A. W. Jones,[1] *Ph.D.*

Disappearance Rate of Ethanol from the Blood of Human Subjects: Implications in Forensic Toxicology

REFERENCE: Jones, A. W., **"Disappearance Rate of Ethanol from the Blood of Human Subjects: Implications in Forensic Toxicology,"** *Journal of Forensic Sciences*, JFSCA, Vol. 38, No. 1, January 1993, pp. 104–118.

ABSTRACT: This article outlines major developments in knowledge about the human metabolism of ethanol. The results of a large number of controlled experiments aimed at measuring the rate of ethanol elimination from the blood are reported. The factors that influence the rate of ethanol elimination from blood, such as the amount of ethanol ingested, the drinking habits of the subjects, and the effect of food taken together with, or before, drinking were investigated. The slowest rate of ethanol disappearance was observed in a healthy male subject who ingested 0.68 g ethanol/kg body weight after an overnight (8 h) fast; the β-slope was 9 mg/dL/h. The fastest rate of ethanol disappearance was observed in a male chronic alcoholic during detoxification; the β-slope was 36 mg/dL/h. This four-fold difference in the rate of ethanol disposal should be considered when the pharmacokinetics of ethanol become an issue in drinking and driving trials, for example, when retrograde estimations are attempted.

KEYWORDS: toxicology, ethanol, blood, analysis, elimination rate, alcoholics, β-slope, metabolism, DWI

The rate of disappearance of ethanol from the blood has important ramifications in forensic toxicology as well as in biomedical alcohol research. It sometimes happens that the blood alcohol concentration (BAC) at the time of driving must be estimated from the BAC existing several hours later, for example, at the time of obtaining a blood sample. This entails making a back-estimation or retrograde extrapolation of the BAC. For this purpose, certain assumptions must be made about the pharmacokinetics of ethanol for a given individual [*1*]. The magnitude of biologic variations in the elimination rate of ethanol should be considered when back-estimation of BAC becomes an issue in drunk driving litigation. Besides an average rate of ethanol elimination, one might consider using a reference interval, that is, a range of values that includes some fixed percentage (95% or 99%) of the β-slopes for the relevant population [*2*]. Those individuals with an unusually swift rate of ethanol disposal, might have developed metabolic tolerance as one of the consequences of prolonged heavy drinking [*3*]. The notion of using biochemical markers to detect increased risk of alcoholism is being investigated by several research groups [*4–6*]. Indeed, a high rate of ethanol disappearance from the blood was suggested as one such marker for overconsumption of ethanol [*7*].

[1]Associate Professor, Department of Forensic Toxicology, National Institute of Forensic Medicine, University Hospital, Linköping, Sweden.

Paper presented at the 43rd Annual Meeting of the American Academy of Forensic Sciences, Anaheim, California, February 1990.

Received for publication 15 Feb. 1992; revised manuscript received 11 May 1992; accepted for publication 13 May 1992.

The seminal work of Erik MP Widmark, published during the first half of the century, has dominated the way that forensic scientists, and others, evaluate and interpret the pharmacokinetics of ethanol [*8*]. Using a reliable method for the determination of ethanol in small volumes of blood, Widmark mapped out the concentration-time profiles and presented the results in quantitative terms. After the peak concentration in the blood was reached, the disappearance stage of ethanol pharmacokinetics seemed to follow a near straight line course. However, the slope of the rectilinear decay phase varied between subjects and was slightly steeper in women compared with men. Widmark denoted the negative slope of the BAC elimination phase with the Greek letter β and reported a mean value of 16 mg/dL/h for healthy individuals with moderate drinking habits. The lowest value obtained was 10 mg/dL/h and the highest 25 mg/dL/h.

It should be noted that the biochemical pathways of ethanol metabolism were unknown at the time of Widmark's work. The Danish physiologist Lundsgaard [*9*] was among the first to demonstrate that the metabolism of ethanol occurred mainly in the liver. The rate of removal of ethanol from blood was considerably slower in eviscerated animals or when a total hepatectomy was performed. However, the β-slope was 5.5 mg/dL/h in hepatectomized dogs compared with 16 mg/dL/h in control animals with an intact liver [*10*]. In 1948, Roger Bonnichsen and his associates working with extracts from horse liver managed to crystallize alcohol dehydrogenase (ADH) in a relatively pure form [*11*]. This basic research furnished samples of the enzyme responsible for ethanol metabolism in all mammals. Later, ADH was also shown to exist in other organs and tissue such as the kidney, the stomach mucosa, and the retina but this enzyme was predominantly located in the liver cytosol [*12*]. Recent work on the genetics of human ADH has identified the existence of multiple molecular forms that give rise to three distinct enzyme subclasses, denoted ADH I, ADH II and ADH III [*13*]. Several isozymes of ADH are present within each subclass, particularly class I, and these have characteristic kinetic properties such as different activities, k_m values for ethanol, as well as specificity for substrates. Differences in the rate of ethanol disposal between individuals might be explained by the particular isozymes of ADH that a person inherits. Moreover, a person's drinking habits, the rate of ethanol metabolism, and predisposition for becoming dependent on alcohol are tightly linked with environmental and genetic influences on the activity of alcohol metabolizing enzymes [*14–18*].

Besides the ADH pathway of ethanol metabolism, the liver microsomes are capable of oxidizing ethanol as well as many other drugs and environmental chemicals [*19*]. This secondary pathway for oxidation of ethanol involves cytochrome P_{450} enzymes and is known as the microsomal ethanol oxidizing system (MEOS). MEOS has a higher k_m value for ethanol, being about 36 to 46 mg/dL compared with 1 to 9 mg/dL for the class I isozyme of human liver ADH [*20*]. A particularly important property of the MEOS pathway is its ability to operate more effectively after repeated and prolonged exposure to ethanol, a process known as enzyme induction [*21*]. This helps to explain the faster rates of ethanol degradation in alcoholics compared with occasional drinkers [*22*]. Moreover, the ethanol-inducible form of cytochrome P_{450} (P-450IIE1) seems to be involved in the metabolism of certain prescription drugs, organic solvents, such as acetone, and volatile hydrocarbons. Accordingly, longstanding abuse of alcohol tends to make alcoholics more prone to the toxic effects of industrial chemicals and solvents that often become transformed in the liver into more reactive metabolites [*23,24*].

It appears feasible to slow down the rate of ethanol metabolism by administration of pyrazole or some of its 4-alkyl derivatives [*25,26*]. These agents are competitive inhibitors of the class I isozymes of ADH. Indeed, 4-methyl pyrazole has been suggested for use in emergency situations to treat patients poisoned with methanol or ethylene glycol. The 4-MP will block conversion of these alcohols into toxic metabolites, formic acid and oxalic acid respectively [*27*]. The activity of ADH is lower in starved or malnourished individ-

uals, particularly those with protein deficiency. Prolonged fasting seems to influence the rate of ethanol disappearance from the blood [*28*]. Diseases of the liver associated with alcoholism, such as cirrhosis, might be thought to decrease the rate of ethanol disposal [*29*]. However, the clinical pharmacokinetics of ethanol in patients with liver cirrhosis is not sufficiently well documented [*30,31*]. Expert opinion on this topic is divided and the results of experiments are equivocal because of the confounding influence of poor nutrition and state of health of the alcoholics used as the test subjects [*32*]. At the present time it is difficult to draw any firm conclusions about the influence of liver disease on the rate of ethanol metabolism. Looking at the literature, one finds that the elimination of ethanol from the blood in cirrhotic patients falls within the same reference interval as for healthy individuals [*33*]. However, patients suffering from cirrhosis with portal hypertension might have a lower capacity to eliminate ethanol but this seems to depend on a less efficient flow of blood through the liver [*34*].

A number of studies have shown that the rate of ethanol oxidation is faster if large doses (1 to 2 g/kg) of fructose are taken together with a moderate dose of ethanol [*35,36*]. Several biochemical mechanisms support this notion, such as, a faster regeneration of NAD^+ from NADH, the redox pair involved in the conversion of fructose into sorbitol [*37*]. However, the efficacy of the fructose-effect on the rate of ethanol metabolism seems to depend on the particular experimental design [*36*]. The dose of ethanol and sugar, or both, and the route and timing of administration are important variables [*38*]. Large doses of fructose enhance the rate of ethanol disposal in those individuals who normally have a low capacity to oxidize ethanol, for example, those with low ADH activity in the liver. However, if ethanol is ingested together with a hypertonic solution of fructose, this might cause delayed gastric emptying because of the osmotic effects of the sugars [*39*]. This leads to a much slower absorption of ethanol, a lower peak BAC and a smaller area under the blood-concentration time profile. However, this effect of sugars should not be confused with a more rapid degradation of ethanol in the liver. Furthermore, if ethanol remains in the stomach for unusually long periods of time, this gives more opportunity for presystemic metabolism to occur by the action of ADH located in the gastric mucosa [*40*]. However, the significance of gastric ADH in the disposal of ethanol is still under debate.

All in all, it seems that the rate of ethanol elimination is highest in heavy drinkers and alcoholics who have been exposed to ethanol for long periods of time. Under these circumstances, the MEOS enzymes are boosted to full capacity. With this background about the factors known to influence the rate of ethanol elimination in humans, it is not surprising to find that the β-slope might differ by three to four fold in the population of drinking drivers.

Materials and Methods

Subjects and Conditions

Healthy male volunteers (N = 150) were recruited for the main series of experiments that involved the ingestion of neat whiskey. Their ages ranged from 20 to 60 years and their body weights ranged from 60 to 109 kg. Ethanol was administered either in the form of neat whiskey (40% v/v) or as pure ethanol (95% v/v) diluted with orange juice to give a 15 to 20% v/v cocktail. The subjects fasted overnight (8 to 10 h) and then ingested alcohol between 8:00 and 9:00 a.m. the next morning. The dose of ethanol was either 0.35, 0.51, 0.68, 0.85 or 1.05 g ethanol/kg body weight and was ingested in 15, 20, 25 or 30 min depending on the dose. Another group of healthy male volunteers (N = 12) took part in a crossover design study and were given a daily dose of either cimetidine (800 mg), ranitidine (600 mg), omeprazole (25 mg) for seven successive days or a no-

drug treatment [*41*]. After an overnight fast and exactly 1 h after the last dose of the drug they drank 0.80 g ethanol/kg within 30 min. This study has been reported in detail elsewhere [*41*]. These drugs are widely prescribed as inhibitors of gastric acid secretion but this treatment had no effect on the pharmacokinetics of ethanol and the β-slopes were combined for the purpose of this review.

In a recent experiment (Jones and Jönsson to be published) healthy male volunteers ($N = 10$) consumed a standard breakfast consisting of 150 mL orange juice, 250 g yogurt, 1 boiled egg, 2 cheese sandwiches and 1 cup of coffee. Immediately after the meal was finished, between 8:00 and 8:30 a.m., the subjects ingested ethanol solvent (0.8 g/kg body weight) diluted with orange juice. Samples of venous blood were obtained through an indwelling catheter for up to 7 h after the start of drinking. The same subjects returned to the laboratory 1 week later and drank the same dose of ethanol after an overnight (10 h) fast. Other healthy subjects ($N = 9$) drank 2 bottles of beer (660 mL) corresponding to between 19 and 25 g ethanol. The beer was ingested either on an empty stomach or together with a meal of pasta [*42*]. Another recently reported study into the effect of food on ethanol pharmacokinetics, involved ingestion of a fairly large dose of ethanol (1.43 g/kg) as mixed drinks together with a large meal over 90 min [*43*].

Chronic alcoholics, 16 men and 4 women, had been drinking heavily for several weeks or months and were admitted to hospital for detoxification. Their BAC on arrival at the clinic was measured indirectly with an Alcolmeter S-D2 breath alcohol analyzer (Lion Laboratories, Barry, Wales). If the estimated blood alcohol concentration exceeded 250 mg/dL, the subjects were recruited for this study. The hospital staff then obtained samples of venous blood at 3 to 6 h intervals for 24 h after admission and no medication was given to the patients during the period of detoxification.

Evaluation of Double Blood Samples from Drunk Drivers

Two consecutive samples of venous blood were taken from each of 188 suspected drunk drivers. The time interval between the double blood samples was about 1 h on the average. The rate of alcohol elimination from the blood was calculated as $(BAC_1 - BAC_2)/(t_2 - t_1)$. In three cases the BAC was rising (1.6%) and in another nine cases there was no change in the BAC (4.7%) over the time interval studied. These 12 cases (6.3%) were removed from the material and a frequency distribution of the apparent rates of disappearance of ethanol from blood was plotted.

Sampling of Blood and Determination of Ethanol

Blood specimens for determination of ethanol were either obtained by pricking a fingertip (capillary blood) or from an indwelling venous catheter. Ethanol was determined in capillary blood by an automated enzymatic procedure [*44*] and in venous blood by headspace gas chromatography HSGC [*45*]. The standard deviation (SD) of both of these methods of analysis increase with the concentration of ethanol in the blood specimens. At a mean BAC of 100 mg/dL, the SD of the HSGC method was about 1 mg/dL. At a mean BAC of 51 mg/dL, the SD of the enzymatic method was 1.6 mg/dL.

Evaluation of Results

Concentration-time profiles of blood-ethanol were plotted for each of the subjects and the rate of alcohol disappearance from the blood was calculated as described by Widmark [*8*]. This method rests on the assumption of a linear decay profile during the postabsorptive phase. The elimination rate constant (β-slope) was either determined by linear regression analysis of the concentration-time data or by fitting the best straight line to the data

points by eye. The y-intercept (C_0) of the regression line denotes the concentration of alcohol in blood if the entire dose was absorbed and distributed immediately after intake without any metabolism occurring. The x-intercept (min_0) gives an estimate of the time for the complete elimination of ethanol from the blood neglecting the nonlinear disappearance phase that starts when the BAC has reached 5 to 10 mg/dL. The ratio C_0/min_0 gives a check on the rate of ethanol disappearance from blood. Other pharmacokinetic parameters such as the apparent volume of distribution and the elimination from the whole body are not reported in this paper.

Results

Figure 1 gives examples of the concentration time profiles of ethanol in capillary blood for 9 different subjects who had ingested neat whiskey; 0.51, 0.68, or 0.85 g ethanol/kg body weight. The peak BAC and the areas under the curves increased as the dose of ethanol ingested increased. The plots in Fig. 1 for some subjects show an abrupt fall in the BAC between 30 to 60 min after the start of drinking this bolus dose of neat whiskey. This provides a good example of the so called "diffusion plunge." If the rate of disappearance of alcohol from the blood (β-slope) was calculated from the change in BAC per unit time on a diffusion plunge, then abnormally high values would be obtained. The relationship between the β-slopes and the dose of ethanol taken as neat whiskey is shown in Table 1. As expected, the average peak BAC was higher when the dose of alcohol was increased. Moreover, the rate of disappearance of ethanol from blood was faster by 28% when the dose was raised from 0.51 to 0.85 g/kg as shown by analysis of variance ($F = 37.0$, d.f = 2 and 77, $P < 0.001$).

The disappearance rates of ethanol from the blood (β-slope) after 65 subjects drank an orange juice cocktail (0.80 g ethanol/kg) are shown in Fig. 2. The values are arranged in rank order of increasing magnitude and 12 of the subjects were tested on four separate occasions. The mean rate of elimination was 14.1 mg/dL/h and the 99% reference interval for a new subject ranged from 11 to 18 mg/dL/h. Figure 3 presents an example of the BAC profile in one healthy male subject who drank ethanol (0.80 g/kg) diluted with orange juice. Note the relatively slow absorption phase and the longer time needed to reach the postpeak phase (2 h after start of drinking). It was difficult to obtain a reliable estimate of the β-slope in this subject. The average β-slope calculated for blood samples obtained between 2 and 6.5 h post drinking was 7.5 mg/dL/h and is the lowest value depicted in Fig. 2 and is clearly an outlier. Two other estimates of the β-slope are shown by the broken diagonal lines in Fig. 3, being 10.8 mg/dL/h and 5.1 mg/dL/h. Interestingly, the rate of elimination of alcohol from blood was boosted by 100% when the subject consumed a meal 4 h after the start of drinking. This example shows the difficulty in obtaining a reliable estimate of the β-slope from the BAC profile for some individuals.

Figure 4 gives examples of BAC profiles for two subjects after they had ingested 0.8 g ethanol/kg on an empty stomach and one week later immediately after breakfast. The β-slopes were steeper in the fed state for both subjects (18 and 19.8 mg/dL/h) compared with after drinking ethanol on an empty stomach (11.7 and 15.9 mg/dL/h). The interaction between ethanol and food components leads to a faster rate of elimination with a lower peak BAC and a smaller area under the curve. The bioavailability of ethanol is clearly less when taken after a meal.

Figure 5 is a frequency distribution of the apparent rate of elimination of alcohol from the blood of apprehended drunk drivers calculated from two consecutive samples. The frequency distribution seems to follow a Gaussian curve; mean 19.1 (SD 6.0), coefficient of skewness 1.01, and kurtosis 4.05. The spread of values was from 2 to 49 mg/dL/h excluding 12 values that were either negative ($N = 3$) or zero ($N = 9$). The average time interval between the double blood samples was 62 min (range 20 to 163) and the

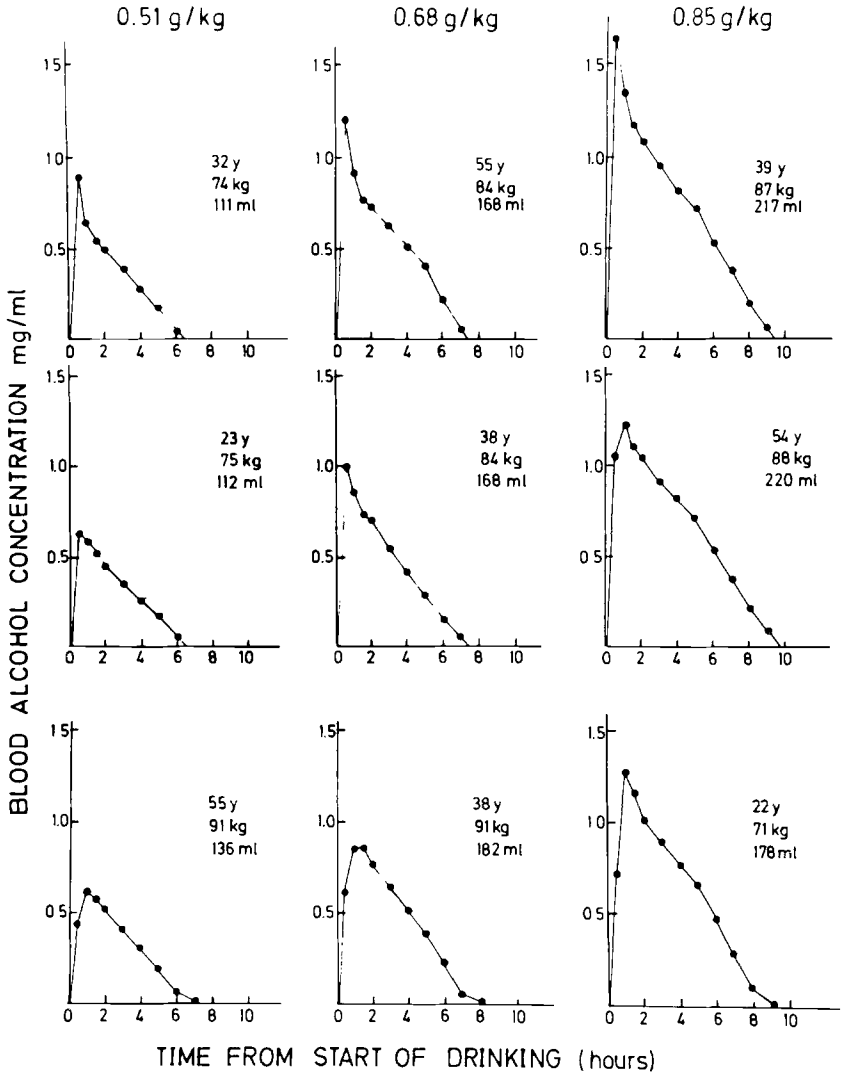

FIG. 1—*Examples of the concentration-time profiles of ethanol after healthy men drank neat whiskey in the morning after an overnight fast. The doses of ethanol ingested were 0.51, 0.68, or 0.85 g ethanol/kg body weight and samples of fingertip blood were analyzed. The age (y), body weight (kg) and volume of whiskey (mL) consumed is shown for each subject.*

TABLE 1—*Relationship between the disappearance rate of alcohol from blood β-slope and the dose of ethanol administered. Healthy men drank 0.51, 0.68 or 0.85 g ethanol/kg body weight in the form of neat whiskey on an empty stomach. N = number of subjects, SD = standard deviation, CV% = coefficient of variation*

Dose of ethanol	N	Peak BAC mg/dL	Mean β-slope mg/dL/h	SD	CV%	Spread mg/dL/h
0.51 g/kg	16	75	11.4	0.75	6.5	9.9–12.6
0.68 g/kg	48	91	12.6	1.2	9.5	10.4–16.9
0.85 g/kg	16	131	14.6	0.90	6.2	12.5–15.6

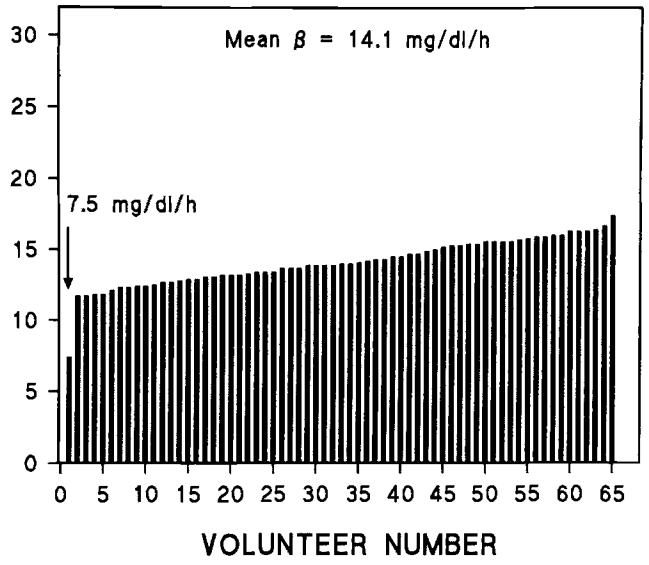

FIG. 2—*The disappearance rates of ethanol from blood (β-slopes) obtained from 65 experiments. The values are arranged in rank order of magnitude. Healthy men drank 0.8 g/kg ethanol in the morning after an overnight fast. Twelve of the subjects were tested on four occasions.*

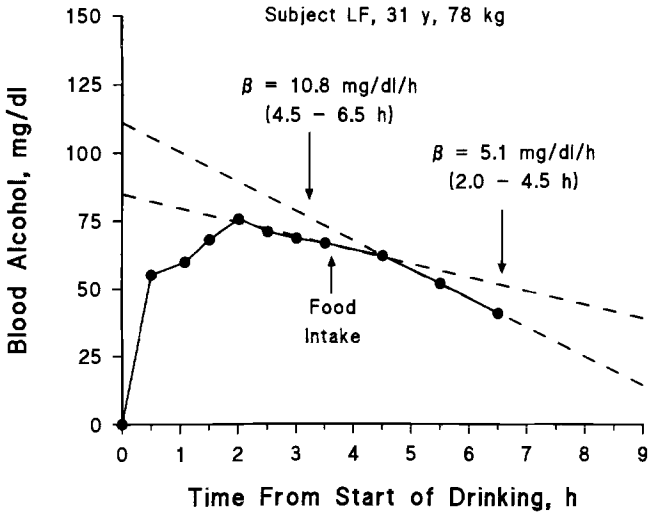

FIG. 3—*Example of an abnormal concentration-time profile of ethanol in one healthy male subject who drank 0.8 g/kg ethanol in the morning after an overnight fast. The average β-slope (7.5 mg/dL/h) was calculated between 2 and 6.5 h after drinking. Two other estimates of the β-slope are given, 5.1 mg/dL/h and 10.8 mg/dL/h, depending on the blood sampling time frame.*

mean BAC at the time of obtaining the first blood sample was 209 mg/dL (SD 71). The disappearance rate of ethanol (y) over the sampling interval and the starting concentration of ethanol in blood (x) were not correlated ($r = 0.16$, $P > 0.05$); the regression equation was $y = 0.15 + 0.013\,x$.

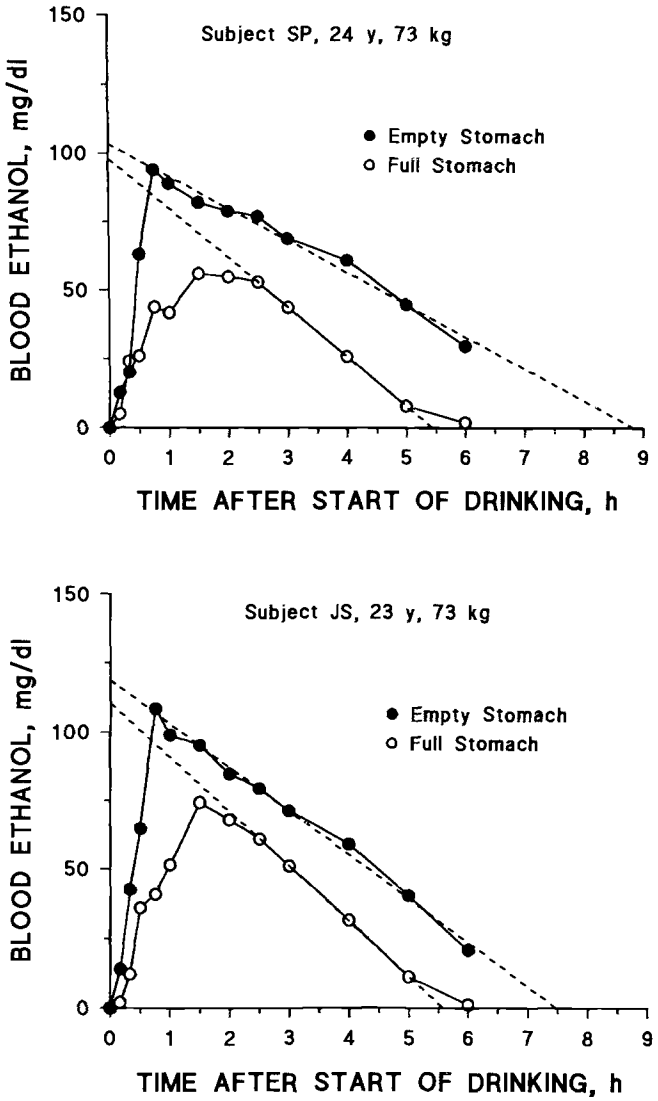

FIG. 4—*Concentration-time profiles of ethanol in venous blood for two male subjects who drank 0.8 g/kg either after an overnight fast (empty stomach) or immediately after breakfast. The peak BAC reached and the areas under the concentration-time profiles were significantly less when alcohol was taken after a meal.*

Figure 6 is a plot of the elimination profiles of ethanol in four alcoholics undergoing detoxification. A linear regression analysis gives a good fit to the data points and the correlation coefficients were 0.99 for the four subjects. The actual rates of elimination of ethanol for these four individuals ranged from 17 to 33 mg/dL/h as shown in Fig. 6.

Table 2 summarizes the results gathered from a large number of studies under different drinking conditions for moderate drinkers and alcoholics with and without food. Overall, the β-slopes ranged from 9 to 36 mg/dL/h and the fastest rate was observed in alcoholics hospitalized for detoxification.

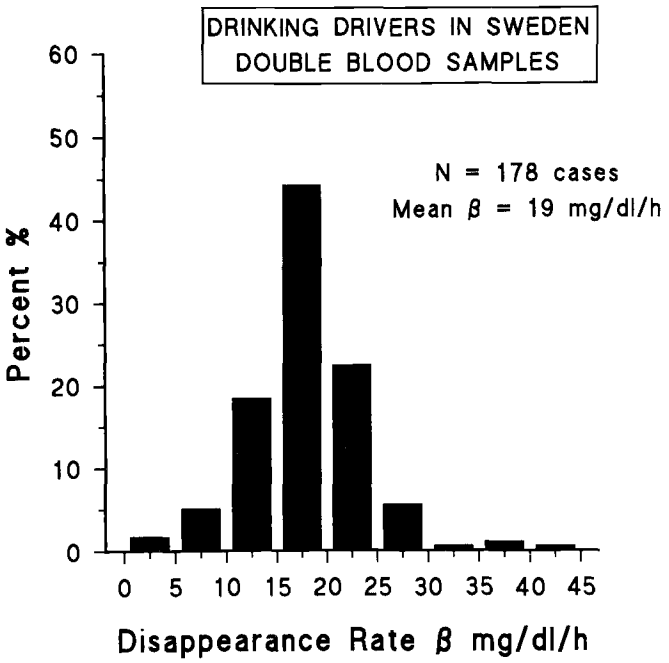

FIG. 5—*Frequency distribution of the apparent rate of disappearance of ethanol from blood of drunk drivers calculated from two consecutive samples.*

Discussion

Human beings show an enormous variation in their response to alcohol. This work shows a large variability in the rate of ethanol disappearance during controlled experiments with healthy male subjects. The experiments reported here suggest that a 4 fold variation might exist for the β-slope with a span from 9 to 36 mg/dL/h, although I am aware that other investigators have reported both lower and higher rates of ethanol disappearance from blood [*46*,*47*]. However, the raw data from these experiments are not published to allow an independent check on the results. Based on many discussions with colleagues and a careful review of the literature on alcohol metabolism, β-slopes of less than 8 mg/dL/h should be considered suspect. Such low values probably reflect a faulty experimental design or incorrect evaluation of the results. This might occur if the dose of ethanol administered was insufficient to ensure obtaining a definite postabsorptive phase [*46*]. If the absorption of alcohol from the gut is unusually prolonged, there might be an insufficient number of data points on the declining part of the curve to map out reliably the concentration-time profile. Note that a decreasing BAC profile does not necessarily mean that the postabsorptive stage of ethanol metabolism has been reached. A decreasing concentration of ethanol in blood indicates that the rate of elimination by all known pathways is occurring faster than the rate of absorption and redistribution of alcohol between the central and peripheral compartments. The absorption of ethanol might be continuing at such a slow rate that a declining concentration-time profile ensues despite part of the dose still remaining in the gut. This situation might account for some abnormally low rates of ethanol disappearance reported in the literature and Fig. 3 gives an example of this phenomenon. Such low values should be considered with reservation.

The calculation of elimination rates based on just two measurements of the BAC and the time lapse between taking the samples can yield highly variable results. Coldwell [*48*]

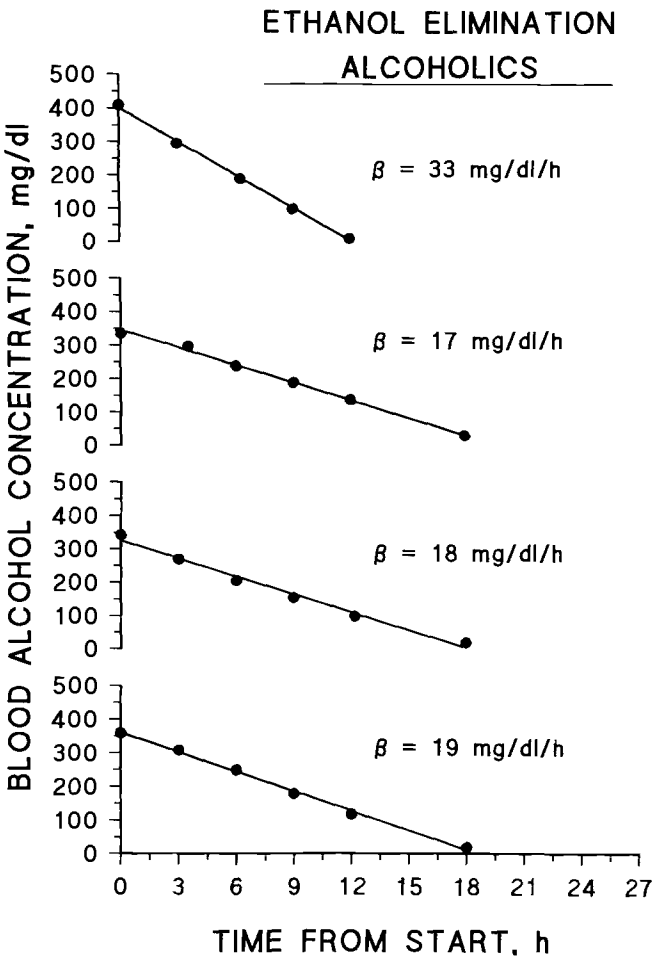

FIG. 6—*Concentration-time profiles of ethanol in four male chronic alcoholics during the first 24 h after they entered a clinic for detoxification.*

TABLE 2—*Summary of the rates of ethanol disappearance from blood (β-slope) for various drinking conditions. N = number of experiments.*

Drinking conditions	N	Mean β-slope	Spread of Values
Straight Whiskey[a]	150	13.4 mg/dL/h	9.0–18.1
Orange Juice + EtOH[a]	65	14.1 mg/dL/h	11.7–17.4
Mixed Drinks + Food	15	15.9 mg/dL/h	13.2–21.2
Two Bottles of Beer[a]	18	15.0 mg/dL/h	10.1–18.5
Alcoholics[a]	20	23.0 mg/dL/h	13.5–36.0

[a]After overnight fast.
[b]During detoxification.

reported that the rate of ethanol disappearance from blood ranged from 0 to 27.4 mg/dL/h (mean 13 mg/dL/h) and many values were less than 6 mg/dL/h. However, these results were obtained from differences in BAC for two successive blood samples divided by the time interval, which ranged from 31 to 107 min. Therefore, the extreme values of β-slope reported by Coldwell [*48*] are unrealistic and difficult to interpret because of the experimental design used, that is, just two samples of blood taken on the presumed elimination stage of the blood-alcohol time profile. The same arguments apply to the results of statistical analysis of double blood samples from drunk drivers presented here and elsewhere [*49*].

A trend toward faster rates of elimination of ethanol (steeper slopes) was noted when the dose of alcohol was raised from 0.51 to 0.85 g/kg body weight. The existence of a steeper slope in the elimination profile of ethanol speaks against the notion of zero-order elimination kinetics operating [*50–52*]. This finding might be rationalized, however, if one accepts the involvement of MEOS in the metabolism of ethanol. This enzyme system becomes more important in the oxidation of ethanol when a higher postabsorptive BAC is attained because the k_m for MEOS is about 36 to 46 mg/dL. If ethanol is ingested together with or after a meal, the emptying time of the stomach is delayed, which might lead to a slower absorption of ethanol into the portal blood. Under these conditions, the peak BAC might be 40% less compared with drinking the same dose on an empty stomach (Jones and Jönsson, to be published). The steeper β-slopes after the subjects had eaten a meal (Fig. 4) is interesting but hard to explain—perhaps the alcohol metabolizing enzymes in the liver suddenly become more active when a fasted subject receives nourishment. But despite the presence of food in the stomach it seems that the greatest rise in BAC occurs within the first 11 min 30 s after the drinking ends. In a recent study, the BAC had reached 80% of the final peak BAC within 0 to 5 min after subjects had drunk alcohol (1.43 g/kg) at the same time as they ate a large meal [*43*].

One unsettled issue about the rate of ethanol elimination is the notion of chronopharmacokinetics operating, that is, variations in absorption, distribution and elimination as a function of the time of day [*53,54*]. In most published studies dealing with the pharmacokinetics of ethanol, the volunteers are dosed in the morning between 7:00 and 9:00 a.m. By contrast, most drunk drivers are apprehended late at night or in the early hours of the morning. The results available to date do not support the notion of a marked circadian variation in the metabolism of ethanol in human beings [*54*]. However, several studies have demonstrated that gastric emptying and therefore the rate of alcohol absorption into the blood is influenced to some extent by the time of day when alcohol ingestion occurs [*55,56*].

The rate of ethanol elimination in drunk drivers has never been established in an unequivocal way. However, one approach to arrive at the rate of disappearance of ethanol in DUI suspects is to make a statistical evaluation of a large number of double blood samples. The change in BAC divided by the time interval between taking the two samples gives an estimate of the rate of alcohol disappearance for that particular time period. Although the mean β-slope derived in this way might be a reasonably good average value for this population of test subjects, many outlying values exist and these are not easy to explain. Figure 5 suggests a mean value of 19 mg/dL/h for this group of heavy drinkers with an initial average BAC of 209 mg/dL.

This work confirms that alcoholics undergoing detoxification eliminate ethanol faster than moderate drinkers. It seems clear that in heavy drinkers and chronic alcoholics other mechanisms operate to boost the rate of alcohol combustion, for example, enzyme induction and the higher activity of MEOS at high BAC [*19,20*]. But the occurrence of relatively low rates of ethanol elimination, such as 13 mg/dL/h observed with one of the alcoholics in this study, requires an explanation. This aberrant finding might be explained if the person is severely malnourished or if the liver has advanced cirrhosis [*57*]. However,

opinion in the literature is divided about the effect of cirrhosis on the rate of ethanol oxidation. Alcoholics with ascites, an accumulation of watery fluid in the peritoneum, have a pool of alcohol available for reabsorption into the blood. A back flux might account for some of the low rates of alcohol elimination observed in alcoholics. A prolonged slow absorption of alcohol back into the blood from the ascites might conceivably decrease the slope of the postabsorptive phase [*58*]. Alcoholics suffering from portal hypertension might also have a low metabolic clearance of alcohol owing to reduced portal blood flow to the liver [*34*]. Moreover, the rate of ethanol metabolism in abstinent alcoholics is less than for those who indulge in heavy drinking at the time of testing [*59–62*]. Indeed, in abstinent alcoholics, it seems that the rate of ethanol metabolism is not much different from values seen in moderate drinkers [*62*]. The higher activity of MEOS developed during the drinking spree seems to be lost after a period of abstinence when the individual is no longer exposed to ethanol [*61*]. The time course of this loss of activity in the microsomal enzymes has not been clearly established in humans [*63,64*]. Interestingly, it appears that the activity of alcohol dehydrogenase is less in liver biopsy specimens from alcoholics compared with healthy control subjects [*65,66*]. Two recent surveys dealt with the rate of ethanol elimination in alcoholics [*67,68*]. Haffner et al. [*67*] reported an average rate of elimination of 23 mg/dL/h (SD 3.8) with a spread of values from 12 to 40 mg/dL/h for 50 alcoholic subjects. Bilzer et al. [*68*] reported a mean β-slope of 20 mg/dL/h with a range from 14 to 32 mg/dL/h for tests with 36 alcoholics. However a single low value of 5 mg/dL/h (subject 2 in Ref *68*) was included in the published data and this abnormally low result deserves comment. A closer look at this single aberrant value shows that only two blood samples were used to arrive at the β-slope. The first was 15 mg/dL/h and the second 0.0 mg/dL/h with a 3 h sampling interval.

In conclusion, the β-slope of the BAC decay phase in healthy individuals of 16 mg/dL/h, first published by Widmark [*8*], still remains a valid and realistic value for male moderate drinkers. However, because of genetic and environmental factors that influence the activity of alcohol metabolizing enzymes, for a randomly selected subject from the population, the β-slope might range from 8 to 25 mg/dL/h. In alcoholics on a drinking binge, higher rates of elimination cannot be ruled out and values above 30 mg/dL/h are not unlikely. However, if blood samples are taken too soon after the end of drinking before the postabsorptive phase becomes fully established, abnormally low estimates of the β-slope are sometimes reported. In starved or malnourished individuals the rate of ethanol elimination is less than for well fed healthy subjects. Accordingly, in forensic science practice the β-slope might be as low as 8 mg/dL/h or as high as 36 mg/dL/h. This wide variation should be considered in legal proceedings dealing with retrograde estimations and related matters, for example, by use of the concept of reference intervals from clinical chemistry. In this connection, it seems reasonable that the elimination rates of ethanol observed in heavy drinkers and alcoholics provides the relevant population when an interval estimate of β-slope for drunk drivers becomes an issue in forensic practice.

References

[*1*] Jones, A. W., "Problems and Pitfalls with Back-Tracking BAC to the Time of Driving," *DWI Journal Law and Science*, Vol. 3, 1988, pp. 1–5.

[*2*] Jones, A. W., "Forensic Science Aspects of Ethanol Metabolism," in *Forensic Science Progress*, Vol. 5, A. Mahley and R. L. Williams, Eds., Heidelberg, Springer Verlag, 1991, pp. 33–91.

[*3*] Bogusz, M., Pach, J., and Stasko, W., "Comparative Studies on the Rate of Ethanol Elimination in Acute Poisoning and in Controlled Conditions," *Journal of Forensic Sciences*, Vol. 22, No. 2, April 1977, pp. 446–451.

[*4*] Crabb, D. W., "Biological Markers for Increased Risk of Alcoholism and for Quantitation of Alcohol Consumption," *Journal of Clinical Investigation*, Vol. 85, 1990, pp. 311–315.

[5] Salaspuro, M., "Characteristics of Laboratory Markers in Alcohol-Related Organ Damage," *Scandinavian Journal of Gastroenterology*, Vol. 24, 1989, pp. 769–780.
[6] Behrens, U., Worner, T., Braly, L., Schaffner, F., and Lieber, C., "Carbohydrate-Deficient Transferin (CDT), a Marker for Chronic Alcohol Consumption in Different Ethnic Populations," *Alcoholism, Clinical & Experimental Research*, Vol. 12, 1988, pp. 427–432.
[7] Olsen, H., Sakshaug, J., Duckert, F., Strømme, J. H., and Mørland, J., "Ethanol Elimination-Rates Determined by Breath Analysis as a Marker of Recent Excessive Ethanol Consumption," *Scandinavian Journal of Clinical & Laboratory Investigation*, Vol. 49, 1989, pp. 359–365.
[8] Widmark, E. M. P., *Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung*, Urban & Schwarzenberg, Berlin, 1932, pp. 1–140.
[9] Lundsgaard, E., "Alcohol Oxidation in Liver and Muscle," *Skandinavischen Archiv für Physiologie*, Vol. 77, 1937, pp. 56–57.
[10] Clark, B. B., Morrissey, R. W., Fazekas, J. F., and Welch, C. S., "The Role of Insulin and the Liver in Alcohol Metabolism," *Journal of Studies on Alcohol*, Vol. 1, 1941, pp. 663–683.
[11] Bonnichsen, R. and Wassén, A. M., "Crystalline Alcohol Dehydrogenase from Horse Liver," *Archives of Biochemistry*, Vol. 18, 1948, pp. 361–363.
[12] Von Wartburg, J. P. and Bühler, R., "Biology of Disease: Alcoholism and Aldehydism—New Biological Concepts," *Laboratory Investigation*, Vol. 50, 1984, pp. 5–15.
[13] Goedde, H. W. and Agarwal, D. P., *Alcoholism: Biomedical and Genetic Aspects*, Pergamon Press, New York, 1989, pp. 1–364.
[14] Agarwal, D. P. and Goedde, H. W., *Alcohol Metabolism, Alcohol Intolerance and Alcoholism*, Springer-Verlag, Berlin, 1990, pp. 1–184.
[15] Chambers, G. K., "The Genetics of Human Alcohol Metabolism," *General Pharmacology*, Vol. 21, 1990, pp. 267–272.
[16] Harada, S., "Genetic Polymorphism of Aldehyde Dehydrogenase and Its Physiological Significance to Alcohol Metabolism," *Isozymes*, Vol. 344, 1990, pp. 289–294.
[17] Thacker, S. B., Veech, R. L., Vernon, A. A., and Rutstein, D. D., "Genetic and Biochemical Factors Relevant to Alcoholism," *Alcoholism Clinical & Experimental Research*, Vol. 8, 1984, pp. 375–383.
[18] Bennion, L. J. and Li, T. K., "Alcohol Metabolism in American Indians and Whites: Lack of Racial Differences in Metabolic Rate and Liver Alcohol Dehydrogense," *New England Journal of Medicine*, Vol. 294, 1976, pp. 9–13.
[19] Rubin, E. and Lieber, C. S., "Hepatic Microsomal Enzymes in Man and Rat: Induction and Inhibition by Ethanol," *Science*, Vol. 162, 1968, pp. 690–692.
[20] Lieber, C. S. and DeCarli, L. M., "The Role of the Hepatic Microsomal Ethanol Oxidizing System (MEOS) for Ethanol Metabolism In Vivo," *Journal of Pharmacology & Experimental Therapeutics*, Vol. 181, 1972, pp. 279–287.
[21] Lieber, C. S., Lasker, J. M., Alderman, J., and Leo, M. A., "The Microsomal Ethanol Oxidizing System and Its Interaction with Other Drugs, Carcinogens, and Vitamins," *Annals of New York Academy of Sciences*, Vol. 492, 1987, pp. 11–23.
[22] Lieber, C. S. and DeCarli, L. M., "Hepatic Microsomal Ethanol Oxidizing System: In-vitro Characteristics and Adaptive Properties In Vivo," *Journal of Biological Chemistry*, Vol. 245, 1970, pp. 2505–2512.
[23] Bock, K. W., Lipp, H. P., and Bockhenning, B. S., "Review—Induction of Drug-Metabolizing Enzymes by Xenobiotics," *Xenobiotica*, Vol. 20, 1990, pp. 1101–1111.
[24] Pelkonen, O. and Sotaniemi, E., "Drug Metabolism in Alcoholics," *Pharmacology & Therapeutics*, Vol. 16, 1982, pp. 261–268.
[25] Lester, D., Krokosky, W. Z., and Felzenberg, F., "Effect of Pyrazoles and Other Compounds on Alcohol Metabolism," *Quarterly Journal of Studies on Alcohol*, Vol. 29, 1968, pp. 449–454.
[26] Blomstrand, R. and Theorell, H., "Inhibitory Effect on Ethanol Oxidation in Man After Administration of 4-methyl Pyrazole," *Life Sciences*, Vol. 9, 1970, pp. 631–640.
[27] Blomstrand, R., Östling-Wintzell, H., Löf, A., McMartin, K., Tolf, B-R., and Hedström, K-G., "Pyrazoles as Inhibitors of Alcohol Oxidation and as Important Tools in Alcohol Research: An Approach to Therapy Against Methanol Poisoning," *Proceedings of the National Academy of Sciences*, Vol. 76, 1979, pp. 3499–3503.
[28] Bode, J. C., "The Metabolism of Alcohol: Physiological and Pathophysiological Aspects," *Journal of the Royal College of Physicians*, Vol. 12, 1978, pp. 122–135.
[29] Hoyumpa, A. M. and Schenker, S., "Major Drug Interactions: Effect of Liver Disease, Alcohol, and Malnutrition," *Annual Reviews of Medicine*, Vol. 33, 1982, pp. 113–149.
[30] McLean, A. J. and Morgan, D. J., "Clinical Pharmacokinetics in Patients with Liver Disease," *Clinical Pharmacokinetics*, Vol. 21, 1991, pp. 42–69.

[31] Ishak, K. G., Zimmerman, H. J., and Ray, M. B., "Alcoholic Liver Disease—Pathologic, Pathogenic and Clinical Aspects," *Alcoholism: Clinical & Experimental Research*, Vol. 15, 1991, pp. 45–66.

[32] Ugarte, G., Insunza, I., Altschiller, H., and Iturriaga, H., "Clinical and Metabolic Disorders in Alcoholic Hepatic Damage Chapter 29 in Alcohol and Alcoholism," In: R. E. Popham, Ed., Addiction Research Foundation, Toronto, 1969, pp. 229–239.

[33] Jokipii, S. G., *Experimental Studies on Blood Alcohol in Healthy Subjects and in Some Diseases*, Thesis, University of Helsinki, Helsinki, 1951, pp. 1–99.

[34] Leube, G. and Mallach, H. J., "Zur Alkoholelimination bei einem Leberkranken mit portocavalem Shunt," *Blutalkohol*, Vol. 17, 1980, pp. 15–25.

[35] Lundquist, F. and Wolthers, H., "The Influence of Fructose on the Kinetics of Alcohol Elimination in Man," *Acta Pharmacoliqica Toxicologica*, Vol. 14, 1958, pp. 290–294.

[36] Crownover, B. P., La Dine, J., Bradford, B., Glassman, E., Forman, D., Schneider, H., and Thurman, R. G., "Activation of Ethanol Metabolism in Humans by Fructose: Importance of Experimental Design," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 236, 1986, pp. 574–579.

[37] Crow, K. E., Newland, K. M., and Batt, R. D., "The Fructose Effect," *New Zealand Medical Journal*, Vol. 93, 1981, pp. 232–234.

[38] Mascord, D., Smith, J., Starmer, G. A., and Whitfield, J. B., "Effect of Oral Glucose on the Rate of Metabolism of Ethanol in Humans," *Alcohol & Alcoholism*, Vol. 23, 1988, pp. 365–370.

[39] Clark, E. R., Hughes, I. E., Letley, E., "The Effect of Oral Administration of Various Sugars on Blood Ethanol Concentrations in Man," *Journal of Pharmacy and Pharmacology*, Vol. 25, 1973, pp. 319–323.

[40] Caballeria, J., Frezza, M., Hernández-Munóz, R., Dipadova, C., Korsten, M. A., Baraona, E., and Lieber, C. S., "Gastric Origin of the First-Pass Metabolism of Ethanol in Humans: Effect of Gastrectomy," *Gastroenterology*, Vol. 97, 1989, pp. 1205–1209.

[41] Jönsson, K. Å., Jones, A. W., Andersson, T., Boström, H., "Lack of Effect of Cimetidine, Ranitidine and Omeperzole on the Pharmacokinetics of Ethanol in Fasting Male Volunteers," *European Journal of Clinical Pharmacology*, Vol. 42, 1992, pp. 209–212.

[42] Jones, A. W., "Concentration-Time Profiles of Ethanol in Capillary Blood After Ingestion of Beer," *Journal of the Forensic Science Society*, Vol. 31, 1991, pp. 429–439.

[43] Jones, A. W. and Neri, A., "Evaluation of Blood-Ethanol Profiles After Consumption of Alcohol Together with a Large Meal," *Canadian Society Forensic Science Journal*, Vol. 24, 1991, pp. 165–173.

[44] Buijten, J., "An Automated Ultra-Micro Distillation Technique for Determination of Ethanol in Blood and Urine," *Blutalkohol*, Vol. 12, 1975, pp. 393–398.

[45] Jones, A. W. and Schuberth, J., "Computer-Aided Headspace Gas Chromatography Applied to Blood-Alcohol Analysis: Importance of Online Process Control," *Journal of Forensic Sciences*, Vol. 34, No. 5, September 1989, pp. 1116–1127.

[46] Winek, C. L. and Murphy, K. L., "The Rate and Kinetic Order of Ethanol Elimination," *Forensic Science International*, Vol. 25, 1984, pp. 159–166.

[47] Alha, A. R., "Blood Alcohol and Clinical Inebriation in Finnish Men: A Medicolegal Study," *Annals Academiae Scientiarum Fennicae*, Vol. 26, 1951, pp. 1–92.

[48] Coldwell, B. B., (Ed.) "Report on Impaired Driving Tests," *Royal Canadian Mounted Police*, Ottawa, 1957, pp. 1–218.

[49] Neuteboom, W. and Jones, A. W., "Disappearance Rate of Alcohol from the Blood of Drunk Drivers Calculated from Two Consecutive Samples: What Do the Results Really Mean?" *Forensic Science International*, Vol. 45, 1990, pp. 107–115.

[50] Holzbecher, M. D. and Wells, A. E., "Elimination of Ethanol in Humans," *Canadian Society Forensic Science Journal*, Vol. 17, 1984, pp. 182–196.

[51] Eggleton, M. G., "Some Factors Influencing the Metabolic Rate of Ethanol," *Journal of Physiology*, Vol. 98, 1940, pp. 239–254.

[52] Newman, H. W., Lehman, A. J., and Cutting, W. C., "Effect of Dosage on the Rate of Disappearance of Alcohol from the Blood Stream," *Journal of Pharmacology & Experimental Therapeutics*, Vol. 61, 1937, pp. 58–61.

[53] Wilson, R. H. L., Newman, E. J., and Newman, H. W., "Diurnal Variation in Rate of Alcohol Metabolism," *Journal of Applied Physiology*, Vol. 8, 1956, pp. 556–558.

[54] Sturtevant, R. P. and Sturtevant, F. M., "Circadian Variation in Rates of Ethanol Metabolism," In: Crow, K. E., and Batt, R. D., (Eds.) *Human Metabolism of Alcohol*, Vol. 1, CRC Press, Boca Raton, Florida, 1989, pp. 23–39.

[55] Lötterle, J., Husslein, E. M., Bolt, J., and Wirtz, P. M., "Tageszeitliche Unterschiede der Alkoholresorption," *Blutalkohol*, Vol. 26, 1989, pp. 369–375.

[56] Goo, R. H., Moore, J. G., Greenberg, E., and Alazraki, N. P., "Circadian Variation in Gastric Emptying of Meals in Humans," *Gastroenterology*, Vol. 93, 1987, pp. 515–518.
[57] Winkler, K., Lundquist, F., and Tygstrup, N., "The Hepatic Metabolism of Ethanol in Patients with Cirrhosis of the Liver," *Scandinavian Journal of Clinical & Laboratory Investigation*, Vol. 23, 1969, pp. 59–69.
[58] Danopoulos, E., Maratos, K., and Logothetopoulos, J., "Studies on Alcohol's Metabolism in Patients with Atrophic Liver Cirrhosis," *Acta Medica Scandinavica*, Vol. CXLVIII, 1954, pp. 485–492.
[59] Kater, R. M. H., Carulli, N., and Iber, F. L., "Differences in the Rate of Ethanol Metabolism in Recently Drinking Alcoholics and Nondrinking Subjects," *American Journal of Clinical Nutrition*, Vol. 22, 1969, pp. 1608–1617.
[60] Bonnichsen, R., Dimberg, R., Maehly, A., and Åqvist, S., "Die Alkoholverbrennung bei Alkoholikern und bei übrigen Versuchspersonen," *Blutalkohol*, Vol. 5, 1968, pp. 301–317.
[61] Keiding, S., Christensen, N. J., Damgaard, S. E., Dejgård, A., Iversen, H. L., Jacobsen, A., Johansen, S., Lundquist, F., Rubenstein, E., and Winkler, K., "Ethanol Metabolism in Heavy Drinkers After Massive and Moderate Alcohol Intake," *Biochemical Pharmacology*, Vol. 32, 1983, pp. 3097–3102.
[62] Bernhard, C. G. and Goldberg, L., "Aufnahme und verbrennung des Alkohols bei alkoholisten," *Acta Medica Scandinavica*, Vol. 86, 1935, pp. 152–215.
[63] Mezey, E. and Tobon, F., "Rates of Ethanol Clearance and Activities of the Ethanol-Oxidizing Enzymes in Chronic Alcoholic Patients," *Gastroenterology*, Vol. 61, 1971, pp. 707–715.
[64] Mezey, E., "Duration of the Enhanced Activity of the Microsomal Ethanol-Oxidizing Enzyme System and Rate of Ethanol Degradation in Ethanol-Fed Rats After Withdrawal," *Biochemical Pharmacology*, Vol. 21, 1972, pp. 137–142.
[65] Nuutinen, H. U., "Activities of Ethanol-Metabolizing Enzymes in Liver Disease," *Scandinavian Journal of Gastroenterology*, Vol. 21, 1986, pp. 678–684.
[66] Panés, J., Soler, X., Parés, A., Caballeria, J., Farrés, J., Rodés, J., and Parés, X., "Influence of Liver Disease on Hepatic Alcohol and Aldehyde Dehydrogenases," *Gastroenterology*, Vol. 97, 1989, pp. 708–714.
[67] Haffner, H. T., Besserer, K., Stetter, F., and Mann, K. "Die Äthanol-Eliminationsgeschwindigkeit bei Alkoholikern unter besonderer Berücksichtigung der Maximalwertvariante der forensischen BAK-Rückrechnung," *Blutalkohol*, Vol. 28, 1991, pp. 46–54.
[68] Bilzer, N., Penners, B. M., and Conrad, A., "Die Methanolkinetik bei chronischem Alkoholismus," *Blutalkohol*, Vol. 28, 1991, pp. 377–392.

Address requests for reprints or additional information to
A. W. Jones, Ph.D.
Department of Alcohol Toxicology
National Laboratory of Forensic Chemistry
University Hospital
581 85 Linköping
Sweden

ERRATUM

In the article by A.W. Jones, JFS Vol 38, No 1, January 1993 pp 104–118, the following change should be made to the text. In the discussion section (page 114, line 24), 11 min 30 s should be replaced by 30 min. The correct sentence now reads "But despite the presence of food in the stomach it seems that the greatest rise in BAC occurs within the first 30 min after the drinking ends."