Ann. Rev. Pharmacol. Toxicol. 1983. 23:87–101

THE TREATMENT OF ACETAMINOPHEN POISONING

L. F. Prescott and J. A. J. H. Critchley

Regional Poisoning Treatment Centre, and University Department of Therapeutics and Clinical Pharmacology, The Royal Infirmary, Edinburgh, EH3 9YW, Scotland

INTRODUCTION

Acetaminophen (paracetamol, N-acetyl-p-aminophenol, 4-hydroxyacetanilide) is a non-prescription antipyretic analgesic that was first introduced into clinical medicine towards the end of the last century (1). It attracted little interest until it was found to be the major metabolite of both acetanilide and phenacetin (2, 3) and in recent years it has become an increasingly popular substitute for aspirin. Acetaminophen seemed to be remarkably safe when taken in recommended doses and formal toxicity studies were never carried out. In 1964 Eder (4) first reported liver damage in cats given 25–50 mg/Kg of acetaminophen daily for 26 weeks, and two years later Boyd & Bereczky described extensive hepatic necrosis in acute toxicity studies in rats (5). At the same time liver damage was first reported in man following acetaminophen overdosage (6, 7). The use of acetaminophen for self-poisoning has since increased dramatically in many countries and acute hepatic necrosis, sometimes fatal, has attracted much attention as the major complication (8–16).

CLINICAL MANIFESTATIONS AND COMPLICATIONS OF ACETAMINOPHEN POISONING

Apart from nausea and vomiting there are no specific early signs of severe intoxication and consciousness is not impaired. However, 12 to 36 hours after ingestion biochemical evidence of acute hepatic injury may become apparent with maximum abnormalities of liver function usually occurring

on the third day. The pattern is characteristic of extensive acute necrosis with gross elevation of plasma aspartate and alanine aminotransferase (AST or SGOT, ALT or SGPT) activity, mild hyperbilirubinemia, and prolongation of the prothrombin time (9–11). Associated abnormalities include impairment of bromsulphthalein clearance (17), abnormal glucose tolerance (7, 18), and increased serum concentrations of bile acids and ferritin (19, 20). In survivors hepatic regeneration is normally rapid and complete with return of liver function tests to normal within one to three weeks.

Fulminant hepatic failure (which is usually fatal) develops on the third to the sixth day in a small minority of severely poisoned patients, and renal failure due to acute tubular necrosis is another uncommon complication (10, 21, 22). Liver biopsies and post-mortem studies reveal extensive centrilobular hepatic necrosis without inflammatory reaction (6, 11, 23, 24). The acute hepatotoxicity of acetaminophen has been confirmed repeatedly in animals but there are marked species differences in susceptibility (25–27).

Contrary to popular belief, severe liver damage (arbitrarily defined as elevation of the plasma AST or ALT activity above 1000 u/l) and fatal hepatic failure are not inevitable complications of acetaminophen overdosage. Indeed, without specific therapy fewer than 10% of unselected patients referred to hospital develop severe liver damage, about 1% suffer acute renal failure, and 1 to 2% die in hepatic failure (26).

Until the development of rational therapy based on the biochemical mechanisms of acetaminophen hepatotoxicity (28), there was no effective treatment for overdosage and the increasing incidence of poisoning was a cause for concern. Allegedly successful treatment with antihistamines and corticosteroids (8) was uncontrolled and had no scientific or statistical basis. Indeed, subsequent studies in animals showed that such treatment actually increased the lethality of acetaminophen without protecting against liver damage (29). A controlled trial of heparin therapy showed no benefit (30). Forced diuresis has been tried but is likewise of no value. The renal clearance of acetaminophen is not pH-dependent, and even after overdosage an insignificant fraction of the dose is excreted unchanged in the urine (31). Hemodialysis was also advocated, but it did not prevent liver damage, and insignificant amounts of drug were removed. In one study, 11 of 15 patients subjected to this procedure had not absorbed enough drug to be at risk of liver damage in the first place (32).

MECHANISMS OF ACETAMINOPHEN HEPATOTOXICITY

The effective treatment of acetaminophen poisoning only became possible with the discovery by Mitchell and his colleagues of the metabolic activation of acetaminophen and the vital protective role played by reduced

glutathione (33–36). These workers showed that a small fraction of a dose of the drug is converted by cytochrome P-450-dependent mixed function oxidase to an electrophilic arylating metabolite that binds covalently to hepatic macromolecules, causing cell damage and necrosis. The reactive metabolite is thought to be N-acetyl-benzoquinoneimine formed by N-hydroxylation (28, 37). It is normally rapidly inactivated by preferential conjugation with reduced glutathione and eventually excreted in the urine as cysteine and mercapturic acid conjugates of acetaminophen. After a toxic dose, hepatic glutathione is depleted; when concentrations fall below 20 to 30% of normal, the excess metabolite binds covalently to essential hepatic proteins and enzymes. Hepatic necrosis is directly related to the extent of glutathione depletion and covalent binding (27, 33–36, 38). The extent of conversion of acetaminophen to its toxic metabolite is reflected in the fraction of the dose recovered in the urine as cysteine and mercapturic acid conjugates. Highly susceptible species such as the hamster excrete much more than resistant species such as the rat (25); liver damage following overdosage of acetaminophen in man is associated with increased urinary excretion of these conjugates (26, 39).

PROTECTION AGAINST EXPERIMENTAL ACETAMINOPHEN HEPATOTOXICITY

Factors that modify hepatic microsomal enzyme activity and glutathione status greatly influence the toxicity of acetaminophen. Thus Mitchell et al showed that liver damage is increased by stimulation of hepatic microsomal enzymes with inducing agents such as phenobarbital, and decreased by inhibition with cobaltous chloride or piperonyl butoxide (28, 33). Similarly, covalent binding and hepatic necrosis are increased if glutathione stores are depleted by prior administration of diethyl maleate, and decreased by glutathione precursors such as cysteine (28, 36). Glutathione depletion produced by fasting and low protein or yeast diets also potentiates experimental acetaminophen hepatotoxicity (40, 41). These general principles have been amply confirmed by other workers and provide a sound basis for the treatment of acetaminophen poisoning in man.

Inhibition of Metabolic Activation

Selective inhibition of the minor route of metabolism that generates the toxic metabolite of acetaminophen is an attractive possibility. However, safe effective inhibition of the metabolic activation of acetaminophen has not yet been investigated adequately in man and this approach has not been exploited clinically. Recent studies have shown that the acute toxicity of acetaminophen in animals is significantly reduced by cimetidine (42–44) and by acute administration of ethanol (45, 46). Protection was attributed

to inhibition of the metabolic activation of acetaminophen but other mechanisms have not been excluded. In the case of ethanol, this hypothesis is supported by the observation that it significantly reduces the excretion of the mercapturic acid conjugate of acetaminophen in rats (46). In man, an acute ethanol load (1.72 g/Kg over 8 hours) markedly decreases the fraction of an oral dose of 20 mg/Kg of acetaminophen excreted as the cysteine and mercapturic acid conjugates, but oral cimetidine in divided doses totalling 2 g over 16 hours has no such effect (J. A. J. H. Critchley and L. F. Prescott, unpublished).

The protective effect of acute ethanol is of particular interest since chronic pretreatment enhances experimental acetaminophen-induced hepatotoxicity (47–50) and increases the urinary excretion of the mercapturic acid conjugate (51), presumably as a result of microsomal enzyme induction. Similarly, chronic alcoholics and patients who have previously been taking agents that induce drug metabolizing enzymes seem to be at increased risk of liver damage following acetaminophen overdosage (26, 52, 53), whereas acute ingestion of ethanol at the same time appears to offer some protection (16). However, in contrast to the findings in experimental animals, chronic heavy ethanol intake in man is not associated with increased metabolic activation of acetaminophen (54). In addition, the urinary excretion of the cysteine and mercapturic acid conjugates of acetaminophen is not increased in patients induced by chronic treatment with anticonvulsants or rifampicin (55). The results of animal studies involving the selective induction and inhibition of acetaminophen metabolism thus cannot be extrapolated directly to man.

Sulphydryl Compounds

Glutathione itself might be considered the ideal antidote for acetaminophen poisoning. However, it is normally synthesized in situ, and because it enters cells with difficulty, glutathione is relatively ineffective even when given in very large doses (56–58). On the other hand, glutathione precursors such as cysteine, N-acetylcysteine, and methionine and other sulphur-containing compounds including cysteamine, S-adenosylmethionine, α-mercaptopropionyl-glycine, dithiocarb, propylthiouracil, and even dimethyl-sulphoxide are very effective in preventing experimental acetaminophen-induced hepatotoxicity (28, 38, 41, 56, 59–66). Most of these agents have been shown to reduce the extent of acetaminophen-induced glutathione depletion. Over the last decade cysteamine, methionine and N-acetylcysteine have been studied extensively in man and the clinical management of severe acetaminophen poisoning has been transformed. Even when administration is delayed for as long as 8 to 10 hours after ingestion they have proved remarkably effective in preventing liver damage, renal failure, and death from acetaminophen overdosage.

Stimulation of Sulphate Conjugation

Acetaminophen is extensively metabolized, with sulphate and glucuronide conjugation accounting for about 30% and 60% respectively of a therapeutic dose in man (67). However, the availability of inorganic sulphate is limited and sulphate conjugation is saturated after overdosage. Slattery & Levy (68) proposed a pharmacokinetic model based on dose-dependent saturation of both sulphate and glucuronide conjugation with increasing conversion of the drug to the toxic metabolite. Unfortunately, their model was based on the results of metabolic studies reported by Davis et al (39), which differ markedly from those observed by other workers using different analytical methods. Sulphate conjugation is undoubtedly saturated with overdosage of acetaminophen but there is no evidence of similar saturation of glucuronide conjugation in man (26). According to the above hypothesis, it was suggested that restoration of sulphate conjugation by provision of inorganic sulphate would significantly enhance the elimination of acetaminophen after overdosage and hence reduce its toxicity. In rats sodium sulphate enhanced the sulphate conjugation of acetaminophen and marginally increased its rate of elimination (69, 70) and it slightly increased the acute LD50 in mice (71). However, the protective effect was minor compared to that produced by glutathione precursors and is unlikely to be of clinical significance.

TREATMENT OF ACETAMINOPHEN POISONING

Clinical assessment of the efficacy of treatment for acetaminophen poisoning is beset with difficulties. There are few specialist units with an interest in drug overdosage and poisoning; placebo-controlled trials cannot now be carried out because of ethical constraints, and the great majority of patients do not absorb enough drug to be at risk of severe liver damage anyway. Toxicity depends primarily on the balance between the rates of formation of the reactive metabolite and synthesis of glutathione and is influenced by many factors including age, diet, nutritional state, fasting, and previous and concurrent intake of other drugs including ethanol (26). Not surprisingly, there is marked individual variation in susceptibility (72) with a variable threshold dose for toxicity that presumably corresponds to the point of critical depletion of hepatic glutathione (36). In man, significant liver damage is very uncommon following absorption of less than 125 mg/Kg of acetaminophen, whereas severe liver damage occurs in some 50% of individuals absorbing 250 mg/Kg, and in virtually all absorbing 350 mg/Kg (26). Unfortunately, self-poisoners are notoriously unreliable historians and unknown amounts of drug may be lost by vomiting and gastric lavage. The

dose absorbed can therefore only be determined by measurement of the plasma concentrations of acetaminophen.

Assessment of Risk

To assess the effects of any treatment it is necessary to define the risk of liver damage according to the plasma concentrations of acetaminophen in relation to the time since ingestion (10, 73–75). Severe liver damage with plasma AST or ALT activity exceeding 1000 u/l occurs in about 60% of patients with plasma acetaminophen concentrations above a "treatment" line joining semilog plots of 200 μg/ml at 4 hours and 30 μg/ml at 15 hours after ingestion. The incidence is 90% above a similar parallel line joining 300 μg/ml at 4 hours and 45 μg/ml at 15 hours, and such patients are at high risk. Plasma concentrations cannot be interpreted less than 4 hours after ingestion, and difficulties also arise when absorption is delayed by combined overdosage with drugs such as narcotic analgesics. The plasma acetaminophen half-life is directly related to the extent of liver damage (10, 31, 74) but its measurement takes time and is not practicable because treatment must be started as soon as possible.

The marked individual variation in response to acetaminophen makes it virtually impossible to determine the effects of treatment unless comparisons are made in substantial numbers of patients, preferably those at high risk. One patient may develop liver damage with relatively low initial plasma acetaminophen concentrations while another with concentrations several times higher may escape completely. Nevertheless, there are many anecdotal accounts of "successful" treatment. The historical control data with which comparisons must be made is very limited and the much-quoted "nomogram" published by Rumack & Matthew (76) as a guide to prognosis was actually taken from the original data obtained in Edinburgh (10, 73).

Further difficulties have arisen through the use of nonspecific analytical methods for the estimation of plasma acetaminophen. Those that depend on direct acid hydrolysis to p-aminophenol without prior extraction also include acetaminophen conjugates present in high concentrations, and may overestimate the true result by as much as 700% (77). Fortunately, cysteamine, methionine, and N-acetylcysteine have been dramatically effective in preventing liver damage after acetaminophen overdosage, and despite all these difficulties their value is not in doubt.

General Measures

Gastric aspiration and lavage are normally carried out in patients admitted within 4 hours of overdosage. Activated charcoal and cholestyramine may reduce the absorption of acetaminophen if given within one hour of inges-

tion (78, 79) but are unlikely to be useful in practice because the great majority of patients do not arrive in hospital in time for such treatment to be effective. Fluid balance should be maintained and complications such as hepatic and renal failure are managed conventionally.

Cysteamine

Mitchell et al (28) showed that cysteamine protected mice against the acute toxicity of acetaminophen even when treatment was delayed for 2 hours. Shortly thereafter we reported the first successful treatment of severe acetaminophen poisoning in man using intravenous cysteamine. Seven adults with a mean plasma acetaminophen concentration of 373 μg/ml at 4 hours were given 3.2 g over 20 hours and treatment was started 4.5 to 10 hours after ingestion of the acetaminophen. None of the patients developed the expected severe liver damage (73). Subsequent reports confirmed the protective action of cysteamine when treatment was started within 10 to 12 hours (80–83). Thus severe liver damage was completely prevented in one series of 27 severely poisoned patients treated within 10 hours (80) and occurred in only one of 14 similar patients in another (83). Douglas et al (84) failed to appreciate the importance of early treatment and claimed that cysteamine therapy was of no advantage despite evidence to the contrary in their patients admitted within 9 hours. With the exception of one report in which plasma acetaminophen was estimated by an inappropriate method (82), treatment after 12 hours was found to be of no benefit. Although effective, cysteamine produced very unpleasant gastrointestinal and central nervous system toxicity and it was not available commercially as a pharmaceutical formulation. Other agents were therefore investigated.

Methionine

Methionine protects rats against acetaminophen-induced liver damage and its incorporation into analgesic tablets was proposed as a simple answer to the problems of acetaminophen overdosage (41). Intravenous and oral methionine usually prevents severe liver damage following overdosage of acetaminophen if given within 10 to 12 hours (80, 83, 85, 86). However, it seems to be less reliable than intravenous cysteamine and N-acetylcysteine (26). Thus severe liver damage occurred in 3 of 15 severely poisoned patients given 20 g of methionine intravenously within 10 hours (80) and in 7 of 96 similar patients given 10 g orally (86). In addition, 3 patients treated with oral methionine within 12 hours developed fulminant hepatic failure (12).

There is some doubt concerning the safety of late treatment with methionine. It may aggravate or precipitate hepatic encephalopathy and late treatment or delayed absorption may therefore be hazardous in patients with

impending severe liver damage (12, 85, 89). Indeed, the mortality in mice with acute acetaminophen poisoning is increased by late treatment with methionine (61). Most patients develop nausea and vomiting within a few hours of ingestion of a toxic dose of acetaminophen and delayed or incomplete absorption may contribute to the failure of oral methionine in some patients (87). Treatment with oral methionine is simple and cheap.

N-Acetylcysteine

Following the demonstration of its protective effects in animals (60), extensive clinical studies have confirmed the efficacy and safety of N-acetylcysteine in the treatment of acetaminophen poisoning (16, 88–91) and it is now considered the treatment of choice. Intravenous N-acetylcysteine given within 10 hours in a dose of 300 mg/Kg over 20 hours prevented liver damage, renal failure, and death in patients with severe acetaminophen poisoning (88, 89), and was completely effective in preventing even trivial liver damage in severely poisoned patients at high risk when given within 8 hours (89). An extensive nationwide multicenter study of oral N-acetylcysteine is currently in progress in the USA. (16, 90). Of 662 patients referred to the coordinating center in Denver, 57 were considered to be at "probable risk" and received oral N-acetylcysteine within 10 hours. Despite the very large total dose of 1330 mg/Kg, N-acetylcysteine appeared to be less effective orally than intravenously. Thus, 7 of the 57 patients developed severe liver damage (16) compared with only 1 of 62 severely poisoned patients given a much smaller dose of intravenous N-acetylcysteine within 10 hours (91). Like all other agents studied in man, the protective effect of N-acetylcysteine falls off rapidly if treatment is delayed beyond 8 to 10 hours, and it is completely ineffective after 15 to 16 hours (16, 91). Unlike methionine, late treatment with N-acetylcysteine does not increase mortality in experimental acetaminophen poisoning (61). There is no clear evidence that it aggravates hepatic failure in man, but treatment after 24 hours is not recommended.

N-acetylcysteine has long been available as a mucolytic and an intravenous formulation was recently introduced in the U.K. specifically for the treatment of acetaminophen poisoning. There have been two reports of transient mild allergic reactions (92, 93), but otherwise no significant adverse effects have been noted.

Other Agents

Dimercaprol and D-penicillamine appear to offer little or no protection against acetaminophen toxicity in man (80, 81, 94).

Oral Versus Intravenous Therapy

There has been controversy over the relative merits of oral and intravenous therapy. The oral route is convenient and has the great advantage that a substantial fraction of the dose should be delivered directly to the liver. However, nausea and vomiting are consistent features of severe acetaminophen intoxication (89, 91) and efficacy must inevitably be compromised by incomplete or delayed absorption. Vomiting occurred in 77% of 52 severely poisoned patients in one report (91), and in all of 416 patients given oral N-acetylcysteine in another (90). It was recently claimed that vomiting occurred in only 12% of 433 patients with acetaminophen overdosage (95). However, the patients were unselected and it is probably no coincidence that only 12% were shown to be severely poisoned. Acetaminophen poisoning is a potentially fatal condition and the ingestion-treatment interval is critical. Severe liver damage has been attributed to failure of absorption of oral methionine (87) and this route cannot be recommended because of the very high incidence of nausea and vomiting in the very patients who need treatment most. Oral therapy is clearly contraindicated in patients who have been given emetics or activated charcoal.

MECHANISMS OF PROTECTION

Precursors such as cysteine, N-acetylcysteine, and methionine probably act primarily by stimulating glutathione synthesis and hence facilitating the glutathione conjugation of acetaminophen (38). Other agents such as cysteamine and dimethylsulphoxide also antagonise the glutathione depletion induced by acetaminophen (59, 64) and indirect stimulation of glutathione synthesis could contribute to their protective action (97). Cysteamine may also act by inhibiting the metabolic activation of acetaminophen (38, 98, 99). Oxothiazolidine carboxylic acid is converted to cysteine by 5-oxo-L-prolinase and stimulates glutathione synthesis. It reverses acetaminophen-induced depletion of hepatic glutathione in animals and has been proposed as an effective intracellular delivery system for cysteine in the treatment of acetaminophen overdosage (100).

Cysteamine, cysteine, N-acetylcysteine, and α-mercaptopropionylglycine have all been shown to react directly with the toxic metabolite of acetaminophen to form the corresponding conjugates (99). However, this is probably not important since conjugation with glutathione is catalysed by glutathione-S-transferase and takes place much more readily (38, 96). Propylthiouracil is unusual in that it can substitute for glutathione as a substrate for glutathione-S-transferase, and its protective action may involve direct conjugation with the reactive metabolite of acetaminophen (66). Methionine,

which does not contain an SH group, does not form an adduct directly with the acetaminophen metabolite (99) and does not prevent its covalent binding in vitro (101). It presumably acts indirectly after conversion to homocysteine and cysteine and the delay may account for its relative lack of efficacy.

Other mechanisms may contribute to protection. Thus acetaminophen may be regenerated from N-acetyl-benzoquinoneimine by reducing agents such as cysteine and ascorbic acid under certain conditions (102). [Ascorbic acid can inhibit the covalent binding of acetaminophen to hepatic microsomes in vitro (103), and it has been reported to reduce the lethality of acetaminophen in mice (104)]. In addition, the metabolism of sulphydryl compounds to inorganic sulphate can undoubtedly promote sulphate conjugation as an alternative route of elimination of acetaminophen. The plasma concentrations of acetaminophen sulphate in poisoned patients are increased by treatment with cysteamine and N-acetylcysteine (67) and subsequently there may be a delayed minor decrease in the plasma half-life of the drug (73). However, enhancement of sulphate conjugation is unlikely to be relevant to the protective effects of sulphydryl compounds in man.

OTHER METHODS OF TREATMENT

The only other recent approach to the treatment of acetaminophen poisoning has been the use of charcoal hemoperfusion. The drug can be removed effectively by this technique and clearances of 70 to 200 ml/min have been reported (105, 106). However, it is inconceivable that this treatment could be instituted early enough to remove sufficient drug to prevent the critical glutathione depletion and irreversible covalent binding that seems to occur 8 to 10 hours after ingestion of a toxic dose. The first controlled trial of early hemoperfusion showed no benefit and the average amount of acetaminophen removed was less than 1.5 g (107). In one anecdotal report claiming success, cysteamine had also been given and treatment was probably not necessary in the first place because plasma acetaminophen concentrations would have been greatly overestimated by the unsuitable analytical method used (108). It is even more difficult to accept recent claims for the benefit of late charcoal hemoperfusion. In one report, treatment was started in 7 severely poisoned patients an average of 23 hours after the acetaminophen was taken and a mean of 2.4 g was removed. According to the elevation of plasma bilirubin and prothrombin time ration, 5 patients developed severe liver damage and one died in hepatic failure. Only 0.38 and 0.36 g of acetaminophen were removed from the two patients who did not develop severe liver damage (106). There seems to be no justification for the use of hemoperfusion in the late treatment of acetaminophen poisoning.

SUMMARY

Acetaminophen has become a very popular over-the-counter analgesic in some countries and as a result it is used increasingly as an agent for self-poisoning. Without treatment only a minority of patients develop severe liver damage and 1 to 2% die in hepatic failure. Until Mitchell and his colleagues discovered the biochemical mechanisms of toxicity in 1973 there was no effective treatment. They showed that the metabolic activation of acetaminophen resulted in the formation of a reactive arylating intermediate, and that hepatic reduced glutathione played an essential protective role by preferential conjugation and inactivation of the metabolite. Early treatment with sulphydryl compounds and glutathione precursors has been dramatically effective in preventing liver damage, renal failure, and death following acetaminophen overdosage. It seems likely that these agents act primarily by stimulating glutathione synthesis. Inhibition of the metabolic activation of acetaminophen is another potential therapeutic approach that has not yet been put to the test clinically. The clinical management of acetaminophen poisoning has been transformed and it is particularly gratifying to have effective treatment based on a well established biochemical mechanism of toxicity. It is likely that effective treatment will be developed for toxicity caused through similar mechanisms by other agents.

Literature Cited

1. Smith, P. K. 1958. *Acetophenetidin. A Critical Bibliographic Review,* p. 3. London: Wiley. 180pp.
2. Brodie, B. B., Axelrod, J. 1948. The estimation of acetanilide and its metabolic products, aniline, N-acetyl-p-aminophenol and p-aminophenol (free and total conjugated) in biological fluids and tissues. *J. Pharmacol. Exp. Ther.* 94: 22–28
3. Brodie, B. B., Axelrod, J. 1949. The fate of acetophenetidin (phenacetin) in man and methods for the estimation of acetophenetidin and its metabolites in biological material. *J. Pharmacol. Exp. Ther.* 97:58–67
4. Eder, H. 1964. Chronic toxicity studies on phenacetin, N-acetyl-p-aminophenol (NAPA) and acetylsalicylic acid on cats. *Acta Pharmacol. Toxicol.* 21:197–204
5. Boyd, E. M., Bereczky, G. M. 1966. Liver necrosis from paracetamol. *Brit. J. Pharmacol.* 26:606–14
6. Davidson, D. G. D., Eastham, W. N. 1966. Acute liver necrosis following overdose of paracetamol. *Brit. Med. J.* 2:497–99
7. Thomson, J. S., Prescott, L. F. 1966. Liver damage and impaired glucose tolerance after paracetamol overdosage. *Brit. Med. J.* 2:506–7
8. MacLean, D., Peters, T. J., Brown, R. A. G., McCathie, M., Baines, G. F., Robertson, P. G. C. 1968. Treatment of acute paracetamol poisoning. *Lancet* 2:849–52
9. Proudfoot, A. T., Wright, N. 1970. Acute paracetamol poisoning. *Brit. Med. J.* 3:557–58
10. Prescott, L. F., Wright, N., Roscoe, P., Brown, S. S. 1971. Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. *Lancet* 1:519–22
11. Clark, R., Thompson, R. P. H., Borirakchanyavat, V., Widdop, B., Davidson, A. R., et al. 1973. Hepatic damage and death from overdose of paracetamol. *Lancet* 1:66–69
12. Canalese, J., Gimson, A. E. S., Davis, M., Williams, R. 1981. Factors contributing to mortality in paracetamol-induced hepatic failure. *Brit. Med. J.* 282:199–201

13. Cohen, S. B., Burk, R. F. 1978. Acetaminophen overdoses at a County Hospital: a year's experience. *South. Med. J.* 71:1359–63
14. Hamlyn, A. N., Douglas, A. P., James, O. 1978. The spectrum of paracetamol (acetaminophen) overdose: clinical and epidemiological studies. *Postgrad. Med. J.* 54:400–4
15. McJunkin, B., Barwick, K. W., Little, W. C., Winfield, J. B. 1976. Fatal massive hepatic necrosis following acetaminophen overdose. *J. Am. Med. Assoc.* 236:1874–75
16. Rumack, B. H., Peterson, R. C., Koch, G. G., Amara, I. A. 1981. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch. Intern. Med.* 141:380–85
17. Davis, M., Ideo, G., Harrison, N. G., Williams, R. 1975. Hepatic glutathione depletion and impaired bromosulphthalein clearance early after paracetamol overdose in man and the rat. *Clin. Sci. Mol. Med.* 49:495–502
18. Record, C. O., Chase, R. A., Alberti, K. G. M. M., Williams, R. 1975. Disturbances in glucose metabolism in patients with liver damage due to paracetamol overdose. *Clin. Sci. Molec. Med.* 49:473–79
19. James, O., Lesna, M., Roberts, S. H., Pulman, L., Douglas, A. P., et al. 1975. Liver damage after paracetamol overdose: comparison of liver function tests, fasting serum bile acids, and liver histology. *Lancet* 2:579–81
20. Eastham, E. J., Bell, J. I., Douglas, A. P. 1976. Serum ferritin levels in acute hepatocellular damage from paracetamol overdosage. *Brit. Med. J.* 1:750–51
21. Kleinman, J. G., Breitenfield, R. V., Roth, D. A. 1980. Acute renal failure associated with acetaminophen ingestion: report of a case and review of the literature. *Clin. Nephrol.* 14:201–5
22. Cobden, I., Record, C. O., Ward, M. K., Kerr, D. N. S. 1982. Paracetamol-induced acute renal failure in the absence of fulminant liver damage. *Brit. Med. J.* 284:21–22
23. Portmann, B., Talbot, I. C., Day, D. W., Davidson, A. R., Murray-Lyon, I. M., Williams, R. 1975. Histopathological changes in the liver following a paracetamol overdose: correlation with clinical and biochemical parameters. *J. Pathol.* 117:169–81
24. Lesna, M., Watson, A. J., Douglas, A. P., Hamlyn, A. N., James, O. F. W. 1976. Evaluation of paracetamol-induced damage in liver biopsies. *Virchows Arch. A Pathol. Anat. Histol.* 370:333–44
25. Jollow, D. J., Thorgeirsson, S. S., Potter, W. Z., Hashimoto, M., Mitchell, J. R. 1974. Acetaminophen-induced hepatic necrosis. VI. Metabolic disposition of toxic and nontoxic doses of acetaminophen. *Pharmacology* 12: 251–71
26. Prescott, L. F. 1982. Paracetamol overdosage: pharmacological considerations and clinical management. *Drugs.* In press
27. Davis, D. C., Potter, W. Z., Jollow, D. J., Mitchell, J. R. 1974. Species differences in hepatic glutathione depletion, covalent binding and hepatic necrosis after acetaminophen. *Life Sci.* 14:2099–2109
28. Mitchell, J. R., Thorgeirsson, S. S., Potter, W. Z., Jollow, D. J., Keiser, H. 1974. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. *Clin. Pharmacol. Ther.* 16:676–84
29. Nimmo, J., Dixon, M. F., Prescott, L. F. 1973. Effects of mepyramine, promethazine, and hydrocortisone on paracetamol-induced hepatic necrosis in the rat. *Clin. Toxicol.* 6:75–81
30. Gazzard, B. G., Clark, R., Borirakchanyavat, V., Williams, R. 1974. A controlled trial of heparin therapy in the coagulation defect of paracetamol-induced hepatic necrosis. *Gut* 15:89–93
31. Prescott, L. F., Wright, N. 1973. The effects of hepatic and renal damage on paracetamol metabolism and excretion following overdosage. A pharmacokinetic study. *Brit. J. Pharmacol.* 49: 602–13
32. Farid, N. R., Glynn, J. P., Kerr, D. N. S. 1972. Haemodialysis in paracetamol self-poisoning. *Lancet* 2:396–98
33. Mitchell, J. R., Jollow, D. J., Potter, W. Z., Davis, D. C., Gillette, J. R., Brodie, B. B. 1973. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. *J. Pharmacol. Exp. Ther.* 187: 185–94
34. Jollow, D. J., Mitchell, J. R., Potter, W. Z., Davis, D. C., Gillette, J. R., Brodie, B. B. 1973. Acetaminophen-induced hepatic necrosis. II. Role of covalent binding in vivo. *J. Pharmacol. Exp. Ther.* 187:195–202
35. Potter, W. Z., Davis, D. C., Mitchell, J. R., Jollow, D. J., Gillette, J. R., Brodie, B. B. 1973. Acetaminophen-induced hepatic necrosis. III. Cytochrome P-450-mediated covalent binding in vitro. *J. Pharmacol. Exp. Ther.* 187:203–10

36. Mitchell, J. R., Jollow, D. J., Potter, W. Z., Gillette, J. R., Brodie, B. B. 1973. Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. *J. Pharmacol. Exp. Ther.* 187:211–17
37. Miner, D. J., Kissinger, P. T. 1979. Evidence for the involvement of N-acetyl-p-quinoneimine in acetaminophen metabolism. *Biochem. Pharmacol.* 28: 3285–90
38. Moldeus, P. 1981. Use of isolated cells in the study of paracetamol metabolism and toxicity: capacity of conjugative pathways and glutathione homeostasis. In *Drug Reactions and the Liver,* ed. M. Davis, J. M. Tredger, R. Williams, pp. 144–56. London: Pitman. 364pp.
39. Davis, M., Simmons, C. J., Harrison, N. G., Williams, R. 1976. Paracetamol overdose in man: relationship between pattern of urinary metabolites and severity of liver damage. *Q. J. Med.* 45: 181–91
40. Pessayre, D., Wandscheer, J. –C., Cobert, B., Level, R., Degott, C., Batt, A. M., Martin, N., Benhamou, J. P. 1980. Additive effects of inducers and fasting on acetaminophen hepatotoxicity. *Biochem. Pharmacol.* 29:2219–23
41. McLean, A. E. M., Day, P. A. 1975. The effect of diet on the toxicity of paracetamol and the safety of paracetamol-methionine mixtures. *Biochem. Pharmacol.* 24:37–42
42. Abernethy, D. R., Greenblatt, D. J., Divoll, M. 1982. Differential effects of cimetidine on drug oxidation vs conjugation: potential mode of therapy for acetaminophen hepatotoxicity. *Clin. Pharmacol. Ther.* 31:198 (Abstr.)
43. Donn, K. H., Rudd, G. D., Grisham, J. W., Koch, G. G. 1982. Prevention of acetaminophen-induced hepatic injury by cimetidine. *Clin. Pharmacol. Ther.* 31:218–19 (Abstr.)
44. Mitchell, M. C., Schenker, S., Avant, G. R., Speeg, K. V. 1981. Cimetidine protects against acetaminophen hepatotoxicity in rats. *Gastroenterology* 81: 1052–60
45. Sato, C., Nakano, M. Lieber, C. S. 1981. Prevention of acetaminophen-induced hepatotoxicity by acute ethanol administration in the rat: comparison with carbon tetrachloride-induced hepatotoxicity. *J. Pharmacol. Exp. Ther.* 218: 805–10
46. Sato, C., Lieber, C. S. 1981. Mechanism of the preventive effect of ethanol on acetaminophen-induced hepatotoxicity. *J. Pharmacol. Exp. Ther.* 218:811–15
47. Moldeus, P., Andersson, B., Norling, A., Ormstad, K. 1980. Effect of chronic ethanol administration on drug metabolism in isolated hepatocytes with emphasis on paracetamol activation. *Biochem. Pharmacol.* 29:1741–45
48. Peterson, F. J., Holloway, D. E., Erickson, R. R., Duquette, P. H., McClain, C. J., Holtzman, J. L. 1980. Ethanol induction of acetaminophen toxicity and metabolism. *Life Sci.* 27:1705–11
49. Teschke, R., Stutz, G., Strohmeyer, G. 1979. Increased paracetamol-induced hepatotoxicity after chronic alcohol consumption. *Biochem. Biophys. Res. Commun.* 91:368–74
50. Strubelt, O., Obermeier, F., Siegers, C. P. 1978. The influence of ethanol pretreatment on the effects of nine hepatotoxic agents. *Acta Pharmacol. Toxicol.* 43:211–18
51. Sato, C., Matsuda, Y., Lieber, C. S. 1981. Increased hepatotoxicity of acetaminophen after chronic ethanol consumption in the rat. *Gastroenterology* 80:140–48
52. Wright, N., Prescott, L. F. 1973. Potentiation by previous drug therapy of hepatotoxicity following paracetamol overdosage. *Scott. Med. J.* 18:56–58
53. McClain, C. J., Kromhout, J. P., Peterson, F. J., Holtzman, J. L. 1980. Potentiation of acetaminophen hepatotoxicity by alcohol. *J. Am. Med. Assoc.* 244: 251–53
54. Critchley, J. A. J. H., Cregeen, R. J., Balali-Mood, M., Pentland, B., Prescott, L. F. 1982. Paracetamol metabolism in heavy drinkers. *Brit. J. Clin. Pharmacol.* 13:276–77P
55. Prescott, L. F., Critchley, J. A. J. H., Balali-Mood, M., Pentland, B. 1981. Effects of microsomal enzyme induction on paracetamol metabolism in man. *Brit. J. Clin. Pharmacol.* 12:149–53
56. Gazzard, B. G., Hughes, R. D., Portmann, B., Dordoni, B., Williams, R. 1974. Protection of rats against the hepatotoxic effect of paracetamol. *Brit. J. Exp. Pathol.* 55:601–5
57. Benedetti, M. S., Louis, A., Malnoë, A., Schneider, M., Lam, R., et al. 1975. Prevention of paracetamol-induced liver damage in mice with glutathione. *J. Pharm. Pharmacol.* 27:629–32
58. Malnoe, A., Louis, A., Benedetti, M. S., Schneider, M., Smith, R. L., et al. 1975. Effect of liposomal entrapment on the protective action of glutathione against paracetamol-induced liver necrosis. *Biochem. Soc. Trans.* 3:730–32

59. Strubelt, O., Siegers, C. P., Schütt, A. 1974. The curative effects of cysteamine, cysteine, and dithiocarb in experimental paracetamol poisoning. *Arch. Toxicol.* 33:55–64
60. Piperno, E., Berssenbruegge, D. A. 1976. Reversal of experimental paracetamol toxicosis with N-acetylcysteine. *Lancet* 2:738–39
61. Piperno, E., Mosher, A. H., Berssenbruegge, D. A., Winkler, J. D., Smith, R. B. 1978. Pathophysiology of acetaminophen overdosage toxicity: implications for management. *Pediatrics* 62:880–89 (Suppl.)
62. Labadarios, D., Davis, M., Portmann, B., Williams, R. 1977. Paracetamol-induced hepatic necrosis in the mouse—relationship between covalent binding, hepatic glutathione depletion, and the protective effect of α-mercaptopropionyl-glycine. *Biochem. Pharmacol.* 26: 31–35
63. Chiu, S., Bhakthan, N. M. G. 1978. Experimental acetaminophen-induced hepatic necrosis: biochemical and electron microscopic study of cysteamine protection. *Lab. Invest.* 39:193–203
64. Siege s, C.–P. 1978. Antidotal effects of dimethyl sulphoxide against paracetamol-, bromobenzene-, and thioacetamide-induced hepatotoxicity. *J. Pharm. Pharmacol.* 30:375–77
65. Stramentinoli, G., Pezzoli, C., Galli-Kienle, M. 1979. Protective role of S-adenosyl-L-methionine against acetaminophen-induced mortality and hepatotoxicity in mice. *Biochem. Pharmacol.* 28:3567–71
66. Yamada, T., Ludwig, S., Kuhlenkamp, J., Kaplowitz, N. 1981. Direct protection against acetaminophen hepatotoxicity by propylthiouracil. *J. Clin. Invest.* 67:688–95
67. Prescott, L. F. 1980. Kinetics and metabolism of paracetamol and phenacetin. *Brit. J. Clin. Pharmacol.* 10(Suppl. 2):291–98S
68. Slattery, J. T., Levy, G. 1979. Acetaminophen kinetics in acutely poisoned patients. *Clin. Pharmacol. Ther.* 25:184–95
69. Galinsky, R. E., Slattery, J. T., Levy, G. 1979. Effect of sodium sulfate on acetaminophen elimination by rats. *J. Pharm. Sci.* 68:803–5
70. Galinsky, R. E., Levy, G. 1979. Effect of N-acetylcysteine on the pharmacokinetics of acetaminophen in rats. *Life Sci.* 25:693–700
71. Slattery, J. T., Levy, G. 1977. Reduction of acetaminophen toxicity by sodium sulfate in mice. *Res. Commun. Chem. Pathol. Pharmacol.* 18:167–70
72. Mitchell, J. R. 1977. Host susceptibility and acetaminophen live injury. *Ann. Intern. Med.* 87:377–78
73. Prescott, L. F., Newton, R. W., Swainson, C. P., Wright, N., Forrest, A. R. W., Matthew, H. 1974. Successful treatment of severe paracetamol overdosage with cysteamine. *Lancet* 1:588–92
74. Gazzard, B. G., Hughes, R. D., Widdop, B., Goulding, R., Davis, M., Williams, R. 1977. Early prediction of the outcome of a paracetamol overdose based on an analysis of 163 patients. *Postgrad. Med. J.* 53:243–47
75. Prescott, L. F. 1978. Prevention of hepatic necrosis following paracetamol overdosage. *Health Bull.* 36:204–12
76. Rumack, B. H., Matthew, H. 1975. Acetaminophen poisoning and toxicity. *Pediatrics* 55:871–76
77. Stewart, M. J., Adriaenssens, P. I., Jarvie, D. R., Prescott, L. F. 1979. Inappropriate methods for the emergency determination of plasma paracetamol. *Ann. Clin. Biochem.* 16:89–95
78. Dordoni, B., Willson, R. A., Thompson, R. P. H., Williams, R. 1973. Reduction of absorption of paracetamol by activated charcoal and cholestyramine: a possible therapeutic measu e. *Brit. Med. J.* 3:86–87
79. Levy, G., Houston, J. B. 1976. Effect of activated charcoal on acetaminophen absorption. *Pediatrics* 58:432–35
80. Prescott, L. F., Pa k, J., Sutherland, G. R., Smith, I. J., Proudfoot, A. T. 1976. Cysteamine, methionine, and penicillamine in the treatment of paracetamol poisoning. *Lancet* 2:109–14
81. Hughes, R. D., Gazzard, B. G., Hanid, M. A., Trewby, P. N., Murray-Lyon, I. M., et al. 1977. Controlled trial of cysteamine and dimercaprol after paracetamol overdose. *Brit. Med. J.* 2: 1395
82. Smith, J. M., Roberts, W. O., Hall, S. M., White, T. A., Gilbertson, A. A. 1978. Late treatment of paracetamol poisoning with mercaptamine. *Brit. Med. J.* 1:331–33
83. Hamlyn, A. N., Lesna, M., Record, C. O., Smith, P. A., Watson, A. J. 1981. Methionine and cysteamine in paracetamol (acetaminophen) overdose, prospective controlled trial of early therapy. *J. Int. Med. Res.* 9:226–31
84. Douglas, A. P., Hamlyn, A. N., James, O. 1976. Controlled trial of cysteamine in treatment of acute paracetamol

(acetaminophen) poisoning. *Lancet* 1:111–15
85. Crome, P., Vale, J. A., Volans, G. N., Widdop, B., Goulding, R. 1976. Oral methionine in the treatment of severe paracetamol (acetaminophen) overdose. *Lancet* 2:829–30
86. Vale, J. A., Meredith, T. J., Goulding, R. 1981. Treatment of acetaminophen poisoning. The use of oral methionine. *Arch. Intern. Med.* 141:394–96
87. Vale, J. A., Meredith, T. J., Crome, P., Helliwell, M., Volans, G. N., 1979. Intravenous N-acetylcysteine: the treatment of choice in paracetamol poisoing? *Brit. Med. J.* 2:1435–36
88. Prescott, L. F., Park, J., Ballantyne, A., Adriaenssens, P., Proudfoot, A. T. 1977. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. *Lancet* 2:432–34
89. Prescott, L. F., Illingworth, R. N., Critchley, J. A. J. H., Stewart, M. J., Adam, R. D., Proudfoot, A. T. 1979. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Brit. Med. J.* 2:1097–1100
90. Rumack, B. H., Peterson, R. G. 1978. Acetaminophen overdose: incidence, diagnosis, and management in 416 patients. *Pediatrics* 62 (Suppl.): 898–903
91. Prescott, L. F. 1981. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. *Arch. Intern. Med.* 141:386–89
92. Walton, N. G., Mann, T. A. N., Shaw, K. M. 1979. Anaphylactoid reaction to N-acetylcysteine. *Lancet* 2:1298
93. Prescott, L. F., Cregeen, R. J. 1982. The hepatotoxicity of paracetamol — clinical aspects. *Agressologie* 23:17–20
94. Prescott, L. F., Wright, N. 1974. B. A. L. in paracetamol poisoning. *Lancet* 2:833–34
95. National Poisons Information Service Monitoring Group. 1981. Analgesic poisoning: a multi-centre, prospective survey. *Hum. Toxicol.* 1:7–23
96. Rollins, D. E., Buckpitt, A. R. 1979. Liver cytosol catalyzed conjugation of reduced glutathione with a reactive metabolite of acetaminophen. *Toxicol. Appl. Pharmacol.* 47:331–39
97. Révész, L., Modig, H. 1965. Cysteamine-induced increase of cellular glutathione level: a new hypothesis of the radioprotective mechanism. *Nature* 207:430–31
98. Prescott, L. F. 1979. The nephrotoxicity and hepatotoxicity of antipyretic analgesics. *Brit. J. Clin. Pharmacol.* 7: 453–62
99. Buckpitt, A. R., Rollins, D. E., Mitchell, J. R. 1979. Varying effects of sulfhydryl nucleophiles on acetaminophen oxidation and sulfhydryl adduct formation. *Biochem. Pharmacol.* 28:2941–46
100. Williamson, J. M., Meister, A. 1981. Stimulation of hepatic glutathione formation by adminstration of L-2-oxothiazolidine-4-carboxylate, a 5-oxo-L-prolinase substrate. *Proc. Natl. Acad. Sci. USA* 78:936–39
101. Tredger, J. M., Smith, H. M., Davis, M., Williams, R. 1981. In vitro interactions of sulfur-containing compounds with the hepatic mixed-function oxidase system in mice: effects on paracetamol activation and covalent binding. *Toxicol. Appl. Pharmacol.* 59:111–24
102. Corcoran, G. B., Mitchell, J. R., Vaishnav, Y. N., Horning, E. C. 1980. Evidence that acetaminophen and N-hydroxy-acetaminophen form a common arylating intermediate, N-acetyl-p-benzoquinoneimine. *Molec. Pharmacol.* 18:536–42
103. Lake, B. G., Harris, R. A., Phillips, J. C., Gangolli, S. D. 1981. Studies on the effects of L-ascorbic acid on acetaminophen-induced hepatotoxicity. I. Inhibition of the covalent binding of acetaminophen metabolites to hepatic microsomes in vitro. *Toxicol. Appl. Pharmacol.* 60:229–40
104. Raghuram, T. C., Krishnamurthi, D., Kalamegham, R. 1978. Effect of vitamin C on paracetamol hepatotoxicity. *Toxicol. Lett.* 2:175–78
105. Winchester, J. F., Gelfand, M. C., Helliwell, M., Vale, J. A., Goulding, R., Schreiner, G. E. 1981. Extracorporeal treatment of salicylate or acetaminophen poisoning—is there a role? *Arch. Intern. Med.* 141:370–74
106. Helliwell, M., Vale, J. A., Goulding, R. 1981. Haemoperfusion in "late" paracetamol poisoning. *Hum. Toxicol.* 1:25–30
107. Gazzard, B. G., Willson, R. A., Weston, M. J., Thompson, R. R. H., Williams, R. 1974. Charcoal haemoperfusion for paracetamol overdose. *Brit. J. Clin. Pharmacol.* 1:271–75
108. Rigby, R. J., Thomson, N. M., Parkin, G. W., Cheung, T. P. F. 1978. The treatment of paracetamol overdose with charcoal haemoperfusion and cysteamine. *Med. J. Aust.* 1:396–99