active compound or one that is more readily excreted. As might be expected though, some metabolites produced by the P-450 system are more active than the parent compound. This biotransformation process has been termed metabolic activation (11,12).

In recent years the hepatotoxicity and carcinogenicity of certain agents have been shown to be due to their metabolic activation (11,13). Thus substances which are not intrinsically toxic to the liver are transformed into toxins by the liver's own metabolic machinery. Furthermore the production of toxic metabolites is subject to the same genetic, nutritional, hormonal, and pharmacological influences as are other P-450 system reactions. This means that under a given set of these conditions very little toxic metabolite may be produced and little or no liver damage will occur. The same dose of agent under different conditions may lead to severe liver damage.

Other organs such as the lung, kidney, adrenals, testes, and intestine also contain cytochrome P-450 systems and, although activities in them are usually considerably less than that of the liver system, these enzymes may play roles in certain types of toxic injury to those organs (14). There has been relatively little investigation of this possibility, however.

Carbon tetrachloride

Carbon tetrachloride (CCl_4) is the prototype for hepatotoxins. It and certain other halogenated alkanes have long been known to cause centrilobular hepatic necrosis and fat accumulation as well as renal damage. In the past when these agents were widely employed as solvents, degreasing cleaners, and fire extinguishers, many fatalities occurred from their ingestion or inhalation. Most of the halogenated hydrocarbons known to produce hepatic necrosis have been withdrawn from common use and accidental poisonings with them have declined. However, occasional reports of hepatitis due to unusual exposures continue to appear. For example, centrilobular necrosis due to sniffing of the cleaning fluid Carbona which contained trichloroethylene was reported in 2 teenagers (15).

As little as 2 ml of CCl_4 has reportedly led to death, but survival has been reported after ingestion of over 100 ml (16). Five to 10 ml is frequently fatal. Immediately after ingestion there is nausea, vomiting, and abdominal pain. The pain can be very severe. If a large enough dose is taken CNS depression can occur. Characteristically signs of hepatic and renal damage become evident on the 2nd or 3rd day. Liver injury varies from a small rise in SGOT to fulminant hepatic failure.

Once hepatic damage is evident the treatment must be expectant. It should be pointed out that unless the liver has been virtually destroyed, it can be expected to regenerate. Therefore vigorous treatment of hepatic coma is required to prevent irreversible CNS changes. Otherwise the patient may recover hepatic function but remain comatose. Although exceptional measures such as exchange transfusion have been shown to have no value in fulminant hepatic failure due to viral hepatitis (17), the possibility exists that they may be of use in some forms of toxic hepatitis (18).

A number of theories have been advanced to explain how CCl_4 damages the liver. The one best accepted at present suggests that some component of the P-450 system interacts with CCl_4 to give a trichloromethyl free radical ($CCl_3^{\cdot}$) which causes damage to the hepatocyte.

That metabolic activation might be involved in CCl_4 hepatotoxicity was appreciated in the 1960's when it was shown that CCl_4 metabolites were actually incorporated into hepatocyte lipids (19), and that $CHCl_3$ and C_2Cl_6, both expected products of $CCl_3^{\cdot}$ were produced in vivo (20). The P-450 system was implicated by the demonstration that induction by phenobarbital caused increased CCl_4 hepatotoxicity and inhibition of the system by various means protected against it (21.22). Chickens and newborn rats, which are resistant to CCl_4 liver damage (23,24), have very little P-450, and development of sensitivity to CCl_4 in the rat parallels development of the P-450 system.

Several studies have pointed to $CCl_3^{\cdot}$ as the toxic metabolite of CCl_4 responsible for tissue injury (19,25). Recently direct evidence for the production of $CCl_3^{\cdot}$ by the P-450 system has been provided by electron spin resonance studies (26).

$CCl_3^{\cdot}$ is a free radical and as such is very reactive. Its toxicity is presumably due to its interacting in a damaging way with constituents of the hepatocyte. There is evidence for several types of interaction.

TABLE I

Effect of Phenobarbital on Binding of ^{14}C to Microsomal Lipids and Proteins after $^{14}CCl_4$

	dpm/mg lipid	% of control	dpm/mg protein	% of control
Control	58	--	23	--
PB	81	140	22	97

Data from ref. 27

Experiments with $^{14}CCl_4$ (Table I) have shown that ^{14}C becomes bound to lipids in the endoplasmic reticulum roughly in proportion to the amount of damage done to the liver (27). This binding presumably leads to altered function of the molecules and ultimately cell death. NADPH + $NADP^+$ falls rapidly after CCl_4 administration (fig. 2) suggesting that it may be destroyed by $CCl_3^{\cdot}$ (28).

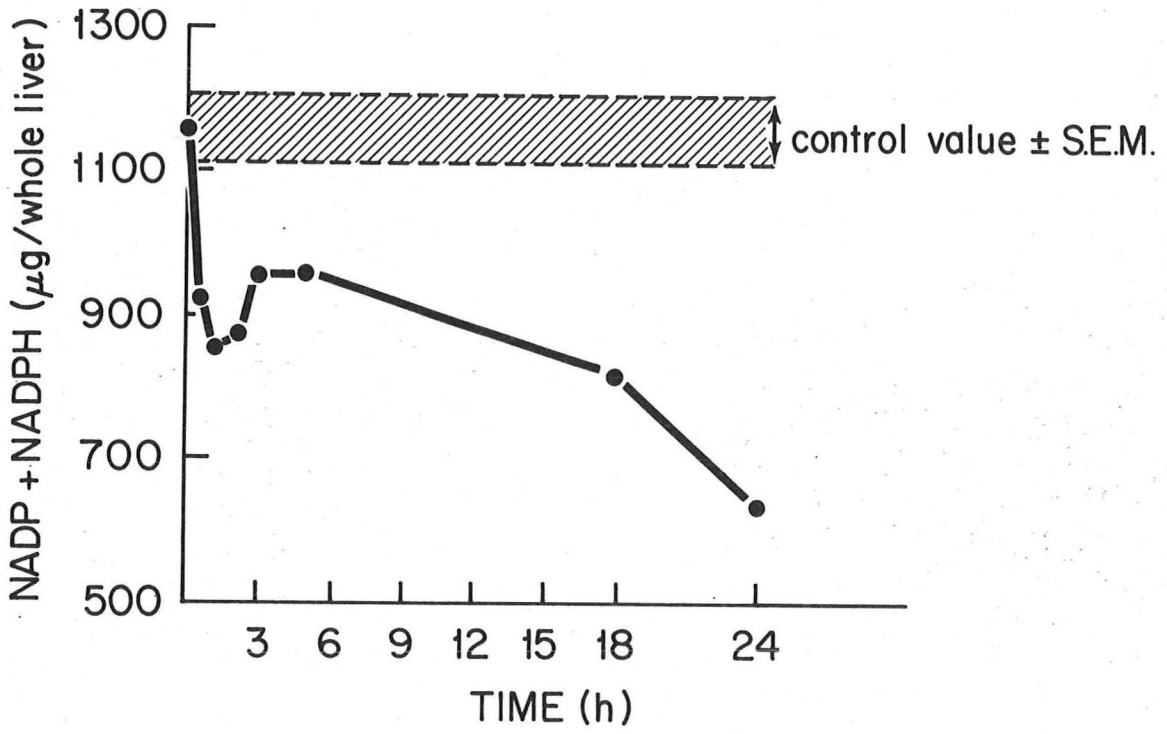

Figure 2. Effect of CCl_4 (1.25 ml/kg) on liver content of NADPH+ AND NADPH. From ref. 28.

A controversial proposed mechanism of damage is lipid peroxidation. A basic scheme of lipid peroxidation is shown in fig. 3. The free radical $CCl_3^{\cdot}$ initiates lipid peroxidation by abstracting a hydrogen from a polyunsaturated fatty acid (PUFA). Then a series of reactions occurs which destroys PUFA and leads to the production of more free radicals capable of starting the sequence over again. This is a chain reaction and will theoretically continue until all the PUFA has been destroyed or until the chain is broken by a free radical scavenger such as vitamin E or a peroxidase such as a glutathione peroxidase.

There is good evidence that all 3 of these mechanisms of tissue damage occur in CCl_4 hepatotoxicity (22,27,28), and it is likely that others occur also. The relative contribution of each of these mechanisms will depend upon the status of defenses against them. Thus lipid peroxidation damage may be greater in vitamin E deficiency (29).

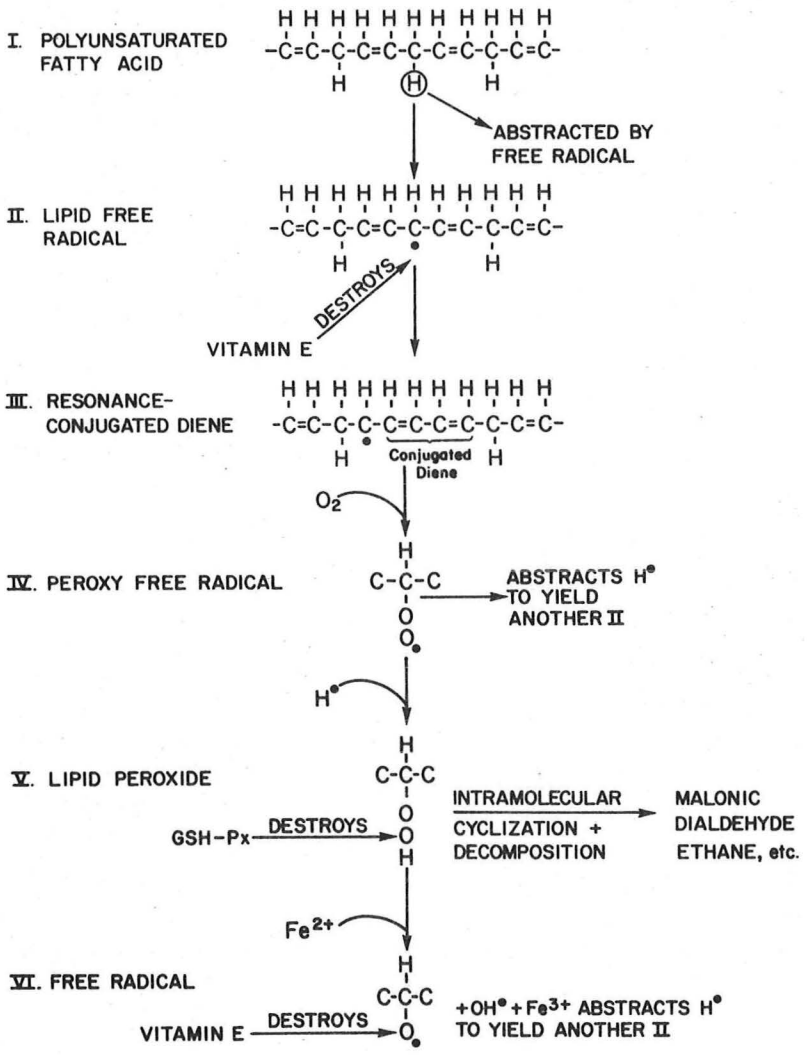

Figure 3. Postulated scheme of free-radical-induced lipid peroxidation. Adapted from ref. 22.

*Acetaminophen**

Acetaminophen, known as paracetamol in England, is a very popular agent there for suicide attempts. There are reportedly over 1000 hospital admissions per year in England for acetaminophen overdose and about 30 deaths (30). Fortunately very few cases occur in the United States but we recently had a case at Parkland:

> S.W. (PMH #14 39 21), a 20 Y/O female, was admitted on 5/21/76 for metabolic acidosis. She had had a subtotal thyroidectomy 7 years PTA and was taking 0.15 mg of T_4 daily. Other meds included oral contraceptives and Tuinal (barbiturate) h.s. On 5/18 she reportedly took 20 of her thyroid tablets and on the evening of 5/19 she took around 100 Tylenol tablets (about 30g). The next day she had nausea, vomiting and abdominal pain but delayed coming to the ER until 5/21.
>
> On admission she was alert and oriented but somewhat agitated and uncomfortable. Temperature was < 96° rectal; pulse was 120 and regular; respirations were 36; and BP was 150/60 without tilt. Her abdomen was slightly distended and diffusely tender. The liver had a 10 cm span and was 2 cm below the costal margin.
>
> Laboratory results included WBC of 30,400 with toxic granulations, hemoglobin 11.8 g%, arterial pH of 6.94, serum bicarbonate of 8, serum lactate of 118 mg%, and a prothrombin time of 48 seconds. Acetaminophen level was 1 mg%. Other lab values are shown in fig. 4.
>
> The patient's hospital course was stormy. During treatment for lactic acidosis she developed hypotension refractory to volume expansion and was successfully treated with dopamine infusion. She developed hepatic and renal failure and pancreatitis which were successfully treated. Other complications included gastrointestinal bleeding and pneumonia.
>
> On June 22, when the patient was readmitted for liver biopsy, the SGOT was 189 and the bilirubin was 9. The biopsy showed tremendous loss of parenchymal cells with bridging necrosis. Regeneration and cholestasis were also present.

This case was unusually severe but illustrates the usual clinical picture of acetaminophen overdose very well. Typically after ingestion there is nausea and vomiting for several hours and then the patient feels much better. Level of consciousness is unaffected. Liver damage has resulted from absorption of 6.2 grams and death has resulted from 25 grams (31-33). If enough drug was taken, signs of liver damage or hepatic failure appear one to three days later. Kidney damage (34,30) occurs in a minority of patients and pancreatitis (30) is found uncommonly. As is the case with CCl_4 the treatment must be expectant after gastric lavage.

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* Tylenol®, Datril®, Tempra®.

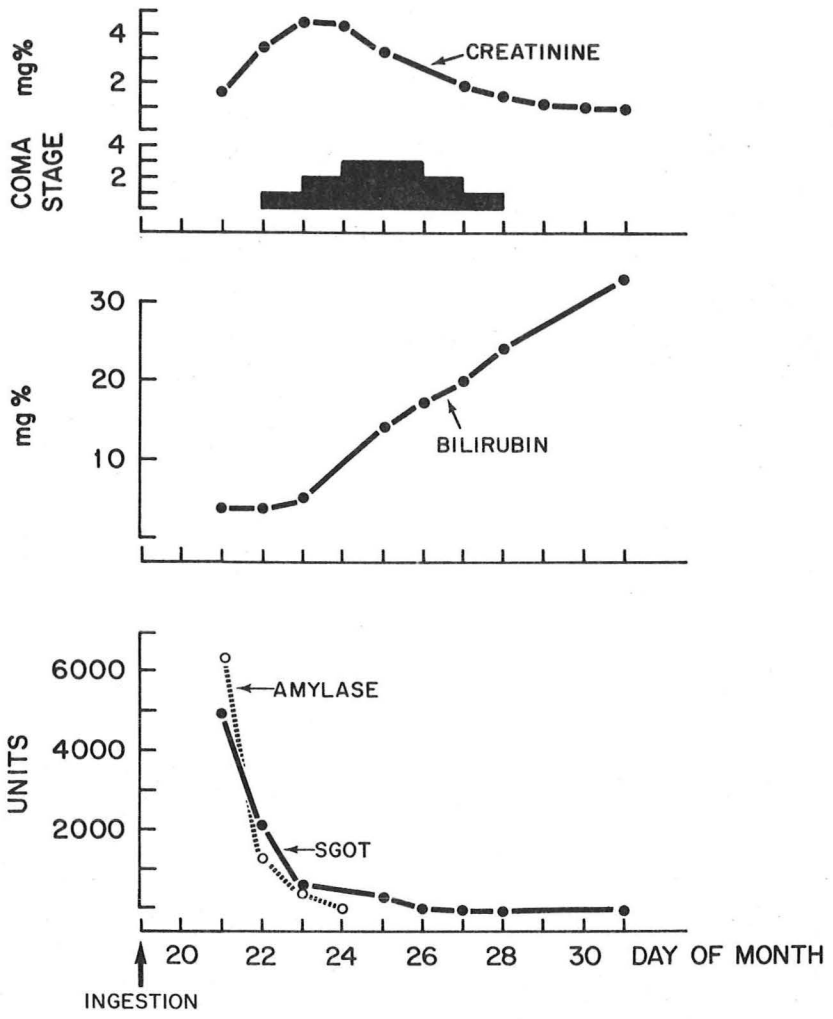

Figure 4. Laboratory tests and coma stage of S.W. Acetaminophen ingestion occurred on May 19.

This case illustrates very well the value of good supportive care during coma in toxic hepatitis. This patient would almost certainly have died if she had not had such good care while her liver was regenerating.

In normal doses acetaminophen is a safe drug. However, when high doses are administered centrilobular necrosis occurs. As is the case with CCl_4, the necrosis is enhanced by many of the conditions which increase the function of the P-450 system and decreased by inhibitors of the P-450 system (Table II) (35). This strongly suggests that metabolic activation is necessary for the hepatotoxicity of acetaminophen. It has been reported that patients receiving drugs known to induce the P-450 system had more severe liver damage from acetaminophen than did patients not taking such drugs (36).

TABLE II

Effect of Pretreatment on Liver Necrosis
in Mice 48 hrs after Acetaminophen

Pretreatment	Dose of Acetaminophen (mg/kg	Severity of Necrosis				
		0	1+	2+	3+	4+
		percent of mice				
None	375	54	24	16	6	0
None	500	24	11	18	33	14
None	750	1	3	8	47	41
PB	375	10	21	40	21	8
$CoCl_2$	500	94	6	0	0	0
$CoCl_2$	750	92	5	3	0	0

data from ref. 35.

Mitchell's group at the NIH was able to correlate degree of hepatotoxicity with covalent binding of radiolabeled acetaminophen to hepatocyte protein in mice (Table III) and concluded that covalent binding of an active metabolite of the drug was the primary mechanism of toxicity (37). They also noted a threshold effect, i.e., acetaminophen failed to produce any hepatotoxicity until a certain amount was administered (38). Then increases in dose caused increased liver damage. A clue to the explanation of the threshold effect was found in the pattern of urinary metabolites of acetaminophen.

TABLE III

Effect Of Treatments On In Vivo Covalent Binding Of
Acetaminophen To Liver Protein

Treatment	Dose of acetaminophen	Severity of liver necrosis	Covalently bound [^{3}H] acetaminophen nmole/mg protein
None	375	1-2+	1.02 ± 0.17
Piperonyl butoxide	375	0	0.33 ± 0.05
Cobaltous chloride	375	0	0.39 ± 0.11
Phenobarbital	375	2-4+	1.60 ± 0.10
None	750	3-4+	1.89 ± 0.15
Piperonyl butoxide	750	0 or 1+	0.78 ± 0.16
Cobaltous chloride	750	0 or 1+	0.85 ± 0.15
Phenobarbital	750	4+	2.08 ± 0.12

From Ref. 13

Most of a dose of acetaminophen is excreted as sulfate and glucuronic acid conjugates. About 4% is excreted as mercapturic acid in man. Phenobarbital pretreatment, which induces the P-450 system and enhances acetaminophen hepatotoxicity, increases the mercapturic acid fraction to 7% (13), suggesting that this fraction may be related to the hepatotoxicity. Since the mercapturic acid fraction originates as a conjugate with the tripeptide glutathione, the group at the NIH investigated the effect of acetaminophen on hepatic glutathione levels (38). They showed that hepatic glutathione was depleted by acetaminophen and that there was no covalent binding until the glutathione had been depleted (Fig. 5). Other measures which lower hepatic glutathione such as a low protein diet can enhance acetaminophen liver damage also (39).

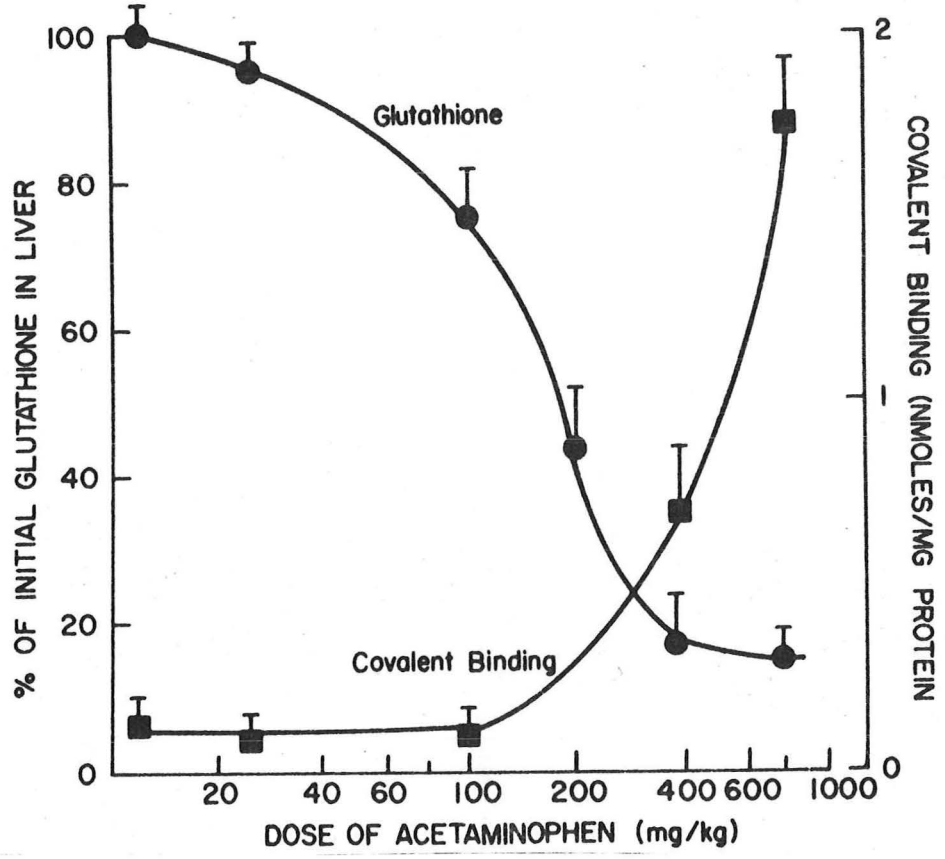

Figure 5. Correlation of hepatic glutathione depletion with covalent binding of ^{3}H-acetaminophen after various doses of acetaminophen. From ref. 13.

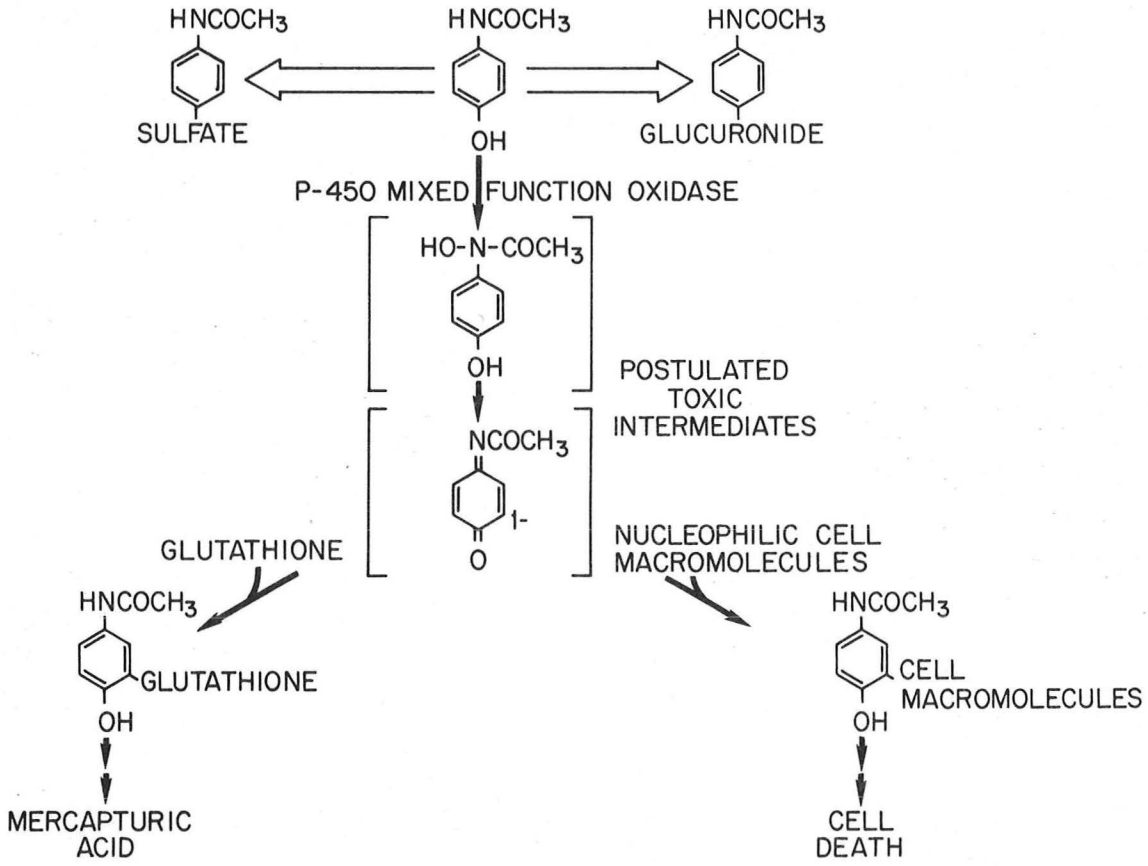

Figure 6. Pathways of acetaminophen metabolism. From ref. 13.

Mitchell presented his conception of the mechanism of acetaminophen hepatotoxicity as follows (fig. 6) (1) A small percentage of administered acetaminophen is activated by the P-450 system; (2) This active metabolite reacts with glutathione to yield ultimately a mercapturic acid which is excreted; (3) If glutathione is depleted, the active metabolite binds to tissue macromolecules and causes cell damage and death. It should be pointed out that glutathione depletion has other effects, such as deprivation of glutathione peroxidase of its substrate glutathione, and these may also contribute to the liver injury.

From this scheme it seemed logical that acetaminophen overdose might be treated by (1) a P-450 system inhibitor or (2) a compound which would raise glutathione levels or itself conjugate with the active metabolite. There is no P-450 system inhibitor which can be used in human beings. Mitchell's group showed in mice that the administration of cysteine, which maintains glutathione levels, diminished covalent binding and liver necrosis (38). On this principle a group in Scotland employed cysteamine in the treatment of acetaminophen overdose. Their uncontrolled study suggested that it might be effective (40). However, a recent controlled study showed no advantage of cysteamine treatment except possible decrease of the peak SGOT (30). Thus, to date there is no specific treatment available.

An important consideration is when to hospitalize a patient who has taken an overdose of acetaminophen. It is well known that patients' estimates of amounts of drugs ingested are notoriously inaccurate. Blood levels of acetaminophen are therefore extensively used in England. However, knowledge of time of ingestion is critical in interpretation and that is also difficult to determine. Finally, it should be pointed out that a dose (or blood level) that is barely toxic to one person may be fatal to another because of differences in activity of their P-450 systems and in hepatic glutathione content. Therefore it would seem wise to observe in the hospital for two days anyone taking an overdose of acetaminophen.

Isoniazid

A.B. (PMH #27 36 16), a 37 Y/O American Indian female, was admitted on 5/1/68 with hepatitis. She had had 10 days of nausea, vomiting, weakness, and mild upper abdominal discomfort. For 3 days she had noticed yellow eyes. She was admitted with a diagnosis of infectious hepatitis but it was noted that she had been taking INH since 1/68 because of a positive tbc skin test. Chest film had been negative in 1/68. INH was stopped on admission and she improved symptomatically over the next 2 weeks. However, her liver tests failed to improve (see below) so on 5/21 she had a liver biopsy which showed submassive necrosis and active hepatitis. Prednisolone was started and she gradually improved. The prednisolone was gradually tapered and liver tests were normal by 11/68. In 6/74 followup liver biopsy showed slight portal fibrosis.

	5/1/68	5/22	6/24	Nov. 68
bilirubin	20.4	24	3.4	normal
alk.phos. (K.A.)	27.5	40	37.5	
SGOT	1522	580	108	
Protime	14.5/12	12/11	13/12.5	

That isoniazid (INH) frequently causes abnormal liver tests and can cause severe hepatitis was not generally appreciated until the last few years. Between its introduction in 1952 and 1965, when it began to be used prophylactically, it was considered to be very safe. Hepatitis occurring during INH administration was usually attributed to concurrently-administered drugs such as PAS or to the basic underlying disease. When widespread prophylaxis was begun, many healthy people were given INH and only then could its affect on the liver be appreciated without the influence of other factors.

Several evaluations of liver tests in subjects given INH prophylaxis have been reported (41-44). These studies indicate that 10-13% of subjects receiving INH develop SGOT elevations during treatment (Table IV). Most of these patients are asymptomatic (Fig. 7); a few of these asymptomatic patients had liver biopsies performed which showed a mild hepatitis (41). The rise in transaminase occurred shortly after starting INH in some patients but was delayed as much as 11 months in others. The transaminasemia was transient in some patients but continuous in others.

TABLE IV

Incidence of Elevated SGOT in Patients Taking INH

Reference	%
Ann. Int. Med. 71:1113, 1969	10
JAMA 220:1471, 1972	10
Ann. Int. Med. 81:200, 1974	12
Chest 68:181, 1975	13

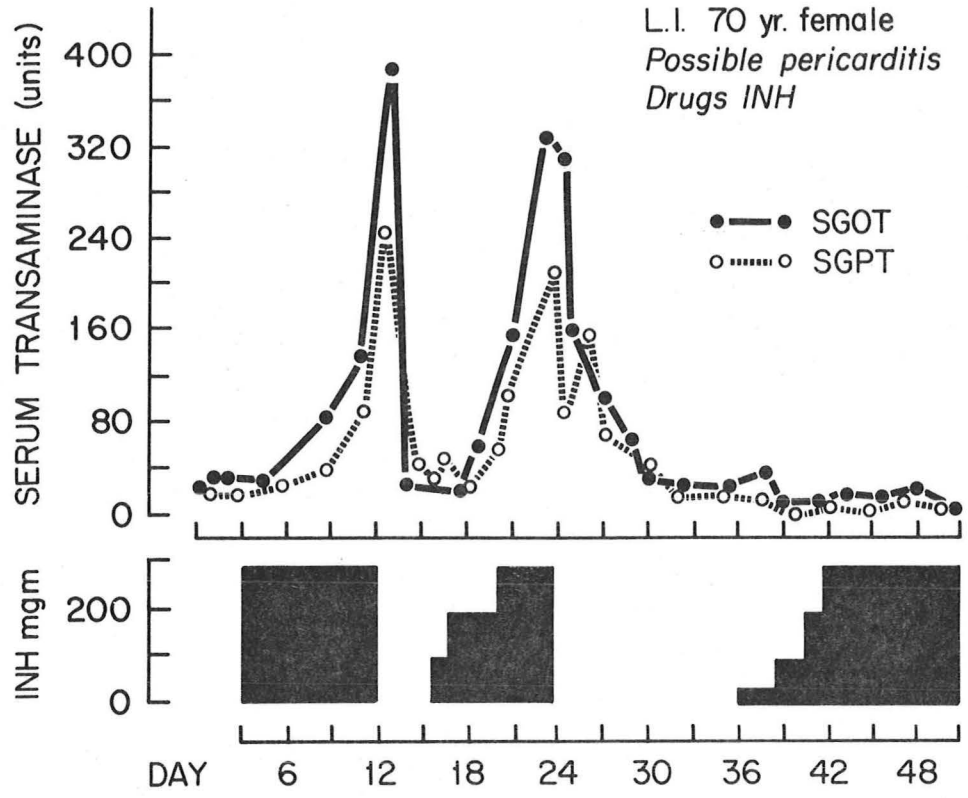

Figure 7. Relationship of serum transaminase levels to INH administration. The first and second challenge with INH resulted in elevated enzymes but the third challenge did not. From ref. 41.

A few patients became ill with overt hepatitis. Older patients seemed to be at greater risk (Table V). A prodrome of malaise, weakness, nausea, and occasionally fever usually occurred. The severity of the illness seemed to correlate with the continued administration of INH after the onset of symptoms (46,47). Liver biopsies were generally indistinguishable from viral hepatitis and revealed the full spectrum of findings from "classical" hepatitis through bridging necrosis to multilobular necrosis. Occasionally centrilobular necrosis predominated. Discontinuation of INH usually led to prompt improvement but some very ill patients died in spite of it.

TABLE V

Report of TB Advisory Committee, CDC

MMWR 23:97, '74

Age range	Incidence of overt INH hepatitis in patients receiving prophylactic INH
< 20	rare
20-34	0.3%
35-49	1.2%
> 50	2.3%

INH hepatitis was first thought to be due to hypersensitivity (46), but several of its features prompted Mitchell's group to investigate its possible hepatotoxicity. They noted that the hepatitis attributed to INH was infrequently accompanied by fever and almost never by such markers of hypersensitivity as rash and arthralgias (47). Furthermore they felt the 10-20% incidence of presumed liver damage was too high for hypersensitivity.

They examined a group of 21 patients who had recovered from INH hepatitis and determined their INH acetylation phenotype (48). Eighteen (86%) were rapid acetylators. Only 45% of the general population are rapid acetylators. Because of this apparent relationship of rapid acetylator phenotype with hepatitis, the effect of acetylator phenotype on the metabolism of a dose of INH was studied (48). Fig. 8 shows the major INH metabolites. The excretion in the urine of all these metabolites except acetylhydrazine was studied after administration of INH and acetylINH to fast and slow acetylators. Table VI shows the results. Rapid acetylators excreted relatively more acetylINH and isonicotinic acid and slow acetylators more hydrazones after INH. Both acetylator types excreted the same amount of acetylINH and isonicotinic acid after receiving acetylINH so the hydrolysis of acetylINH is unaffected by acetylator type.

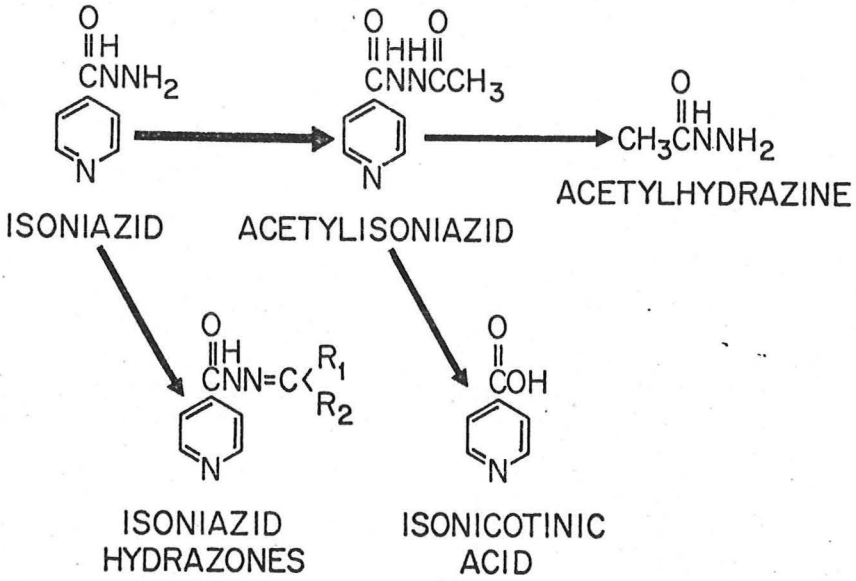

Figure 8. Metabolism of INH. From ref. 49

TABLE VI

Metabolites Of INH And Acetyl INH In Fast And Slow Acetylators

Drug	Patients' Acetylation Rate (N)	INH	INH Hydrazones	AcINH	INA Derivatives	Estimated Acetyl Hydrazine	Estimated Hydrazine
AcINH	FAST (2)	-	-	54.9 ± 2.2	45.1 ± 2.7	45.1 ± 2.7	-
AcINH	SLOW (3)	-	-	53.8 ± 1.2	46.2 ± 1.1	46.2 ± 1.1	-
INH	FAST (3)	2.8 ± 0.4	3.6 ± 0.4	49.2 ± 1.9	44.4 ± 3.9	41.0 ± 3.8	3.4 ± 0.1
INH	SLOW (4)	10.9 ± 0.8	26.5 ± 4.8	32.1 ± 1.2	30.5 ± 3.5	26.8 ± 3.3	3.7 ± 0.2

From Ref. 49

Thus, rapid acetylators produce more isonicotinic acid and acetylhydrazine than do slow acetylators. Mitchell's group tested these compounds for hepatotoxicity in rats and found that acetyl hydrazine caused liver necrosis (49) which could be worsened by phenobarbital pretreatment suggesting P-450 system involvement. When acetylhydrazine with a radioactive label on the acetyl was given, the label was covalently bound to hepatocyte protein.

Mitchell's group has postulated that the acetylhydrazine interacts with the P-450 system (fig. 9) to give a reactive acyl compound -- possibly a free radical (48,49). Thus the mechanisms of injury put forth for CCl_4 could be active with INH as well.

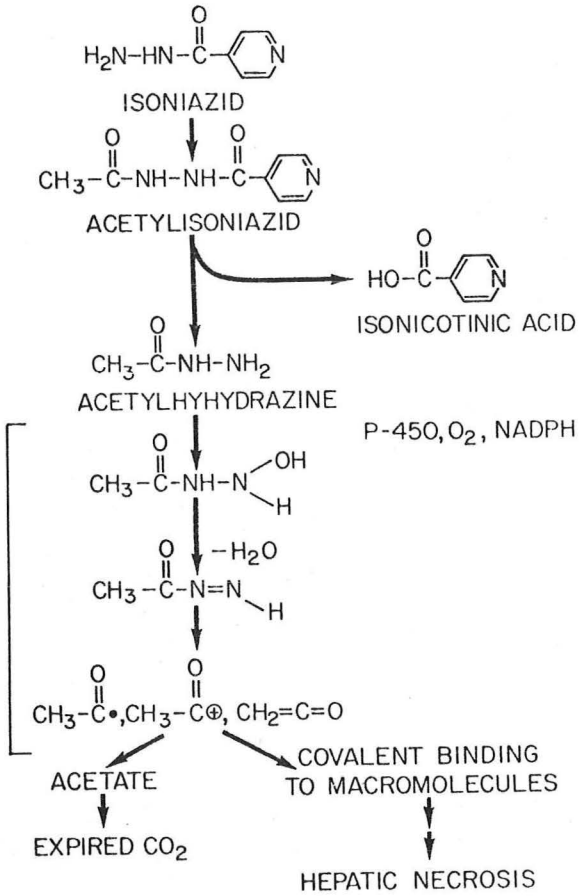

Figure 9. Proposed metabolic activation pathway of INH to toxic metabolites. From ref. 49.

Interestingly, large single doses of INH caused no liver damage in rats (49). However, the same amount of INH in divided doses did. The liver necrosis caused by single doses of acetyl INH and acetylhydrazine was dose dependent. The interpretation given was that a large dose of INH saturated the acetylation pathway, leading to increased excretion of INH as hydrazones and decreased acetylhydrazine production. Dividing the dose enabled a greater percent of INH to be acetylated and cause toxicity. This shows that the toxicity of INH is not directly dose dependent.

This whole theory of INH hepatotoxicity cannot be considered proven yet. It does not explain why patients suddenly develop hepatitis months after starting the drug. It does not explain why some slow acetylators develop hepatitis. If the theory is correct though, the variation in patient response may be related to cellular defense mechanisms against the toxic metabolite.

Other toxins

There are many other hepatotoxins. Aflatoxin causes hepatic necrosis under one set of conditions and hepatic carcinoma under another (50). Evidence gathered so far suggests that different metabolites of the toxin are responsible for the two responses and that the metabolites are dependent on the P-450 system (50-52). Many years of exposure to vinyl chloride causes hepatic fibrosis and angiosarcoma of the liver and the P-450 system has been implicated in these conditions (53).

Much more work on the mechanisms of toxicity of these and other agents will be necessary. In addition the possibility that drugs like chlorpromazine and methyldopa (54,55) might act through a toxic rather than hypersensitivity mechanism must be considered.

Implications

The theory of INH hepatotoxicity illustrates how an agent can cause damage to a genetically predisposed group. It is apparent that there must be other determinants of toxicity nutritional, environmental, and pharmacological in nature. Thus, an agent which is usually not hepatotoxic may become so under appropriate genetic, nutritional, environmental, and pharmacological conditions. The rarity of the concurrence of all of these conditions can make the hepatotoxicity rare and unpredictable in its onset. Since these are usually considered to be properties of hypersensitivity reactions, a reconsideration of the mechanisms of liver damage by a number of agents will be necessary.

The importance in understanding mechanisms of toxicity lies in being able to identify vulnerable patients and predisposing conditions so toxicity can be avoided and possibly in providing rational therapy for the toxicity once it has occurred. The prevention of toxic reactions such as may occur with a major therapeutic agent like INH is certainly an important goal. The prevention of chronic liver disease or cancer which may occur remote to exposure to such an agent may be even more important.

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