Acetaminophen in chronic liver disease

The safety of acetaminophen in therapeutic doses was evaluated in subjects with stable chronic liver disease. Six subjects with chronic liver disease were given 4.0 gm daily for 5 days. Although the mean half-life (t½) acetaminophen was 3.42 hr, there was no evidence of drug cumulation or hepatotoxicity. A double-blind, two-period crossover design was also used to evaluate acetaminophen in 20 subjects. Acetaminophen, at a dose of 4.0 gm daily for 13 days, was well tolerated by these subjects with stable chronic liver disease. One subject developed symptoms, which worsened and were associated with deterioration in the results of laboratory studies, while taking acetaminophen. Subsequent challenges with 4.0 gm acetaminophen daily for periods of 10 and 14 days were well tolerated, which indicates that the deterioration was not related to the drug. During this study there were no abnormalities indicative of an adverse reaction to acetaminophen. There is, therefore, no contraindication to the use of acetaminophen in therapeutic doses in the presence of stable chronic liver disease.

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Hepatic toxicity due to acetaminophen,[3, 5, 16, 18, 37] has been reported after acute ingestion of 10 gm or more, an event almost invariably associated with intentional overdose. The incidence and severity of hepatic injury increases with progressively larger overdoses,[4, 6, 14, 16, 23, 39] with toxicity predictable only when blood levels exceed 200 μg/ml 4 hr after dosing.[31, 32] Hepatotoxicity is presumed to result from a highly reactive arylating intermediate metabolite formed from that small fraction of acetaminophen that is metabolized through the cytochrome P-450–dependent mixed-function oxidase system.[7, 19, 21, 26] Ordinarily, this toxic metabolite is inactivated by conjugation with glutathione.[22, 23] After overdose, early treatment with *N*-acetylcysteine reduces morbidity and almost always prevents death.[25, 29, 32]

Since acetaminophen is metabolized by the liver and the liver is the major site of injury after overdose, there has been speculation that patients with chronic liver disease may be at risk when using the drug at therapeutic doses. Theoretically, hepatotoxicity could develop in subjects with chronic liver disease if high blood levels of acetaminophen develop because of delayed metabolism or if there is increased production of the toxic metabolite because of increased activity of the cytochrome P-450 enzyme system or as a result of diminished glutathione stores.

This study was designed to determine if patients with chronic liver disease develop adverse reaction or deterioration in results of liver-related laboratory tests after 4.0 gm daily acetaminophen for 2 wk.

The experiment was preceded by an open-pilot examination of single-dose kinetics of

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Table I. *Results of pilot study in six subjects with advanced cirrhosis*

Subject No.	*Age (yr)*	*Diagnosis*	*Duration of disease (yr)*	*Initial BSP retention (%)*	*t½ (hr)*	*Daily acetaminophen levels (range, μg/ml)*
1	57	Laennec's cirrhosis	2	32.7	5.77	11.4-13.1
2	42	Cirrhosis (unspecified type)	7	18.2	2.35	14.9-26.7
3	59	Laennec's cirrhosis	2	25.8	2.13	4.5-15.9
4	56	Postnecrotic cirrhosis	1	26.1	3.10	12.0-19.5
5	64	Postnecrotic cirrhosis	4	39.7	2.97	14.2-22.0
6	66	Laennec's cirrhosis	7	36.7	3.28	13.2-21.7
Mean ± SD				35.3 ± 9.1	3.42 ± 2.5	

acetaminophen in patients with chronic liver disease and to determine if cumulation of the drug occurs with continued daily doses of 4.0 gm. These investigations have substantial clinical importance because patients with chronic liver disease are commonly advised to use acetaminophen rather than aspirin when they require an analgesic or antipyretic. The problems related to the use of salicylates in this population are well established.[9]

Methods

In the pilot study, six patients with stable chronic liver disease (see Table I) were evaluated clinically and with laboratory studies, including those for levels of total and direct bilirubin, alkaline phosphatase, 5-nucleotidase, serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), gamma glutamyl transpeptidase (GGTP), bile acids (fasting), creatinine, prothrombin time, partial thromboplastin time, and protein electrophoresis. The severity of the chronic liver disease was assessed by measurement of sulfobromopthalein (BSP) retention at 45 min. The half-life (t½) of acetaminophen was calculated from plasma samples obtained over a 6-hr period after oral doses of 1.0 gm. During the 5 days of the study, 4.0 gm acetaminophen daily was taken (1.0 gm at 8:00 A.M., 12:00 noon, 4:00 P.M., and 8:00 P.M.) and acetaminophen plasma levels were determined at approximately 6:00 P.M. The laboratory studies were performed before and at the completion of the 5-day period of dosing. Standard clinical laboratory procedures were used. Serum bile acids were determined by the spectrofluoremetric assay system with 3^{α}-hydroxysteroid dehydrogenase.[24] Acetaminophen was measured by gas-liquid chromatography.[28]

The pilot study was followed by a more comprehensive study to compare the safety of acetaminophen in patients with stable chronic liver disease. The experimental design was a double-blind, two-period crossover with an initial 1-wk period of observation to assess the stability of the disease process. The diagnosis of the liver disease in all subjects had already been confirmed by liver biopsy. Diagnosis included: alcoholic liver disease in six, Laennec's cirrhosis in four, cirrhosis, type unspecified, in one, postnecrotic cirrhosis in one, chronic active hepatitis in six, chronic persistent hepatitis in four, and primary biliary cirrhosis in two. After 1-wk baseline period, 27 patients were randomly assigned to either 4.0 gm of acetaminophen daily or placebo in identical capsules for a 13-day period, after which they were crossed over to the alternate treatment for 13 days.

Four patients withdrew for personal reasons during the initial baseline (placebo) period. Three additional subjects were not included in the analysis; one developed a skin rash suggestive of a hypersensitivity reaction after taking acetaminophen for 10 days, one was excluded because of a protocol violation, and one developed nausea and malaise during the placebo period followed by deterioration during the acetaminophen period. This last patient was evaluated and subsequently given acetaminophen in a single 1.0-gm dose and in doses of 4.0 gm daily for periods of 10 and 14 days (see Results). Pregnant women and subjects with histories of drug reactions or with known allergies to ace-

Table II. *Results of laboratory tests in double-blind experiment*

Laboratory test	*Normal range*	*Baseline period*		*Acetaminophen period*		*Placebo period*	
		$\bar{X}$	*SD*	$\bar{X}$	*SD*	$\bar{X}$	*SD*
Bilirubin (mg/dl)							
Total	0.2-1.2	1.3	0.8	1.4	1.1	1.4	1.0
Direct	0.0-0.3	0.7	0.6	0.7	0.8	0.7	0.8
Alkaline phosphatase (Bodansky units)	0-4.5	8.8	14.2	7.8	9.8	8.5	11.1
5-Nucleotidase (units)	0-2.5	6.4	16.7	6.9	15.6	6.4	14.5
SGOT (units)	2-18	42.5	26.3	39.5	23.1	55.0	71.6
SGPT (units)	0-18	58.6	55.7	53.3	48.8	77.3	126.2
GGTP (units)	3.2-24.8	79.0	88.9	91.0	105.5	83.0	86.8
Serum bile acids (fasting) (μmol/*l*)	0-10.0	39.9	39.5	58.5	62.5	64.2	89.4
Serum creatinine (mg/dl)	0.7-1.4	0.8	0.2	0.8	0.3	0.9	0.3
Prothrombin time (%)	80-100%	89.3	14.6	93.0	9.6	91.1	10.5
Serum albumin (gm/dl)	3.2-5.6	3.99	0.53	4.09	0.46	3.98	0.48

Values are given for end of baseline period and the end of the two 13-day treatment periods during which the subjects took placebo or 4.0 gm acetaminophen daily. Values for the treatment groups are pooled since there were no differences related to treatment sequence.

taminophen were excluded from the study. Patients were instructed to continue their prescribed intake of other medications during the study. Detailed patient evaluations, including the laboratory tests, were performed initially and at 7, 14, 21, 28, and 35 days. Participants were instructed to take two capsules at 8:00 A.M., 12:00 noon, 4:00 P.M., and 8:00 P.M. each day during the 7-day baseline period (placebo) and the two 13-day periods (1.0 gm acetaminophen or placebo).

Statistical data. Comparability of the two treatment sequence groups with respect to initial laboratory values was assessed by means of Student's t test for each of the laboratory variables. The analyses were repeated using the natural logarithms of the raw data and nonparametric procedures based on the relative ranks of the data (Wilcoxon rank-sum test[38]) because the nature of the data was such that assumptions of normality and homogeneity of variance were questionable.

Analysis of variance for a two-period crossover design[15] was performed for each of the laboratory variables at two separate times—after 1 wk on treatment and after 2 wk on treatment. The analyses were also repeated with the use of the natural logarithms of the raw data and nonparametric procedures based on the relative ranks of the data.[20]

Fisher's exact test was used to test for an association between the treatments and changes in status of each of the dichotamous variables used in the clinical evaluation (history and physical examination).

Results

Results of the pilot study are listed in Table I. The severity of chronic liver disease was documented by previous liver biopsy and BSP retention, which ranged from 18.2% to 39.7% at 45 min. The acetaminophen t½ ranged from 2.13 to 5.77 hr (mean 3.42 hr). The plasma acetaminophen levels, determined for 5 consecutive days midway between the third and the fourth 1.0-gm dose of acetaminophen, ranged between 4.5 μg/ml and 26.7 μg/ml. At no time did acetaminophen plasma concentrations approach potentially toxic levels. No progressive increase in acetaminophen plasma concentration occurred over the 5-day period. There were no changes in clinical status or in the laboratory tests.

Twenty subjects completed the larger double-blind study. There was no change in the clinical status of any subject. The results after 13 days on acetaminophen or placebo are listed in Table II. After 1 wk on treatment there were no differences between acetaminophen and placebo for any variable except alkaline phosphatase, 5-nucleotidase, and gamma glutamyl transpetidase. For each of these three variables, mean values for both acetaminophen and placebo

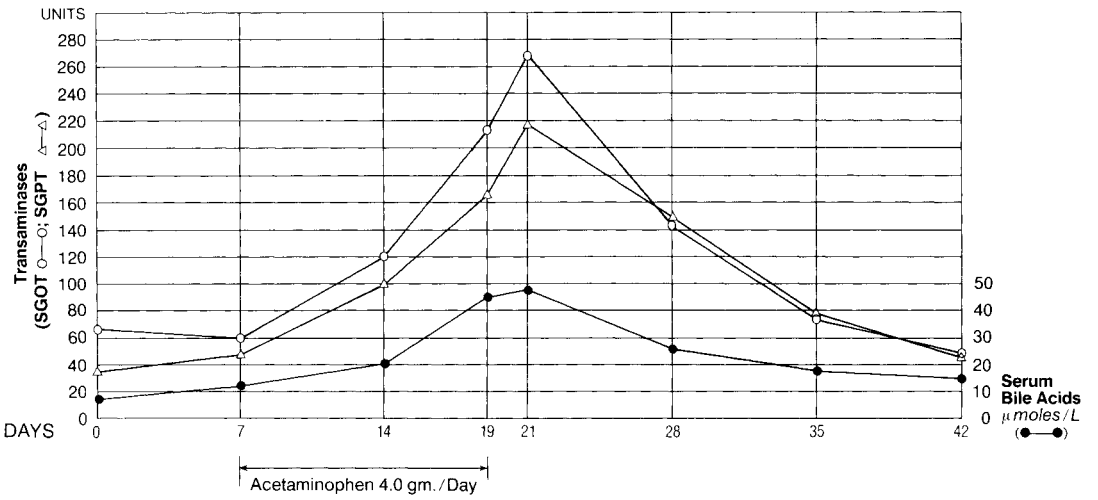

Fig. 1. Sequential changes in serum transaminases and fasting serum bile acids in the 42-yr-old man who had an exacerbation of chronic liver disease coincidental with acetaminophen (see text).

were above the normal range, but the mean during the acetaminophen period was significantly lower than the placebo value. After 2 wk on treatment there were no differences for any variable except serum albumin, for which the means for both the acetaminophen and placebo periods were within the normal range, the acetaminophen value being higher than the placebo. Also, there was no change in the clinical status of any subject. Therefore, in this experiment the continuous use of acetaminophen at a dose of 4.0 gm daily for a period of 13 days did not aggravate the clinical features or laboratory tests in 20 patients with stable chronic liver disease.

Case history. The history of a patient who developed symptoms and worsening of laboratory values during the initial acetaminophen treatment period and who subsequently was rechallenged with the drug is as follows:

A 42-yr-old man with a 7-yr history of chronic active hepatitis (type B) with progression to postnecrotic cirrhosis was included in the study while continuing on his prescribed medications (20 mg prednisone daily and 100 mg azathioprine daily). Mild nausea, malaise, and abdominal discomfort were noted during the latter part of the baseline period (placebo). These symptoms increased in severity during the initial drug period and were associated with right upper abdominal pain. Because of his symptoms and associated abnormalities in the laboratory tests (Fig. 1), the code was broken on day 12 and it was determined that he was receiving acetaminophen. The acetaminophen t½ in the patient was 2.7 hr at this time. Acetaminophen was stopped and his condition was followed with studies according to the protocol. Since the onset of symptoms preceded the taking of acetaminophen and the t½ was not markedly prolonged, it was believed that the symptoms were probably a result of a fluctuation of his underlying liver disease and not related to the drug.

At a time when his disease appeared stable (3 mo later), the patient was given a single 1.0-gm dose of acetaminophen. The t½ was 3.3 hr and there were no changes in liver studies at 2, 3, 4, 6, 8, and 24 hr. Since there was no evidence of any adverse effect after the single dose, he was given 4.0 gm acetaminophen daily for 10 days. No adverse symptoms or significant alterations in laboratory studies were noted during this period. Later, 4.0 gm acetaminophen daily was taken for 14 days. During this period he had no adverse symptoms and there were no changes in laboratory findings (Fig. 2). It was therefore concluded that the earlier symptoms and laboratory test results were not related to acetaminophen, but were the result of an exacerbation of his chronic liver disease.

Discussion

Acetaminophen is metabolized by the liver, predominantly to sulfate and glucuronide conjugates that are excreted in the urine. A small fraction is metabolized by the cytochrome P-450–dependent mixed-function oxidase enzyme pathway to form a highly reactive arylating intermediate.[8, 30, 36] At therapeutic doses this potentially toxic metabolite is rapidly inac-

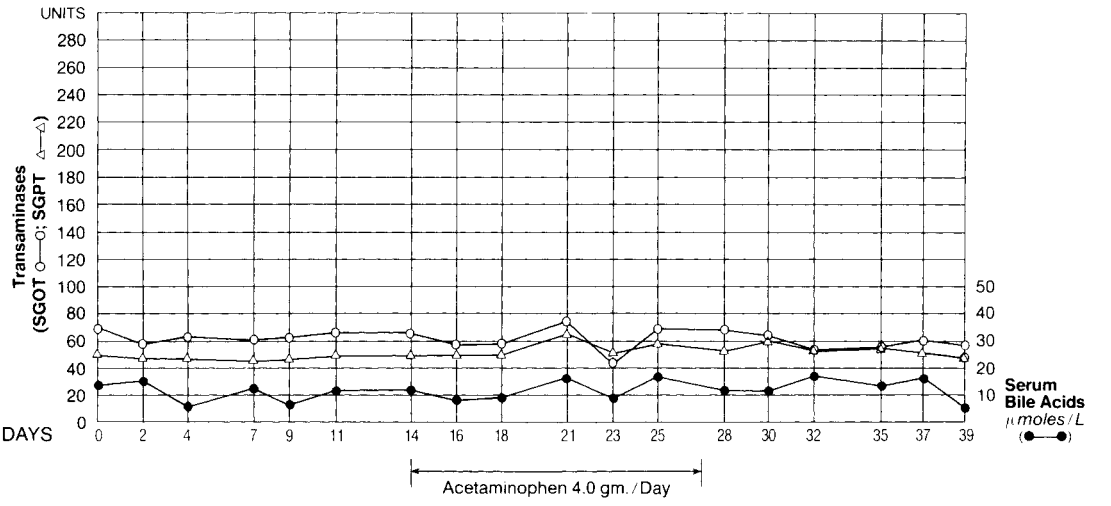

Fig. 2. Subject was challenged with 4.0 gm acetaminophen daily for periods of 10 and 14 days. Values for the 14-day period are shown. During these two periods there were no adverse symptoms or significant alterations in the serum transaminases or fasting serum bile acids.

tivated by conjugation with glutathione and then excreted by the kidney as cysteine and mercapturic acid conjugates.[23] After an overdose of acetaminophen, hepatic stores of glutathione may be depleted and the chemically reactive metabolite may then bind covalently to tissue macromolecules, causing cellular necrosis[19, 26]; hepatocellular necrosis correlates with the extent of this covalent binding.[7]

Liver disease could conceivably result in sufficient impairment of drug metabolism to permit acetaminophen to cumulate to potentially toxic levels at therapeutic doses. The six subjects in the pilot study had advanced chronic liver disease and they had neither cumulation nor evidence of hepatotoxicity during 5 consecutive days on 4.0 gm daily. The t½ was prolonged to a mean of 3.42 hr, representing a 70% rise over the normal 2.04 hr (Table I). This prolongation was less than might be anticipated in patients with liver disease, indicating that the acetaminophen t½ is not markedly prolonged, even with significant hepatic functional and structural impairment. These findings are consistent with those of others[1, 2, 12, 35] in patients with liver disease in whom the mean t½ of acetaminophen ranged from 2.9 to 4.75 hr. Also, daily blood levels 2 hr after the third dose did not indicate cumulation during the 5-day period of acetaminophen dosing in the pilot study. At no time were plasma acetaminophen levels higher than would be expected 2 hr after a single 1.0-gm dose.

Tissue levels of cytochrome P-450, an integral component of the microsomal oxidase system, appear to influence the development of hepatotoxicity after an overdose with acetaminophen.[4, 26] This has been demonstrated in experimental animals[19, 21, 23] and may be true in man, since induction of this pathway is associated with enhanced toxicity after an overdose.[40] Chronic liver disease might also result in enhanced hepatotoxicity if there was increased activity of the cytochrome P-450–dependent mixed-function oxidase system or preferential metabolism of the drug via this pathway. Although the number of reported studies is small, cytochrome P-450 levels are not increased in the presence of liver disease[10, 13, 33]; actually, they are decreased in severe liver disease, particularly in alcoholic hepatitis or severe viral hepatitis.[10, 13] Patients with severe chronic liver disease also appear to lose the capacity for induction of cytochrome P-450.[10] Liver disease of mild to moderate severity is usually associated with normal levels of cytochrome P-450[13, 33] and the excretion of the various conjugates of acetaminophen is unchanged in liver disease.[11] There is, therefore, no evidence to support the speculation of possible enhanced metabolism of

acetaminophen via the cytochrome P-450 pathway in chronic liver disease. This possibility is not supported by cytochrome P-450 assays in liver biopsies[10, 13, 33] or by differences in the urinary excretion of acetaminophen conjugates.[11] Available data suggest that patients with severe liver disease may in fact tolerate larger doses of acetaminophen than normal individuals. There is no evidence to suggest any propensity for toxicity at therapeutic doses because of delayed metabolism or enhanced formation of the toxic metabolite.

Depression of hepatic glutathione levels could predispose to hepatotoxicity since the toxic metabolite is inactivated by conjugation with glutathione, but in the presence of liver disease the levels of glutathione are either normal or are increased.[27]

There is a possibility that acetaminophen might induce hepatocellular injury in chronic liver disease by an unknown mechanism such as occurs with salicylates in juvenile rheumatoid arthritis and systemic lupus erythematosis,[9, 34] but this does not appear to be the case since there were no changes in any of the tests (Table II). This is true not only for the transaminases, but also for the serum bile acids, a most sensitive index of liver injury.[17]

Caution must be used in evaluating potential drug reactions. Experience with the subject who had evidence of deterioration in association with acetaminophen use is illustrative of the problem and demonstrates the importance of a drug challenge study. Because of the associated events, adverse reaction might have been assumed, but challenges with acetaminophen in therapeutic doses for periods of 10 and 14 days did not reveal any evidence of an adverse reaction, which indicates that the clinical deterioration and changes in the laboratory studies initially associated with acetaminophen were coincidental.

References

1. Andreasen PB, Hutters L: Paracetamol (acetaminophen) clearance in patients with cirrhosis of the liver. Acta Med Scand **624:**99-105, 1979.
2. Arnman R, Olsson R: Elimination of paracetamol in chronic liver disease. Acta Hepato-Gastroenterol **25:**283-286, 1978.
3. Barker JD, de Carle DJ, Anuvas S: Chronic excessive acetaminophen use and liver damage. Ann Intern Med **87:**299-301, 1977.
4. Black M: Acetaminophen hepatotoxicity. Gastroenterology **78:**382-392, 1980.
5. Bonkowsky HL, Mudge GH, McMurtry RJ: Chronic hepatic inflammation and fibrosis due to low doses of paracetamol. Lancet **1:**1016-1018, 1978.
6. Clark R, Thompson RPH, Borirakchanyavat V, Widdop B, Davidson AR, Goulding R, Williams R: Hepatic damage and death from overdose of paracetamol. Lancet **1:**66-70, 1973.
7. Davis M, Harrison NG, Ideo G, Portmann B, Labadarios D, Williams R: Paracetamol metabolism in the rat: Relationship to covalent binding and hepatic damage. Xenobiotica **6:**249-255, 1976.
8. Davis M, Simmons CJ, Harrison NG, Wiliams R: Paracetamol overdose in man: Relationship between pattern of urinary metabolites and severity of liver damage. Q J Med **45:**181-191, 1976.
9. Editorial: Aspirin or paracetamol? Lancet **2:** 287-289, 1981.
10. Farrell GC, Cooksley WGE, Powell LW: Drug metabolism in liver disease: Activity of hepatic microsomal metabolizing enzymes. CLIN PHARMACOL THER **26:**483-492, 1979.
11. Forrest JAH, Adriaenssens P, Finalyson NDC, Prescott LF: Paracetamol metabolism in chronic liver disease. Eur J Clin Pharmacol **15:**427-431, 1979.
12. Forrest JAH, Finlayson NDC, Adjepon-Yamsak KK, Prescott LF: Antipyrine, paracetamol, and lignocaine elimination in chronic liver disease. Br Med J **1:**1384-1387, 1977.
13. Gabrielle L, Leterrier F, Molinie C, Essioux H, Cristan P, Laverdant C: Determination of human liver cytochrome P-450 by a micromethod using the electron paramagnetic resonance. Study of 141 liver biopsies. Gastroenterol Clin Biol **1:**775-782, 1977.
14. Gazzard BG, Hughes RD, Widdop B, Goulding R, Davis M, Williams R: Early prediction of the outcome of a paracetamol overdose based on an analysis of 163 patients. Postgrad Med J **53:** 243-247, 1977.
15. Grizzle JE: The two period change-over design and its use in clinical trials. Biometrics **21:**467-480, 1965.
16. Hamlyn AN, Douglas AP, James O: The spectrum of paracetamol (acetaminophen) overdose: Clinical and epidemiological studies. Postgrad Med J **54:**400-404, 1978.
17. James O, Lesna M, Roberts SH, Pulman L, Douglas AP, Smith PA, Watson AJ: Liver damage after paracetamol overdose. Comparison of liver-function tests, fasting serum bile acids, and liver histology. Lancet **2:**579-582, 1978.
18. Johnson GK, Tolman KG: Chronic liver disease

and acetaminophen. Ann Intern Med **87:**302-304, 1977.

19. Jollow DJ, Mitchell JR, Potter WZ, Davis DC, Gilette JR, Brodie BB: Acetaminophen-induced hepatic necrosis. II. Role of covalent binding in vivo. J Pharmacol Exp Ther **187:**195-202, 1973.
20. Koch GG: The use of nonparametric methods in the statistical analysis of the two period change-over design. Biometrics **28:**577-584, 1972.
21. Mitchell JR, Jollow DJ, Potter WZ, Davis DC, Gillette JR, Brodie BB: Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. J Pharmacol Exp Ther **187:**185-194, 1973.
22. Mitchell JR, Jollow DJ, Potter WZ, Gillette JR, Brodie BB: Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. J Pharmacol Exp Ther **187:**211-217, 1973.
23. Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Keiser H: Acetaminophen-induced hepatic injury: Protective role of glutathione in man and rationale for therapy. CLIN PHARMACOL THER **16:**676-684, 1974.
24. Osuga T, Mitamura K, Mashige F, Imai K: Evaluation of fluroimetrically estimated serum bile acid in liver disease. Clin Chem Acta **75:**81-90, 1977.
25. Peterson RG, Rumack BH: Treating acute acetaminophen poisoning with acetylcysteine. JAMA **237:**2406-2407, 1977.
26. Potter WZ, Davis DC, Mitchell JR, Jollow DJ, Gillette JR, Brodie BB: Acetaminophen-induced hepatic necrosis. III. Cytochrome P-450–mediated covalent binding in vitro. J Pharmacol Exp Ther **187:**203-210, 1973.
27. Poulsen HE, Ranek L, Andreasen PB: Elevated hepatic glutathione in liver diseases. Gastroenterology **79:**1120, 1980.
28. Prescott LF: The gas-liquid chromatographic estimation of phenacetin and paracetamol in plasma and urine. J Pharm Pharmacol **23:**111-115, 1971.
29. Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT: Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet **2:**432-434, 1977.
30. Prescott LF, Wright N: The effects of hepatic and renal damage on paracetamol metabolism and excretion following overdosage. A pharmacokinetic study. Br J Pharmacol **49:**602-613, 1973.
31. Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics **55:**871-876, 1975.
32. Rumack BH, Peterson RC, Koch GG, Amara IA: Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med **141:**380-385, 1981.
33. Schoene B, Fleischmann RA, Remmer H, Oldershansen HF: Determination of drug-metabolizing enzymes in needle biopsies of human liver. Eur J Clin Pharmacol **4:**65-73, 1972.
34. Seaman WE, Plotz PH: Effect of aspirin on liver tests in patients with RA or SLE and in normal volunteers. Arthritis Rheum **19:**155-160, 1976.
35. Shamszad M, Soloman H, Mobarhan S, Iber FL: Abnormal metabolism of acetaminophen in patients with alcoholic liver disease. Gastroenterology **69:**865, 1975.
36. Slattery JT, Levy G: Acetaminophen kinetics in acutely poisoned patients. CLIN PHARMACOL THER **25:**184-195, 1979.
37. Wade AJ, Upchurch KS, Eigenbrodt EH, Norman DA: Acetaminophen and the liver. Inn Intern Med **88:**267-268, 1978.
38. Wilcoxon F: Individual comparisons by ranking methods. Biometrics **1:**80-83, 1945.
39. Williams R, Davis M: Clinical and experimental aspects of paracetamol hepatotoxicity. Acta Pharmacol Toxicol **41:**282-298, 1977.
40. Wright N, Prescott LF: Paracetamol overdose: Potentiation of hepatotoxicity by previous drug therapy. Scott Med J **18:**56-59, 1973.