

# Absorption, Distribution and Elimination of Alcohol: Highway Safety Aspects

KURT M. DUBOWSKI, Ph.D.

Department of Medicine, and Toxicology Laboratories, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73190

IT IS well established and universally accepted that the concentration of alcohol<sup>1</sup> in blood or breath, properly determined and interpreted, constitutes the best and most objective indicator of the absence or presence and degree of acute alcohol-induced impairment of driving ability in living subjects. Hence, understanding and appreciation of the major physiological and pharmacological factors affecting such alcohol concentrations are important to appropriate use and interpretation of chemical tests for alcohol in traffic law enforcement, and in research on driving impairment by alcohol. Recognition of the complexity of the relationships between dose of alcohol, time and pharmacological effect is also essential to both research and public education in this field.

Most of the relevant factors and considerations affecting the alcohol contents of various body tissues and fluids and the dose-time-effect relationships fall into the field of pharmacokinetics, which broadly concerns the absorption, distribution, biotransformation and excretion of drugs. The interrelationship of the alcohol concentrations of different body fluids and tissues, such as the blood:breath ratio of alcohol as a prime example, is an important and complex consideration in alcohol determination. Further, in the use of chemical tests for alcohol in traffic law enforcement, a sufficient time interval often elapses between the significant event, such as a crash or an alleged violation, and sample collection to produce a marked and very significant difference in the respective alcohol concentrations of blood or other specimen materials. Time relationships involving ingestion, distribution, storage and elimination of alcohol are, therefore, important in relation to highway safety and evidentiary use of chemical test results, sometimes overwhelmingly so.

Pharmacokinetic parameters thus affect both the validity and usefulness of alcohol determinations as indi-

cators of driver impairment by alcohol in such respects as choice of sample materials and the probative value and interpretation of results of alcohol analysis. An understanding of alcohol pharmacokinetics is also needed for the proper evaluation and assessment of the validity and significance of studies correlating alcohol concentrations in body fluids with driver performance or impairment, and for proper appreciation of differences between studies. In the present paper, several of the more relevant and problematic aspects of alcohol pharmacokinetics are considered from the aspect of highway safety.

Several of these matters have become critically important with the advent and wide adoption of per se drinking-driving laws,<sup>2</sup> also called absolute or blood alcohol concentration offense laws. Body fluid alcohol concentrations constitute an element of the offense in per se laws, and are often the controlling evidence irrespective of driver impairment. The onus on the accuracy of the alcohol analysis and the validity of the blood or breath alcohol concentration *at the relevant time* is vastly greater in such settings than in the previous traditional evidentiary use of alcohol analysis results to document presence of alcohol to an extent corroborative of the observed driver impairment and sufficient to explain the crash involvement or moving violation, or to establish a *rebuttable* presumption of the existence of the influence of alcohol to an impermissible extent.

## Aspects of Absorption, Distribution and Elimination of Alcohol

Alcohol is unusual, if not unique, among drugs in

<sup>1</sup> The unmodified term *alcohol* in this article refers to ethanol.

<sup>2</sup> Per se statutes are generally modeled after Section 11-902(a) of the Uniform Vehicle Code and employ a speed limit concept, an element of the offense being motor vehicle operation by a person whose blood or breath alcohol concentration equals or exceeds a specified limit, commonly 0.10 g/dl of blood or 0.10 g/210 L of breath.

several aspects of its pharmacokinetics. Particularly striking are the great biological intersubject variabilities in alcohol consumption tolerance and in alcohol elimination, in the pattern of short-term fluctuations from the trend line of the time course of the blood and breath alcohol concentrations and in alcohol partition between blood and other body fluids and tissues even at equilibrium. Also significant is that alcohol is absorbed and distributed in an unaltered state and is not bound to proteins or complexed with other transport systems.

### Alcohol absorption

Consideration of the variability and anomalies of the uptake and elimination of alcohol is facilitated by reference to the theoretical schematic time course of the blood alcohol concentration often termed the *Widmark Curve* (Elbel and Schleyer, 1956; Wallgren and Barry, 1970; Widmark, 1932) illustrated in Figure 1, despite the many limitations of this schematic representation.

Absorption of alcohol from the gastrointestinal tract, including the stomach, occurs by simple passive diffusion along concentration gradients and does not involve an active transport system. A small, weakly charged molecule, alcohol readily penetrates cell membranes and boundaries. Its distribution is largely governed by the water content of the various organs and tissues, especially at equilibrium, because it is polar and completely water soluble (Wallgren and Barry, 1970). The distri-

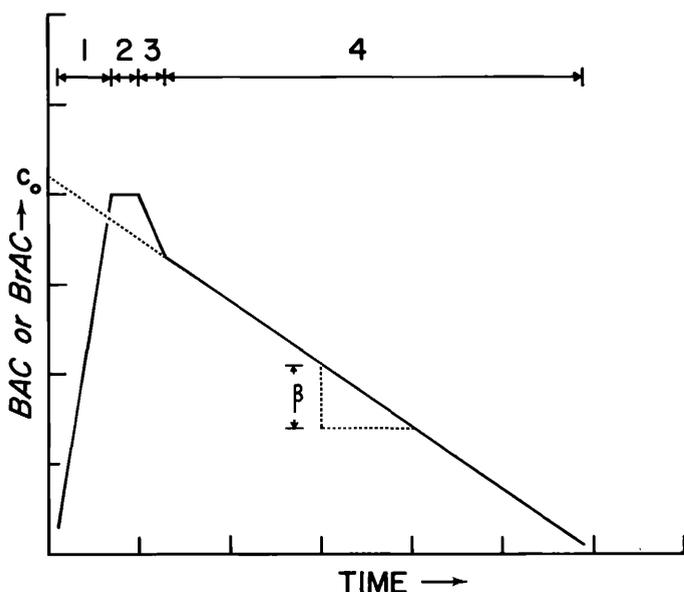


FIGURE 1. Theoretical blood alcohol or breath alcohol curve (after Widmark): 1 = absorption phase, 2 = plateau, 3 = diffusion-equilibration, 4 = elimination phase.

bution process is much speeded by vascularization and blood flow. Organs with a rich blood supply, such as the brain and the lungs, achieve the highest initial concentrations of alcohol. A positive differential, which may be as great as 50–100% (Forney, 1971), persists between the arterial and venous blood alcohol concentrations during the active absorption and prior to equilibration (Forney et al., 1964; Harger and Hulpieu, 1956). The time lag from initial absorption of alcohol to the beginning of the postabsorptive phase is a key variable in relation to highway safety. It brings about significant differences in the magnitude and timing of alcohol concentrations in different organs. The resultant effects on the central nervous system are earlier and more marked than those on the skeletal musculature and other somatic systems.

The rate of alcohol absorption after oral intake is greatly influenced by the nature and concentration of the alcoholic beverage, food intake and a multitude of other physical, biological, psychological and time factors that combine with the individual's sex, body weight and body water, and related habitus characteristics as well as offsetting metabolic disposition to determine the ultimate peak blood alcohol concentration and other characteristics of the time course of the blood alcohol concentration. The term *consumption tolerance* is often applied to all of these combined factors and effects, in distinction to the *constitutional tolerance*, which denotes the differences between persons in the *effects* of alcohol at the tissue and organ level and in individual resistance to those effects at identical blood and tissue alcohol concentrations.

The peak blood alcohol concentration and the time for its achievement are important parameters in various respects. The peak often marks, for example, the changeover between the rising and falling blood alcohol concentrations, reflecting the absorption ( $\alpha$ ) and elimination ( $\beta$ ) phases of distribution—a matter related to acute adaptation to the effects of alcohol (Mitchell, 1985).

These two variables also illustrate splendidly the substantial biological variability in alcohol pharmacokinetics, even under controlled experimental conditions. In single-dose experiments with both men and women, Dubowski (1976a) found elapsed time from end of alcohol intake to peak blood alcohol concentration varying from 14 to 138 min, a nearly 10-fold variation, with mean times for men and women 57 and 42 min, respectively. In subsequent additional studies on men, with a different experimental protocol (Dubowski, 1976b), the data summarized in Table 1 were obtained. A 14-fold variation between absorption times to the peak blood alcohol concentrations in different subjects was demonstrated even in a reasonably homogeneous healthy

TABLE 1. Time to reach peak blood alcohol concentrations and peak blood alcohol : dose relationship in healthy adult men

Pharmacokinetic factor	N	Mean $\pm$ SD	Coefficient of variation (%)	Range
Time to peak blood alcohol concentration, min <sup>a</sup>	79	29.3 $\pm$ 17.1	58.5	9-114
Time to peak blood alcohol concentration, min <sup>b</sup>	69	52.0 $\pm$ 34.6	66.5	12-166
Peak blood alcohol concentration : dose, mg/dl g/kg	145	127.5 $\pm$ 21.1	16.5	78-192

<sup>a</sup> Subjects ingesting 0.5 g alcohol/kg body weight.

<sup>b</sup> Subjects ingesting 1.0 g alcohol/kg body weight.

population. Total population variability is obviously much greater. Other investigators have reported comparable intersubject variability of experimentally measured peak blood alcohol times after the end of drinking (Naeve, 1973).

Peak blood alcohol concentrations reached after ingestion of identical weight-adjusted doses of alcohol typically also vary two- to threefold, even in homogeneous experimental subject populations and under identical experimental conditions (Dubowski, 1976a; O'Neill et al., 1983). Of healthy men given an alcohol dose of 1.0 g/kg, 95% can be expected to reach peak blood alcohol concentrations of 85-170 mg/dl; the remaining subjects will fall outside that range. For a given total alcohol dose, divided-dose drinking, as commonly occurs in social settings, typically produces slower stepwise increases in blood alcohol concentrations than the single dose often ingested experimentally (Forney and Hughes, 1963). Accumulation of alcohol in the blood and other tissues occurs whenever the rates of alcohol intake and absorption exceed the drinker's rate of alcohol elimination.

#### Alcohol elimination

Elimination of alcohol occurs principally through enzymatic oxidation in the liver, with usually minor nonhepatic oxidation pathways and minor excretion of unaltered alcohol in the urine, breath and perspiration (Hawkins and Kalant, 1972; Khanna and Israel, 1980; Lieber, 1977; Majchrowicz, 1975). The pharmacokinetics involved have been explained variously as corresponding to a one compartment open model with zero-order (constant rate) elimination, a one compartment open model with Michaelis-Menten (1913) elimination kinetics (Lundquist and Wolthers, 1958), and a two compartment open model with Michaelis-Menten elimination kinetics. The first-listed theory was initially advanced by Mel-

lanby (1919) and is the original basis for the schematic Widmark Curve (Figure 1).

However, zero-order kinetics, characterized by constant-rate elimination independent of alcohol dose or initial blood alcohol concentration, is an inappropriate description for the elimination of alcohol in humans, at least in a significant portion of the population (Dubowski, 1976a, 1976b; Lundquist and Wolthers, 1958; Wilkinson, 1980). In most subjects and circumstances, the decrease in blood alcohol concentration per unit time in the fully postabsorptive state is a valid reflection of the instant rate of alcohol elimination. It is most appropriately described by a one compartment open model with Michaelis-Menten (1913) elimination kinetics when only a single specimen material (e.g., expired alveolar breath) or blood from a single site (e.g., vein, capillary or artery) is examined. Such a process describes a mixed pattern of zero-order (constant elimination rate) kinetics, which occurs when the rate-limiting enzymatic alcohol oxidation step is saturated, with first-order kinetics when there is an excess of enzyme and which is characterized by an exponential rate of change (i.e., a constant *fraction* of alcohol is eliminated per unit time). The usual graphical presentation of the Michaelis-Menten equation is that of a rectangular hyperbola. The characteristics of this process include a slope of the apparent or pseudolinear decline rate in blood alcohol concentration, which increases with increases in body dose of ingested alcohol and in initial blood alcohol concentration (Wagner and Patel, 1972; Wagner et al., 1976). Both the absorption and elimination rates of alcohol are significantly subject to the effects of food (Sedman et al., 1976; Vitale et al., 1953), and to a much smaller extent to the effects of type and dilution of the ingested alcoholic beverage (Dubowski, 1976b).

Quantitative data on alcohol elimination have been obtained in profusion, mostly from repeated measurement of blood or breath alcohol concentrations. In addition to these controlled pharmacokinetic studies, considerable information has been published on blood alcohol concentration changes with time in drivers who drink, usually by calculation from testing at two points along the elimination curve. The number of subjects tested and the variability of the results encountered have been much greater than in the laboratory studies. Moreover, the blood alcohol concentrations involved were usually much higher in the studies of drivers who drink. For example, in 922 men traffic offenders, Abele (1955) found a blood alcohol decrease rate range of 6 to 40 mg/dl/hr, with a mean of 18.4 and a mode of 18.0. In other studies in which two samples were tested, ranges of 1 to 80 mg/dl/hr (mean  $\pm$  SD, 20.4  $\pm$  10.5) among 1512 subjects (Schweitzer, 1968), 0 to 26 mg/dl/hr (mean, 17.2  $\pm$  9.1) among 1655 subjects (Ponsold

and Heite, 1960), and 9 to 30 mg/dl/hr (mean,  $18.6 \pm 6$ ) for 1142 subjects (Hilgermann and Schleyer, 1971) were reported. In 16 traffic offenders, the breath alcohol decrease range measured by two tests was 7 to 17 mg/210 L/hr<sup>3</sup> (mean,  $11.1 \pm 2.8$ ) (Loomis, 1974). Several of these and other authors found alcohol elimination rates to be normally distributed (Lund, 1979), as has the present author.

Results of observations limited to two points on the elimination curve have many obvious shortcomings and limitations for determining functional blood or breath alcohol decrease rates, but they do illustrate the wide range encountered. The other extreme of studies is represented by controlled pharmacokinetic experiments in which the rate of alcohol decrease in blood or breath is determined by appropriate individual mathematical modeling of each multipoint alcohol concentration versus time curve. In 134 adult men in the postabsorptive state, Dubowski (1976b) obtained the data shown in Table 2 and illustrated in Figure 2. The data were determined by infrared spectrometry and computer modeling of each subject curve.

The underlying data follow a Gaussian distribution. From these data, it can be estimated that the mean hourly breath alcohol concentration decrease for 95% of such a population lies between 5.9 and 23.9 mg/230 L/hr and for 99.7% of such a population lies between 1.4 and 28.4 mg/230 L/hr.

Different studies have been variously reported as indicating blood alcohol decrease rates to be independent of initial alcohol concentrations or positively correlated with initial blood alcohol concentrations, thus corresponding to zero-order and first-order pharmacokinetics, respectively. Abele (1955) reported dependence of mean blood alcohol decrease rates on the blood alcohol concentration, as did others (Dubowski, 1976a, 1976b; Schweitzer, 1968; Wagner et al., 1976). Dose dependence of the blood alcohol decrease rate was found by Alha (1951), Vitale et al. (1953) and others. No significant effect of blood alcohol concentration on alcohol decrease rates was reported by Ponsold and Heite (1960) and many early investigators. The term *acute metabolic tolerance* has been recently applied to an increase in blood alcohol elimination rate within a few hours for most subjects after a second dose of alcohol (Wilson et al., 1984).

It deserves emphasis that the rate of decrease of blood alcohol concentration does not directly and exclusively reflect the metabolic disposition of alcohol because the changes in concentration are also, in part, a product of alcohol elimination through urine, breath,

TABLE 2. Rates of breath alcohol decrease in the postabsorptive state for healthy adult men, determined from individual subject breath alcohol concentration vs time regressions

N	Breath alcohol concentration decrease, mg/230 L/hr		
	Mean $\pm$ SD	Coefficient of variation %	Range
134	14.94 $\pm$ 4.50	30.1	5.9-27.9

perspiration and other routes. Excretion through those routes would be expected to be positively correlated with the plasma alcohol concentration because it involves passive diffusion of alcohol in accordance with its concentration gradients for the route involved.

#### *Aspects of alcohol distribution*

Most state drinking-driving laws limit reference to alcohol concentrations to those in blood regardless of the specimen material actually analyzed, although an increasing number of jurisdictions are adopting the definition of *alcohol concentration* of the Uniform Vehicle Code,<sup>4</sup> which relates that term to the analyzed specimen. Common statutory terminology refers to "the amount of alcohol in the person's blood at the time alleged as shown by chemical analysis of the person's blood, urine, breath or other bodily substances." Consequently, the alcohol distribution process and the partition ratios for alcohol between blood and other specimen materials are of great practical importance. Often they are the subject of vigorous attacks against trial evidence of "blood" alcohol concentrations derived from the analysis of other body fluids.

Breath alcohol analysis is by far the most commonly employed form of chemical testing in traffic law enforcement. Hence the true blood : breath ratio for alcohol, originally used to calibrate breath alcohol analyzers to indicate the supposedly corresponding blood alcohol concentration, has been a subject of much scientific investigation and debate for about 50 years. It is evident from considerations of quantitative human biology that a single ratio or conversion factor will not apply to all persons (Mason and Dubowski, 1974, 1976). Nevertheless, for half of that period, there was general acceptance of 2100 : 1 as the partition ratio of alcohol between blood and alveolar breath, as a population mean (Borkenstein et al., 1972; Harger et al., 1950; National Safety Council, 1953). Quantitative evidential breath alcohol analyzers are still currently factory-calibrated in

<sup>3</sup> The conversion factor is: 1 L of blood = 2100 L of expired alveolar air.

<sup>4</sup> As changed in 1979, Uniform Vehicle Code Section 11-902.1(a)(5) reads: "Alcohol concentration shall mean either grams of alcohol per 100 milliliters of blood or grams of alcohol per 210 liters of breath."

grams of alcohol per 210 L of breath. Some official guidelines incorporate this calibration (National Highway Traffic Safety Administration, 1984), thus in effect retaining a 2100 : 1 blood alcohol : breath alcohol concentration ratio for those jurisdictions statutorily requiring the reporting of evidentiary alcohol concentrations in terms of blood.

Later studies on larger subject groups, with more sophisticated chemical analyses of blood and breath for alcohol and more extensive data treatment, indicated that the mean alcohol partition factor between blood and breath in the postabsorptive phase in healthy adult men is very close to 2300 : 1 (Dubowski, 1975; Dubowski and O'Neill, 1979; Jones, 1976; Jones et al., 1975). However, significant variations from this population mean exist during active alcohol absorption and in some individuals even in the postabsorptive phase. The typical biological variability of human alcohol pharmacokinetic parameters is well illustrated by the data from studies of Dubowski and O'Neill (1979). These are summarized in Table 3, for the ratio of alcohol concentrations in whole blood and end-expiratory breath in healthy adult men in the fully postabsorptive phase.

These experimentally determined ratios have a Gaussian distribution. Hence a postabsorptive blood alcohol : breath alcohol concentration ratio range of 1797 : 1 to 2763 : 1 can be estimated for 95% and 1555 : 1 to 3005 : 1 for 99.7% of such a population. Those statistical projections agree closely with the experimentally found range of values.

The various scientific, technical and forensic aspects of this complex matter have been reviewed in detail by Mason and Dubowski (1976). They proposed that the offense of driving under the influence of alcohol be statutorily defined in terms of the concentration of alcohol in the breath and in the blood, that breath alcohol analysis continue to be employed in traffic law enforcement but that conversion of breath alcohol concentrations to blood alcohol concentrations be abandoned for forensic purposes. These recommendations have been implemented in an increasing number of jurisdictions.

There is massive documentation that the blood alcohol

concentration cannot be established sufficiently reliably for forensic purposes from the alcohol concentration of a pooled bladder urine specimen because of the extensive variability of the blood : urine ratio of alcohol. Partition ratios of 0.21 : 1 to 2.66 : 1 have been reported (Flanagan et al., 1977; Kaye and Cordona, 1969; Morgan, 1965; Stevens et al., 1966). From the data reported by Kaye and Cordona (1969), it can be determined that the urine : blood alcohol concentration ratios are normally distributed and it can be estimated that 95% of such ratios in the population will fall between 0.36 : 1 and 2.20 : 1, and 99.7% between near 0 and 2.66 : 1. These problems have been recognized in policy statements of the National Safety Council's Committee on Alcohol and Drugs (1979) and of the National Highway Traffic Safety Administration (1975), which list blood and breath as specimens of choice for alcohol analysis and discourage use of urine for alcohol determination in law enforcement.

Analysis of alcohol in saliva has been limited to research applications because of the inherent problems in field collection of specimens. Modern studies using refined analytical methods and small sample volumes have shown mean partition ratios for alcohol of 1.04 : 1 for parotid saliva : plasma (DiGregorio et al., 1978) and 1.08 : 1 for pooled saliva : blood (Jones, 1979).

Alcohol is excreted in part in sweat. Based on that fact, an adhesive pad for sweat collection from the skin for periods up to 8 days has been suggested as an indicator of alcohol consumption (Phillips and McAloon, 1980). The validity and usefulness of alcohol measurement in sweat thus collected by sweat patch over a period of days as an indicator of alcohol abstinence or use is still under evaluation, with divergent results (Phillips, 1984; Phillips et al., 1984).

For historical reasons, and because drinking-driving laws uniformly refer to blood alcohol in the whole-blood sense, studies of driving impairment by alcohol and of alcohol distribution between body fluids have mostly used *whole* blood as the specimen when blood was sampled. Because alcohol is not uniformly distributed between the cellular and noncellular components of blood and because of the relative frequency of hematological abnormalities in the population as well as circadian and other shifts of fluid volumes, use of whole blood alcohol concentrations further complicates the physical, chemical and biological factors involved in alcohol distribution and partition (Mason and Dubowski, 1976). Plasma is a physiologically and pharmacokinetically more appropriate specimen.

#### *Sex, age and time-related differences*

In many of the pharmacokinetic parameters for alcohol, marked differences related to sex and age exist.

TABLE 3. Functional ratio of alcohol concentrations in venous whole blood and end-expiratory breath in the postabsorptive phase, in healthy adult men

Blood alcohol concentration : Breath alcohol concentration			
<i>N</i>	Mean $\pm$ SD	Coefficient of variation %	Range
393	2280 $\pm$ 241.5	10.6	1706-3063

In regard to the former, differences in body composition, especially in body water and adipose tissue proportions, are usually cited to explain the documented population differences, with less frequent attention to stage of the menstrual cycle and use of oral contraceptives (Zeiner, 1983). Some of the differences are significant. In parallel studies of oral alcohol intake in men and women, using identical weight-adjusted alcohol doses and drinking times, Dubowski (1976a) found the mean time to peak blood alcohol concentration after end of drinking to be 1.35 times as long in men as in women, the mean peak blood alcohol concentration : dose relationship to be 12.8% higher in women than in men and the mean hourly rate of decrease of the blood alcohol concentration to be 23.6% greater in women than in men. Women during the premenstrual phase of the ovulation cycle reached significantly higher peak blood alcohol concentrations for identical weight-adjusted moderate acute doses and showed greater absorption rates than men, or than women tested during the menstruum and around the time of ovulation (Jones and Jones, 1976). Women taking oral contraceptives reached lower peak blood alcohol concentrations and had significantly lower body alcohol elimination rates and blood alcohol disappearance rates than women not on oral contraceptives (Jones and Jones, 1984; Zeiner, 1983). Michaelis-Menten maximum velocity values for alcohol disappearance from the blood, reflecting alcohol metabolizing capacity, have been found to be 1.9 times as great in women as in men (Sutker et al., 1983).

Age-related differences in alcohol pharmacokinetics have not been studied extensively in humans. Data for men in five age groups showed consistent and significant increase in blood alcohol elimination rates with increasing age (Schweitzer, 1968). Intravenous alcohol infusion of a weight-adjusted dose produced slightly higher alcohol concentrations in blood water in older subjects than in younger men and the peak alcohol concentrations in blood water were age correlated. The rate of alcohol disappearance from the blood water, however, was not significantly correlated with age (Vestal et al., 1977). The differences were considered mostly attributable to age-related changes in body composition, such as a decreased lean body mass and total body water in older subjects.

The possible effects of time of day on alcohol pharmacokinetics as well as on effects of alcohol have been considered, although not studied extensively in human subjects. Circadian rhythms have been claimed to affect peak blood alcohol concentrations (Zeiner, 1974) and alcohol elimination rates (Jones, 1974; Wilson et al., 1956). Others were unable to demonstrate significant time of day-related differences in these pharmacokinetic parameters (Lawrence et al., 1983). Reviews

of the relationship of time of day to alcohol pharmacokinetics have appeared (Minors and Waterhouse, 1980; Sturtevant, 1976).

#### **Anomalies and Short-Term Fluctuations of Blood Alcohol Curves**

For many purposes, the fitting of regression lines to experimental data points by manual or computerized mathematical modeling is satisfactory. The complete blood alcohol or breath alcohol versus time curve usually requires nonlinear regression analysis, in keeping with the pharmacokinetic phenomena discussed above. However, for some purposes, a trend-line curve is markedly inappropriate or useless. That is especially true for attempts to engage in retrograde or forward extrapolation of blood or breath alcohol concentrations beyond observed values. Among the major reasons for the infeasibility of retrograde extrapolation, three stand out: (1) lack of knowledge, usually, about the timing of the alcohol concentration peak and absorption-postabsorption status; (2) ignorance about the mathematical characteristics (e.g., linear, pseudolinear, exponential) and the mean rate of change of the individual's blood or breath alcohol elimination curve; and (3) unpredictable irregularities of the curve, especially short-term fluctuations from the best-fit trend line of the blood or breath alcohol curve.

The nature, extent and frequency of the breath alcohol curve irregularity and especially the short-term fluctuations have been illustrated in other reports (Loomis, 1974; Schmutte et al., 1972; Shumate et al., 1967; Terfloth and Wuermeling, 1968). The same phenomena of blood alcohol curves have been exemplified elsewhere (Ditt and Forster, 1964; Leithoff, 1964; Naeve et al., 1971; Schleyer, 1959; Schmutte et al., 1972; Wehner, 1972). The reports by Leithoff and by Wehner are particularly persuasive of the existence and extent of short-term blood alcohol fluctuations because these investigators employed automated analysis of blood continuously sampled through an indwelling venous catheter.

The same phenomenon is illustrated in Figure 2, which consists of six representative breath alcohol versus time curves obtained in the studies of Dubowski (1976b).

Under highly standardized conditions, healthy adult men ingested alcohol doses of 0.5, 0.8 or 1.0 g/kg body weight after a 4-hr fast, according to a Latin-square design, by rapid (20 min) or slow (40 min) drinking of one of four alcoholic beverages (champagne, beer, diluted whisky, straight whisky), accompanied by snack foods. Alcohol concentrations of end-expiratory breath were measured at frequent intervals, usually every 5 min, by infrared spectrometry with an Intoxilyzer apparatus, calibration of which was closely monitored

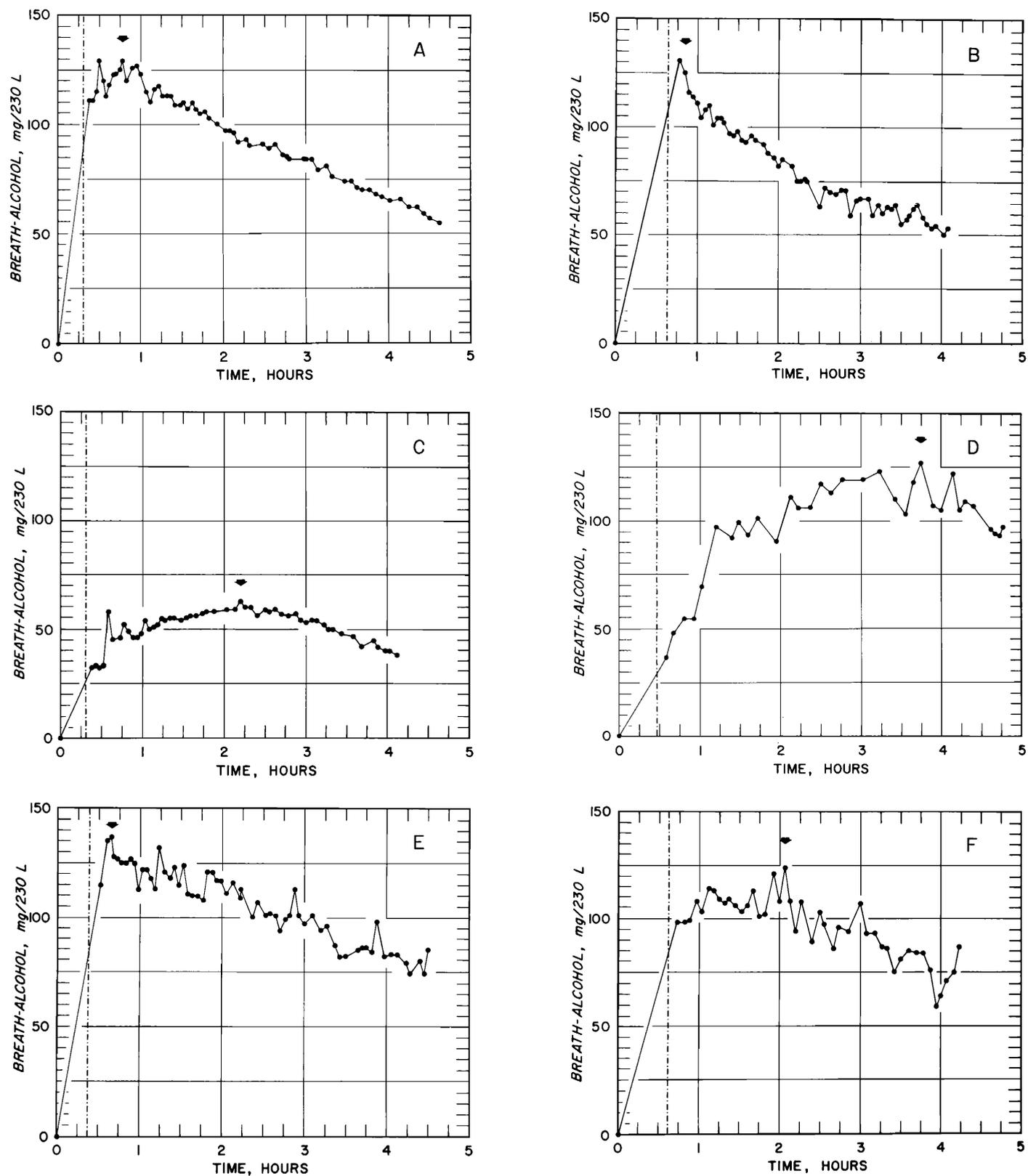


FIGURE 2. Experimental human breath alcohol curves showing a typical Widmark pattern (2A) and various anomalies and short-term breath alcohol fluctuations (2B-2F). Each plotted point represents a separate breath alcohol measurement in g/230 L. The dotted line near the left ordinate indicates the end of alcohol ingestion. The arrow shows the apparent peak breath alcohol concentration at least 15 min. after the end of alcohol ingestion.

by analysis of vapor-alcohol samples and was verified by frequent comparison with simultaneous blood samples.

Figures 2A-F reflect the following protocol conditions, and individual breath alcohol curve characteristics as determined from family regression analysis of breath alcohol concentration vs time during the postabsorptive elimination phase of each curve. The notations used for all regression equations are the following:  $y$  = breath alcohol concentration in g/230 L,  $x$  = hour after apparent peak of breath alcohol concentration,  $R^2$  = coefficient of determination for the regression, SEE = standard error of the estimate, i.e., square root of the residual variance.

In Figure 2A, alcohol intake is straight 86-proof whisky, 0.8 g/kg, fast drinking. The curve displays a typical regular Widmark pattern with minimal fluctuations from the trend line. The most appropriate mathematical description of the elimination period is a linear model:  $y = 0.116 - 0.017x$ ,  $R^2 = 0.981$ , SEE = 0.003. In Figure 2B, alcohol intake is straight whisky, 0.8 g/kg, slow drinking. The curve displays moderate positive and negative fluctuations from the trend line. The most appropriate description of the elimination period is an exponential model:  $y = 0.113e^{-0.247x}$ ,  $R^2 = 0.958$ , SEE = 0.052. In Figure 2C, alcohol intake is champagne, 0.5 g/kg, fast drinking. The curve displays minimal fluctuations from the trend line and the breath alcohol concentration remains in a narrow range for several hours. The most appropriate description of the elimination period is a parabolic model:  $y = 0.061 - 0.006x - 0.003x^2$ ,  $R^2 = 0.966$ , SEE = 0.001.

In Figure 2D, alcohol intake is champagne, 1.0 g/kg, fast drinking. The curve displays a markedly delayed peak, with marked fluctuations from the trend line. No mathematical model provides excellent correlation, but the most appropriate description of the elimination period is a parabolic model:  $y = 0.115 + 0.005x - 0.012x^2$ ,  $R^2 = 0.564$ , SEE = 0.007. The most appropriate description for the entire curve is also a better correlated parabolic model:  $y = 0.005 + 0.72x - 0.011x^2$ ,  $R^2 = 0.927$ , SEE = 0.007. In Figure 2E, alcohol intake is beer, 1.0 g/kg, fast drinking. The curve generally follows a Widmark pattern, but with significant fluctuations from the trend line and marked positive and negative spiking throughout the entire curve. The most appropriate mathematical description of the elimination period is a linear model:  $y = 0.129 - 0.013x$ ,  $R^2 = 0.891$ , SEE = 0.005. In Figure 2F, alcohol intake is straight 86-proof whisky, 1.0 g/kg, slow drinking. The curve displays marked irregularities and positive and negative spiking as great as 0.030 g/230 L in less than 10 min. No mathematical model provides excellent correlation, but the most appropriate description of the elimination period

is a linear model:  $y = 0.107 - 0.017x$ ,  $R^2 = 0.652$ , SEE = 0.008.

All of these curves share the fluctuations phenomenon to an extent and degree varying considerably between subjects. Particularly striking are portions of the curves in Figures 2D, E and F around the 100 mg/230 L concentration region. It is evident from these rather typical curves that breath alcohol analysis results even under highly controlled conditions can and do rapidly oscillate in short time periods above or below any given concentration. This should be recognized in both research on alcohol and in evidentiary use of blood or breath alcohol concentrations in the prosecution of per se law violations.

These phenomena are *not* limited to breath alcohol analysis, as shown by comparable curve patterns for discrete or continuous blood alcohol monitoring in the studies cited, and by the very close correlation of numerous separately measured simultaneous blood alcohol and breath alcohol concentrations in the course of the experiments that yielded the curves in Figures 2A-F (Dubowski and O'Neill, 1979).

#### Summary and Conclusions

Key aspects of the pharmacokinetics of alcohol are highly relevant to highway safety. Of particular pertinence are the partition of alcohol between various body tissues and fluids and the resulting alcohol concentration ratios for blood : breath and other body fluids, as well as the irregularity and short-term fluctuations of the blood and breath alcohol curves.

Most alcohol pharmacokinetics parameters are subject to wide intersubject variability, as exemplified by peak blood alcohol concentrations reached on ingestion of identical weight-adjusted doses, time to peak after end of drinking and the rate of alcohol elimination from the blood. This great biological intersubject variability, when combined with sex-, age- and time-related differences, makes the blood alcohol information in widely distributed alcohol consumption nomograms and tables based on mean data inappropriate as a guide for the drinking behavior of individuals.

Although there is good statistical correlation between the alcohol concentration of different body tissues and fluids in the fully postabsorptive state, wide individual variations from the population mean alcohol partition values exist. It is often impossible to determine whether the postabsorptive state has been reached at any given time. Those factors make it impossible or infeasible to convert the alcohol concentration of breath or urine to the simultaneous blood alcohol concentration with forensically acceptable certainty, especially under per se or absolute alcohol concentration laws. Inclusion of

breath alcohol concentrations in drinking-driving statutes, as definitions or per se offense elements, makes unnecessary the conversion of breath alcohol analysis results into equivalent blood alcohol concentrations. Urine alcohol concentrations are inadequately correlated with blood alcohol concentrations or with driver impairment, and analysis of bladder urine is, therefore, inappropriate in traffic law enforcement.

Significantly large sex-related differences in pharmacokinetic parameters have been demonstrated (e.g., in peak blood alcohol concentrations for weight-adjusted doses). The effects of age and time of day have been less extensively studied and are less clear.

Breath and blood alcohol time curves are subject to short-term fluctuations from the trend line and other irregularities, and often do not follow the typical Widmark pattern. From the existing information on pharmacokinetics of alcohol and the characteristics and variability of blood and breath alcohol versus time curves, the following conclusions can be reached. First, not all blood and breath alcohol curves follow the Widmark pattern, nor is the elimination phase necessarily linear. Second, alcohol absorption is not always complete within 60 to 90 min, as often claimed. Third, the peak alcohol concentration cannot be validly predicted or established in an individual instance without frequent and timely measurement of alcohol concentrations. Fourth, it is not possible to establish whether an individual is in the absorption or elimination phase, or to establish the mean overall rate of alcohol elimination from the blood or breath, from the results of two consecutive blood or breath alcohol measurements, however timed. Fifth, significantly large short-term fluctuations occur in some subjects and result in marked positive and negative departures from the alcohol concentration trend line. Sixth, short-term, marked oscillation of the blood or breath alcohol concentration can occur at various points of the curve, resulting in repeated excursions of the alcohol concentration above and below a given concentration (such as 80 or 100 mg/dl) within a few minutes or for hours. Finally, no forensically valid forward or backward extrapolation of blood or breath alcohol concentrations is ordinarily possible in a given subject and occasion solely on the basis of time and individual analysis results.

#### **Future Research Needs**

Most research on alcohol pharmacokinetics and on the effects of alcohol on driving has been conducted with low or moderate quantities of alcohol ingested in a single dose. Research subjects have been predominantly young and middle-aged adult men. Because of the pharmacokinetics considerations reviewed above, there is often uncertainty about whether and when the subjects

are in the postabsorptive phase. These limitations and extreme variability in previous experimental protocols and conditions make comparisons among the results of different studies as difficult as practical application of many of those findings to alcohol and highway safety settings.

There is need for standardization of research protocols, especially for studies of alcohol-relating driving impairment. Because of the many factors and variables involved, it may be best to develop consensus on the most appropriate protocol(s) through one or more conferences of experienced investigators, under the sponsorship of a cognizant body such as the National Institute on Alcohol Abuse and Alcoholism or the National Research Council. The protocol(s) should make suitable provision for alcohol dosing (e.g., by divided-dose drinking); for study of sex-, age- and time-related effects; and for frequent enough, accurate alcohol measurement (preferably by proper breath alcohol analysis) to provide valid information for correlation with observed subject effects. Because results of studies on normal, healthy subjects who use alcoholic beverages lightly or moderately may not be equally applicable to heavy drinkers, separate provisions are needed to investigate the applicability of general findings and conclusions to the latter group.

The major shortcomings of currently available alcohol consumption charts, graphs and nomograms for general public use include the likelihood of dangerous underestimation for many persons of the blood alcohol concentration reached by ingesting a given quantity of alcohol. Self-test devices for breath alcohol measurement are similarly flawed. There is need, therefore, to develop and validate alternate and better means of providing valid information to the public on blood alcohol concentrations likely to be reached, or actually achieved, for a given amount of alcohol intake.

The proliferation of per se or absolute alcohol concentration offense laws makes it likely that the results of blood and breath alcohol analyses will continue to constitute a primary form of evidence in trials of alcohol-related traffic offenses. Testing of suspected violators under forensically acceptable standards is infeasible at the time of first contact. Extrapolation of a later alcohol test result to the time of the alleged offense is always of uncertain validity and therefore forensically unacceptable. The laws of different jurisdictions address this problem in various ways, as by specifying that the analysis result at the time of the test shall govern, or by judicially approving retrograde extrapolation of results, or by defining the offense to consist of driving a vehicle after having consumed sufficient alcohol to reach a specified alcohol concentration "at any relevant time after the driving." There is need to develop one or more legally acceptable and

scientifically valid schemes for specifying the alcohol concentration element of alcohol-related traffic offenses, and for obtaining forensically reliable alcohol analysis results, while avoiding the pitfalls and dilemmas of current practices.

Also needed are further studies on some methodological problems. The nature, extent and population frequency of the anomalies and fluctuations of blood and breath alcohol time curves should be established by carefully controlled large-scale studies at appropriate alcohol concentrations in men and women, and the underlying mechanisms need elucidation. The utility of the sweat-patch test for alcohol consumption requires further investigation.

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