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Variability of acetaminophen metabolism in Caucasians and Orientals

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Acetaminophen (paracetamol) is extensively conjugated with glucuronic acid and sulfate prior to renal excretion. A minor metabolic route involves microsomal oxidation of acetaminophen to a hepatotoxic reactive intermediate, which subsequently undergoes glutathione (GSH) conjugation, yielding cysteine and mercapturate conjugates, both of which are excreted in the urine (Slattery *et al.*, 1987). Data collected by de Morais *et al.* (1989) indicated that in comparison with normal subjects, glucuronidation of acetaminophen was impaired in subjects with Gilbert's syndrome, a genetically-based impairment of bilirubin glucuronidation. Thus, inter-subject and ethnic differences in acetaminophen disposition have pharmacogenetic and toxicological implications. This study was conceived to explore these differences.

Urinary excretion of acetaminophen and its metabolites was observed in 125 Caucasian and 33 Oriental subjects. No appreciable difference was noted in the mean fraction of drug excreted as glucuronide between the two groups (51.5% in Caucasians vs 51.8% in Orientals). However, the data strongly indicated that the excretion of acetaminophen glucuronide was not normally distributed. Bimodality was apparent in both groups, with 20% of Caucasian and 33% of Oriental subjects displaying relatively extensive glucuronidation. In addition, glucuronidation displayed a strong negative correlation with sulfation ($r = -0.97$), suggesting the existence of a compensatory mechanism between the two metabolic pathways.

The mean fractional excretions of cysteine and mercapturate conjugates did show significant differences between Caucasians and Orientals ($p < 0.005$). In addition, the ratio of mercapturate to total GSH-derived conjugates recovered appeared to be bimodal, indicating possible heterogeneity in the conversion of the cysteine conjugate to mercapturate via *N*-acetylation.

Introduction

Acetaminophen (paracetamol) is a widely used analgesic and antipyretic agent. When administered in therapeutic doses, the major pathways for its disposition result in the formation of sulfate and glucuronide conjugates (Prescott *et al.*, 1981; Kalow, 1982) (Fig. 1). A minor parallel pathway, involving hepatic cytochrome P450-dependent oxidation, results in the formation of *N*-acetyl-*p*-benzoquinoneimine (NAPQI) (Dahlin *et al.*, 1984), a highly reactive hepatotoxic intermediate. Normally, NAPQI is eliminated through glutathione (GSH) conjugation, catalysed by glutathione-*S*-transferase (Mitchell *et al.*, 1974). Subsequent cleavage of the γ-glutamyl portion of the GSH conjugate, followed by further hydrolysis results in the formation of a cysteine conjugate (Moldeus *et al.*, 1980). The cysteine conjugate may then be excreted in urine or further metabolized into mercapturate by the membrane-bound enzyme cysteine-*S*-conjugate *N*-acetyltransferase (Duffel & Jakoby, 1982).

In cases of overdosage, hepatic GSH stores may become depleted, resulting in the covalent binding of NAPQI to hepatic macromolecules, which is thought to result in cellular necrosis (Potter *et al.*, 1974). *N*-acetylcysteine, a precursor of GSH, has been used to counter the effects of acetaminophen overdose (Prescott *et al.*, 1979).

Hepatotoxicity arising from acetaminophen is dose-related. However, individual differences in susceptibility are significant (Mitchell & Jollow, 1975). The basis of this inter-individual variation is not clear. The extent of NAPQI formation through the oxidative pathway, and the capacity for GSH synthesis, reflect-

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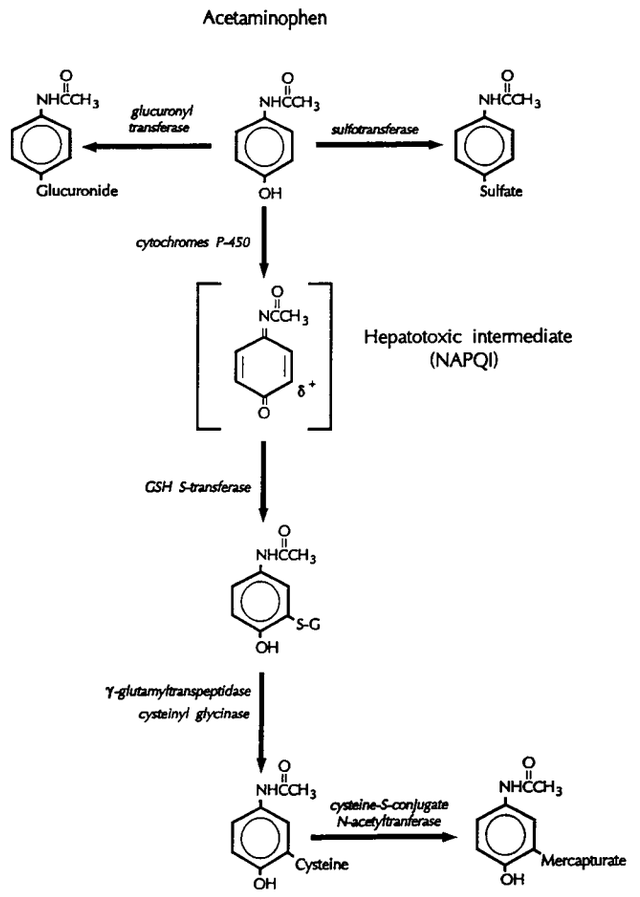

Fig. 1. Metabolic pathways involved in the elimination of acetaminophen.

ing the ability to eliminate the hepatotoxic metabolite, have been associated with individual susceptibilities to acetaminophen toxicity (Mitchell & Jollow, 1975).

Dose-dependent variations in the nonoxidative pathways of acetaminophen elimination are potentially important factors in individual susceptibilities to acetaminophen toxicity. Saturation of elimination via sulfate conjugation is known to occur at relatively low doses of acetaminophen, and may be reversed by the administration of *N*-acetylcysteine, which increases the hepatic availability of the cofactor 3′-phosphoadenosine-5′-phosphosulfate (Lin & Levy, 1981; Slattery *et al.*, 1987). Due to the ample availability of UDP-glucuronate *in vivo*, glucuronidation is considered to be an important protective mechanism in cases where sulfation may have reached maximal capacity.

Individual deficiencies in the capacity of either one of these nonoxidative pathways may be significant in contributing to the potential for acetaminophen toxicity. Various studies have reported inter-individual and ethnic differences in acetaminophen metabolism. Mucklow *et al.* (1980) have reported lower clearances and longer half-lives of acetaminophen in Asian immigrants as compared to white Caucasians residing in London. Sommers *et al.* (1987) found higher acetaminophen clearances in black villagers in Southern Africa than had been previously observed in Caucasians. Critchley *et al.* (1986), while reporting markedly lower recoveries of GSH and glucuronide conjugates in black Ghanaians and Kenyans as compared to Caucasians, found no ethnic differences in the recovery of sulfate esters.

Genetic factors involved in the glucuronidation of endo- and xenobiotics have been inferred to be significant contributors to inter-individual variability in the disposition of acetaminophen and other drugs. De Morais *et al.* (1989) reported a 31% decrease in the formation of acetaminophen glucuronide in subjects with Gilbert's syndrome, a condition which is caused by the deficient activity of bilirubin glucuronyl transferase, resulting in the accumulation of bilirubin *in vivo*. Yue *et al.* (1989) have found that, upon administration of codeine, Caucasian subjects phenotyped as poor debrisoquine hydroxylators excreted significantly less morphine-3- and morphine-6-glucuronides, and significantly more codeine-6-glucuronide (C6G), as compared to extensive hydroxylators of debrisoquine. In addition, C6G excretion accounted for 45% of the codeine dose in Oriental subjects and 62% of the dose in Caucasians. It was not clear, in this particular study, whether the lower formation of C6G in Orientals was independent of their capacity for the parallel dispositional pathways of *O*- and *N*-demethylation. However, in a more recent report, a significantly lower partial clearance via glucuronidation was shown to be responsible for a decreased overall clearance of codeine in Orientals (Yue *et al.* 1991).

Inter-subject and ethnic differences in acetaminophen disposition have pharmacogenetic and toxicological implications. This study was conceived to investigate the differences in acetaminophen metabolism between ethnic groups, and between individual subjects in those groups. Environmental factors have been shown to significantly influence acetaminophen metabolism. Enzyme induction as a result of cigarette smoking, chronic intake of anticonvulsants such as phenytoin and carbamazepine (Miners *et al.*, 1984), oral contraceptive steroids (Miners *et al.*, 1986), and ethanol (Critchley *et al.*, 1982) have been reported to change the metabolic profile of acetaminophen *in vivo*. Such confounding environmental factors must be controlled when the influence of genetic factors on the metabolism of acetaminophen is being considered.

Methods

Subjects

Two groups of subjects were studied: (1) 125 white Caucasians; and (2) 33 Orientals. Of the Caucasian subjects, 41 were female (32.8%), whereas 11 of the Oriental subjects were female (33.3%). All subjects were healthy students or university staff residing in Toronto. Although more than 158 subjects were originally tested, a number of individuals were excluded from the study according to their intake of known enzyme inducers. Individuals included in the analysis were non-smokers and did not regularly ingest ethanol or enzyme-inducing medications, including oral contraceptives.

Protocol

Food intake was regulated immediately prior to and during the study period. Each subject was given 650 mg of acetaminophen before retiring to sleep, and all overnight urine (8 h) was collected. After measurement of urine volume and pH, the individual samples were stored as frozen aliquots at $-20°C$ for future analysis.

Chromatographic assay

Acetaminophen, its sulfate, glucuronide, mercapturic acid, and cysteine conjugates were estimated by reversed-phase high performance liquid chromatography. A Waters model 590 programmable pump was used to supply the mobile phase at a rate of 1.2 ml min^{-1}. After the frozen aliquot was thawed to room temperature, 50 μl of the sample was diluted in 2 ml of the mobile phase, which consisted of 4% methanol and 1% isopropanol, in 1% acetic acid. 50 μl of the internal standard, 1,7-dimethylxanthine, was added, and 15 μl of the mixture was injected onto the column (25 cm × 4.6 mm, 5 μm OSD Ultrasphere). Samples were injected using Waters WISP 710B programmable injector. The compounds were detected with a Waters model 490 programmable wavelength UV detector. Detection wavelength was 250 nm, with AUF = 0.02. Chromatograms were analysed with the use of a Shimadzu C-R4A Chromatopac.

Analysis

The observed quantities of the parent drug acetaminophen and its metabolites were converted to percentages of the total amount recovered in the urine in 8 h. Statistical and probit analyses were performed using the computerized statistical package SAS (SAS Institute Inc., Cary, NC, USA), and the normality test variable (NTV) plot (Endrenyi & Patel, 1991). The probit and NTV analyses are sensitive graphical tests for normality (Caldwell *et al.*, 1982) and were utilized in a complementary manner. When comparisons were made between the two ethnic groups, Student's t-test was used, with $p < 0.05$ (two-tailed) accepted as the minimum level of significance.

Results

The amounts of acetaminophen and its metabolites were expressed as percentages of the total recovered in 8 h urine for each of the two ethnic groups (Table 1). No significant differences were indicated between the Caucasian and Oriental groups with respect to the mean percentages recovered as sulfate (44.1 ± 0.91 vs 44.0 ± 1.70) or glucuronide conjugates (51.5 ± 0.94 vs 51.8 ± 1.74). However, the Caucasian group showed significantly greater percentages recovered as mercapturic acid (1.12 ± 0.04 vs 0.83 ± 0.07, $p < 0.005$) and cysteine conjugates (1.50 ± 0.05 vs 1.14 ± 0.42, $p < 0.005$), as compared to the Oriental group.

Both probit and NTV analyses indicated that the distributions of sulfate and glucuronide conjugates of acetaminophen recovered in 8 h urine included at least two modes in each of the two ethnic groups (Figs 2 and 3). As indicated by the inflection points of the probit plots, approximately 20% of Caucasian subjects and 33% of Oriental subjects represent groups with a relatively *larger* percentage of the dose as glucuronide (Fig. 2a). These proportions are more sensitively indicated by the corresponding NTV plots (Fig. 2b). In addition, the probit plot appeared to indicate that six of 125 (4.8%) Caucasian subjects appeared to excrete a *very small* percentage of the dose as glucuronide (Fig. 2a). This observation was not confirmed by the corresponding NTV plot (Fig. 2b). Graphical analysis of the respective distributions of sulfate ester excreted in 8 h urine indicates that 26% of Caucasians and 33% of Orientals excreted a *smaller* percentage of the dose as sulfate (Fig. 3).

Figures 4 and 5 show the distributions of mercapturic acid and cysteine excretion percentages respectively. Both probit plots indicate the differences in the mean excretion percentages between the Caucasian and Oriental groups (Figs 4a and 5a). In addition, among Caucasian subjects, 4.8% and 13.6% excreted

Table 1. Statistical parameters (mean ± SE) of the fractional recoveries (expressed as percentages) of acetaminophen metabolites in 8 h urine for Caucasian and Oriental subjects

Metabolite	*Caucasian* (125 *subjects*)	*Oriental* (33 *subjects*)
Glucuronide	51.5 ± 0.94	51.8 ± 1.74
Sulfate	44.1 ± 0.91	44.0 ± 1.70
Mercapturate	1.12 ± 0.04	0.89 ± 0.07*
Cysteine	1.50 ± 0.05	1.14 ± 0.42*

*$p \leq 0.005$.

relatively high amounts of the dose as cysteine and mercapturate conjugates respectively (Figs 4 and 5). All putative modal proportions are indicated in Table 2.

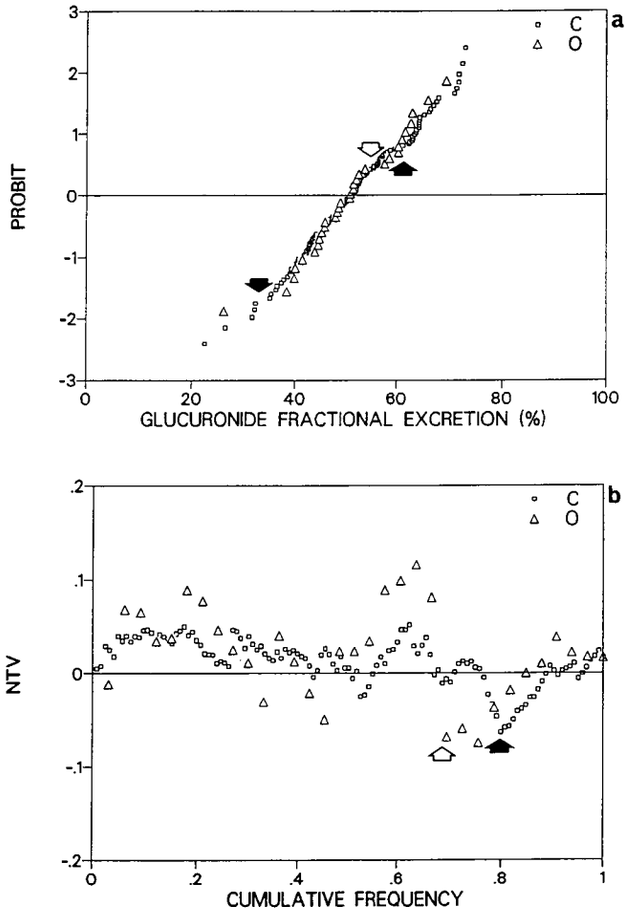

Fig. 2. Distributions of the fractional excretion of acetaminophen glucuronide as represented by (a), probit and (b), NTV plots. Solid arrows mark potential modal divisions in the Caucasian group, whereas open arrows mark potential modal divisions in the Oriental group. Note that the putative group of very slow glucuronidators is indicated only by the probit plot.

The ratio of mercapturate to total GSH-derived metabolites (cysteine and mercapturate conjugates) did not conform to a normal distribution (Fig. 6). Bimodality was apparent in both groups, with 61% of Caucasians and 39% of Orientals showing a lower ratio.

Discussion

Glucuronidation and sulfation of acetaminophen were characterized by multimodal distributions in both the Caucasian and Oriental groups. The modal proportions were different in each group, with 20% of Caucasians, and 33% of Orientals appearing to be relatively extensive glucuronidators (Table 2). Conversely, 26% of Caucasians, and 33% of Orientals were conspicuously *slow* sulfators. These proportions indicate that, among the tested individuals, a negative

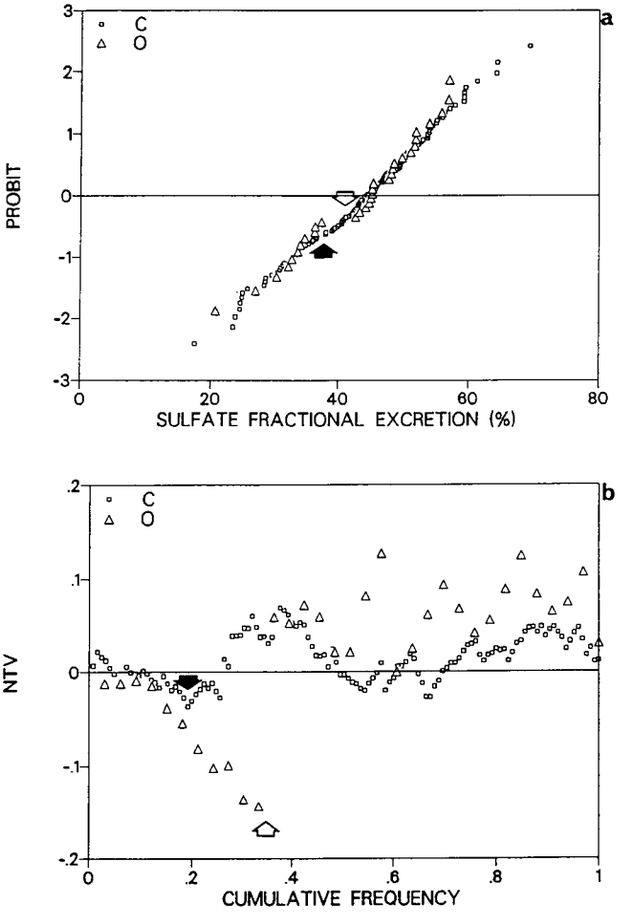

Fig. 3. Distributions of the fractional excretion of acetaminophen sulfate ester as represented by (a), probit and (b), NTV plots. Solid arrows mark potential modal divisions in the Caucasian group, whereas open arrows mark potential modal divisions in the Oriental group.

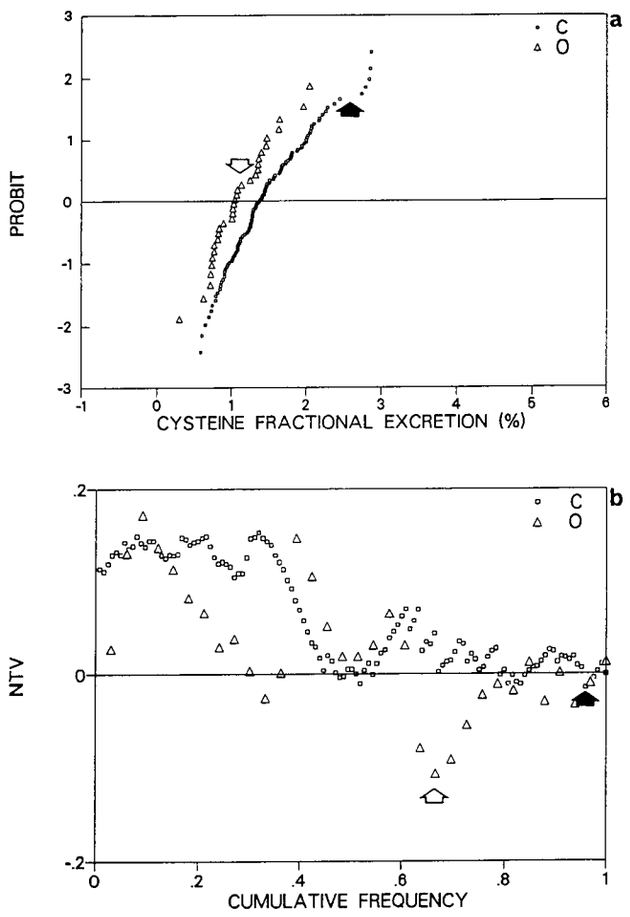

Fig. 4. Distributions of the fractional excretion of the cysteine conjugate as represented by (a), probit and (b), NTV plots. Solid arrows mark potential modal divisions in the Caucasian group, whereas open arrows mark potential modal divisions in the Oriental group.

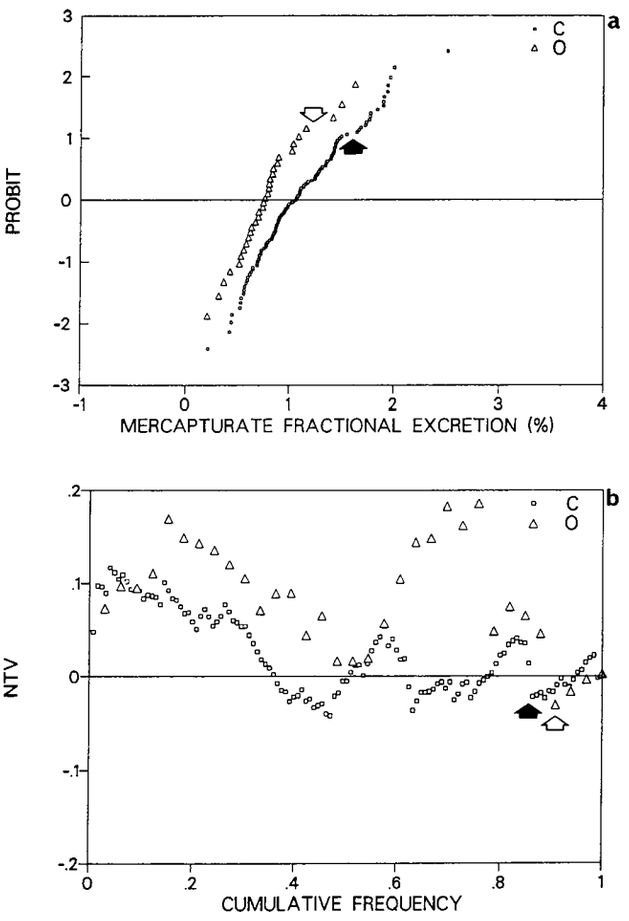

Fig. 5. Distributions of the fractional excretion of the mercapturic acid conjugate as represented by (a), probit and (b), NTV plots. Solid arrows mark potential modal divisions in the Caucasian group, whereas open arrows mark potential modal divisions in the Oriental group.

correlation may exist with respect to the fraction of acetaminophen recovered as glucuronide, and the fraction recovered as sulfate. A confirmation of this is illustrated in Fig. 7a. The correlation coefficient between sulfate and glucuronide recovery approaches unity in the negative direction ($r = -0.97$). Caldwell *et al.* (1981) have previously reported that the ratio of urinary acetaminophen glucuronide to sulfate (G/S ratio) displayed skewness, and possibly bimodality in a test group of 62 medical students and laboratory staff.

Critchley *et al.* (1986) have reported highly significant ethnic differences in the mean fractional recoveries of mercapturic acid and cysteine conjugates of acetaminophen between Caucasians and Africans from Ghana and Kenya. The Africans were observed to have markedly lower recoveries of these metabolites as compared to Caucasians. Even lower recoveries have been reported in Oriental and Indian Asians in Singapore (Koh, 1985). These findings, and the lower mean fractional recoveries of cysteine and mercapturic acid conjugates observed in this study (Table 1) are consistent with the reduced capacity for microsomal oxidation in Africans and Asians.

As stated previously, the conversion of the cysteine conjugate of acetaminophen to mercapturate is catalysed by the membrane-bound enzyme cysteine-*S*-conjugate *N*-acetylcysteine (Duffel & Jakoby, 1982). The ratio of mercapturate to total GSH-derived metabolites excreted is theoretically indicative of the activity of this enzyme. Both Caucasian and Oriental groups displayed evidence of bimodality with respect to the *N*-acetylation of the cysteine conjugate to mercapturate (Fig. 6). It should be noted that the distinction between those subjects with relatively low ratios (61% of Caucasians and 39% of Orientals) and those with

Table 2. Observed polymorphic proportions (expressed as percentages) from the distributions of acetaminophen metabolites in Caucasian and Oriental subjects

Metabolite	*Phenotype*	*Caucasian (125 subjects)*	*Oriental (33 subjects)*
Glucuronide	Fast	20.0	33.0
	Slow	75.2	67.0
	Very slow	4.8*	
Sulfate	Fast	74.0	67.0
	Slow	26.0	33.0
Cysteine	Very fast	4.8	36.4
Mercapturate	Very fast	13.6	12.1

*Indicated only by the probit plot, not by the NTV plot.

higher ratios was not obviously striking, being better demonstrated by the more sensitive NTV analysis than by the probit analysis.

Lower formation of acetaminophen glucuronide in subjects with Gilbert's syndrome, with a concurrently higher formation of mercapturic acid and cysteine conjugates has been reported by de Morais *et al.* (1989). The 4.8% of Caucasians found to be very slow glucuronidators of acetaminophen (Table 2) may form a potential group of subjects with Gilbert's syndrome (occurring in 5–7% of humans) (Arias *et al.*, 1969). However, they did not correlate with the 4.8% of Caucasians who excreted a relatively high percentage of cysteine conjugate. Figure 6b indicates no significant correlation, either negative or positive, between glucuronidation and GSH conjugation. Therefore it is not clear whether the findings of this study are consistent with those of de Morais *et al.* (1989). It must be noted however, that the metabolic collection protocols were not consistent between this study and that carried out by de Morais *et al.* (1989). Although no correlation was observed between the oxidative pathway and glucuronidation alone (Fig. 7b), there was a significant negative correlation between the oxidative pathway and the sum of glucuronide and sulfate conjugation ($r = -0.82$, Fig. 7c). This seems to indicate that susceptibility to acetaminophen toxicity may be related to decreased activity of both nonoxidative pathways rather than glucuronidation alone.

The factors underlying the phenotypic proportions of slow and fast glucuronidators were not specifically sought in this study. However, it is possible to infer from the strong negative correlation between sulfate and glucuronide conjugates in both ethnic groups, that a compensatory mechanism may be at work. For example, an increase in glucuronidation may compensate for relatively low sulfation under conditions which compel sulfation to reach its maximal capacity relatively quickly. In addition, the observed ethnic differences in the proportions of slow and fast glucuronidators and sulfators indicate that genetic factors may be partially responsible for the metabolic variability.

Nash *et al.* (1984), following a study in mono- and dizygotic twins, concluded that environmental rather than genetic factors were primarily responsible for observed individual differences in acetaminophen metabolism. Although environmental influences on the disposition of acetaminophen are well-documented as being important, the results of this investigation suggest that genetic influences may also be significant. This is consistent with recent molecular studies which confirm that defects at the genetic level affect

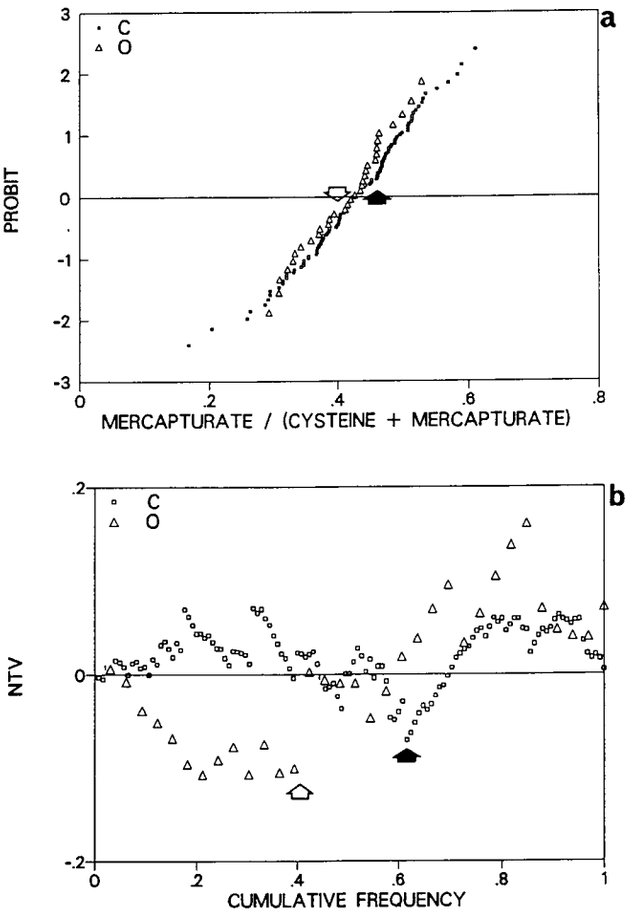

Fig. 6. Distributions of the ratio of mercapturate to total GSH-derived conjugates excreted in urine represented by (a), probit and (b), NTV plots. The ratio is indicative of the catalytic activity of cysteine-*S*-conjugate *N*-acetyltransferase. The solid arrows mark a potential modal division in the Caucasian group, and open arrows indicate a potential division in the Oriental group.

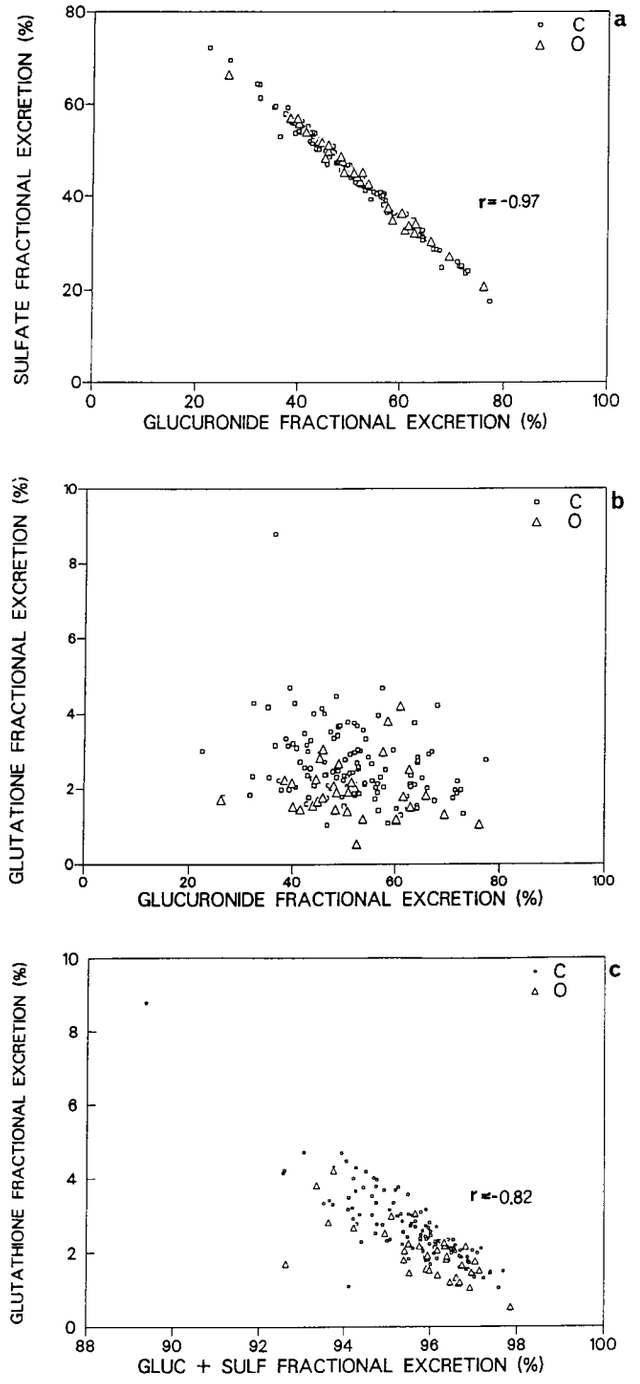

Fig. 7. Correlation plots between the fractional excretions of (a) acetaminophen glucuronide and the sulfate ester, (b) acetaminophen glucuronide and the glutathione conjugates, and (c) acetaminophen GSH conjugates and the sum of glucuronide and sulfate conjugates.

glucuronidation capability *in vivo* (Sato *et al.*, 1991), and that differential processing of the human phenol/bilirubin UDP glucuronyltransferase gene may result in the expression of two functionally different isozymes (Wooster *et al.*, 1991).

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