Joshua A. Perper,[1] *M.D., LL.B., M.Sc.; Abraham Twerski,*[2] *M.D.; and Jerry W. Wienand,*[1] *J.D.*

Tolerance at High Blood Alcohol Concentrations: A Study of 110 Cases and Review of the Literature

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ABSTRACT: One hundred ten consecutive alcoholics who voluntarily entered a detoxification center were studied to determine their ability to perform certain designated functions (a) while under the influence of alcohol at admission and (b) four days later, after they had undergone detoxification. Their blood alcohol concentrations (BACs) within an hour of admission were determined by using the DuPont Automated Clinical Analyzer (ACA), following standard procedures. The results of the tests performed by these subjects were then studied to ascertain the level of psychomotor impairment in alcoholics at elevated BACs. The results were broken down by age, sex, race, and BAC. The findings indicate that alcoholics develop an increased tolerance to alcohol at BACs, which are extremely high, including levels generally considered to be potentially fatal.

KEYWORDS: pathology and biology, alcohol, intoxication

A reliable correlation between blood alcohol concentration (BAC) and clinical intoxication is very important both from a medical and medico-legal point of view.

Medically, one must address the questions of alcohol analgesia hiding internal trauma [*1-4*], interference with the management of anesthesia [*5,6*], and synergistic action with other central nervous system depressants [*7,8*]. From a forensic science point of view, the relationship between blood alcohol concentrations and physico-mental impairment or death is crucial to the outcome of many legal issues.

Most studies have measured the physiological and biochemical effects of alcoholic intoxication associated with slight or moderate degrees of blood alcohol concentration. However, there is a remarkable paucity of publications on the effects of alcohol at high blood alcohol concentrations.

Clinical experience contradicts the generally accepted dogma that "regardless of the degree of tolerance, blood alcohol levels above 400 mg. per 100 ml. produce stupor and/or coma . . . [*9*]. The purpose of the present study was to evaluate the magnitude and range of the variability in the manifestations of clinical intoxication at high blood alcohol concentrations in alcoholics.

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[1]Coroner and senior deputy coroner, respectively, Allegheny County Coroner's Office, Pittsburgh, PA.
[2]Clinical director, St. Francis Hospital, Department of Psychiatry, Pittsburgh, PA.

Methods and Materials

One hundred ten consecutive alcoholics, who voluntarily applied for admission at the St. Francis Hospital Detoxification Center in Pittsburgh, were studied. The degree of clinical intoxication was evaluated in terms of motor performances and general behavior characteristics. The following elements were assessed: (1) vision, (2) pupillary size, (3) speech, (4) verbal comprehension, (5) coordination, and (6) ability to undress. In evaluating visual impairment, blurred vision and diplopia were considered. The speech capability was rated as normal, slurred, or incoherent. The evaluation of coordination was based on the ability of the subject to follow directions, move arms and hands when so instructed, hold the thermometer, get up on a carriage, and so forth. The degree of impairment was graded as slight, moderate, or severe.

Blood alcohol concentrations were determined at admission by using a DuPont Automated Clinical Analyzer (ACA).

Blood samples were drawn from the subjects of this study by registered nurses, using standard hypodermic syringes. The blood was removed from veins in the antecubital fossa, after the dermis had been sterilized with a Betadine® preparation. This method was used to preclude the finding of a distorted ethanol level as a result of the use of an alcohol based disinfectant. Ten cubic centimetres of whole blood were drawn, placed into a sterile vial, and submitted for analysis.

In the laboratory, the vial was placed in a centrifuge for 10 min. Immediately thereafter, a portion of the specimen was introduced into a DuPont Automated Clinical Analyzer (ACA), using approved procedures to prevent contamination.

Two standards, from E.M. Science Division of E.M. Industries, Inc., were used, the first being 0.5 mg and the second, 1.5 mg. Plastic packs prepared by the manufacturer were then introduced into the analyzer. A portion of the sample was aspirated and the plastic pack passed through the sample, at which time the sample and the contents of the pack were combined through a number of breakers, mixers, and incubators.

The mechanism of the analysis was as follows: alcohol dehydrogenase catalyzed the oxidation of ethanol to acetaldehyde with simultaneous reduction nicotinamide-adenine dinucleotide (NAD), alkaline pH, and an aldehyde trapping agent forced the reaction to completion. One mole of NAD was reduced to one mole of NADH for each mole of alcohol present. The absorbence caused by NADH and, thus, the alcohol concentration, was determined by using a two-filter (340 to 383 nm) and point technique.

The level of alcohol in the blood was measured by a spectrophotometer, calibrated for accuracy with regard to the particular batch of testing agents used. The results of the analysis were then printed out.

The psychomotor performance of the subject was evaluated at the facility, by the same examiners, four days after the initial evaluation and following total abstinence from alcohol.

Results

Out of the 110 admissions studied, 87 (80%) had positive blood alcohol concentrations. The blood alcohol concentration was 0.015 to 0.444 g/dL with 64.4% having BAC values above 0.2 g/dL (Table 1). The majority of the patients were in the 30 to 49 years age group, and most of the high blood alcohol levels were within this age group (Fig. 1). It is worthy to note that, in spite of the high blood alcohol concentrations in many of the subjects, all walked under their own power to submit voluntarily for treatment.

Out of the 87 with positive blood alcohol, 35% were normal in every respect of the criteria used.

Out of the 54 subjects with blood alcohol concentrations of 0.2% or higher (Fig. 1), 13 (24%) showed no sign of clinical intoxication. The following numbers of subjects exhibited normal reactions in the areas indicated: 31 (57%)—speech, 22 (40.7%)—gait, 31 (57%)—vision, 24

TABLE 1—*Sex and race.*

Blood Alcohol Concentration		Male		Female		
g/dL	(mg/L)	Black	White	Black	White	
0.01-0.04	(100-400)	3	3		1	
0.05-0.09	(500-900)	3	2		1	
0.10-0.14	(1000-1400)	2	3		2	
0.15-0.19	(1500-1900)	3	7	1	1	
0.20-0.24	(2000-2400)	6	6	1		
0.25-0.29	(2500-2900)	1	8	2	3	
0.30-0.34	(3000-3400)	4	8		2	
0.35-0.39	(3500-3900)	1	4		1	
0.40-0.44	(4000-4400)	3	1			
0.45-0.49	(4500-4900)					
0.50-0.54	(5000-5400)					
0.55-0.59	(5500-5900)					
0.60-0.64	(6000-6400)					
Negative						
Totals		26	42	4	11	83[a]

[a]Of the 87 subjects with positive BACs, 83 were identified both as to race and sex.

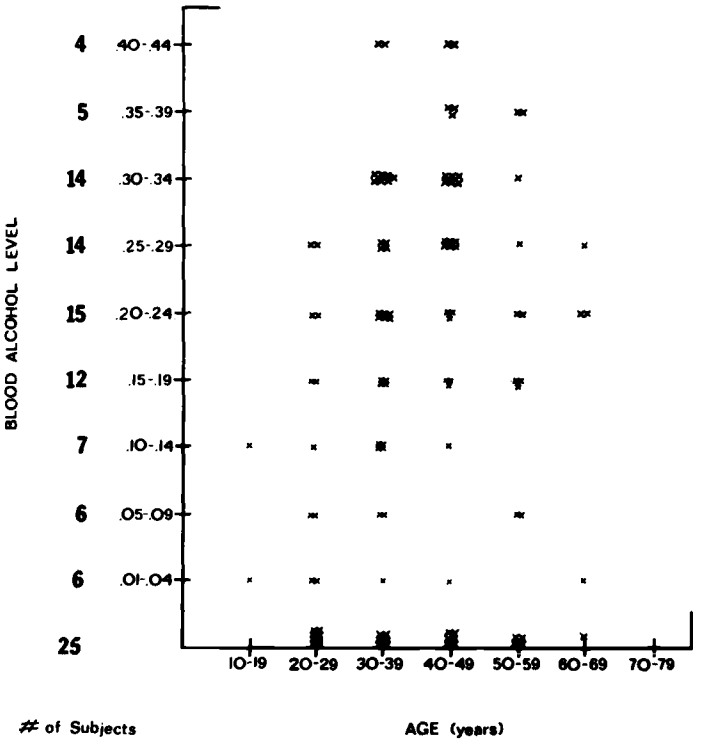

FIG. 1—*Age distribution and acute alcoholic intoxication.*

(44.4%)—verbal comprehension, 41 (75.9%)—ability to undress, 27 (50%)—pupils, and 20 (35.1%)—coordination. When the BACs reached 0.30% or higher, none of the subjects exhibited sobriety in all fields of examination. However, the proportion of subjects showing a normal performance on some of the tests is still impressive. Out of 26 subjects with BACs of 0.3% or higher (Fig. 1), the following numbers of subjects were normal in the areas indicated: eleven—speech, eight—verbal comprehension, six—gait, eleven—pupils and vision, and two—coordination.

Even when the BACs reached 0.35 g/dL, out of ten individuals, five showed normal speech; two stable gait; eight unimpaired ability to undress; and three normal vision, average sized pupils, and adequate verbal comprehension.

In correlating the blood alcohol concentrations with regard to the sex of the subjects, it became readily apparent that, of those with positive BACs, a smaller percentage of women subjects (20%) had high blood alcohol concentrations (0.30% or higher) as compared to men (31%). The highest BAC among women subjects was 0.37%, while four male subjects had levels between 0.40 and 0.44. However, our data for women show a somewhat better tolerance than men at similar blood alcohol concentrations.

White women showed less impairment than white men, or at least essentially the same magnitude of impairment, with regard to vision, pupillary dilatation, gait, speech, verbal comprehension, and coordination. Only in ability to undress did women show less tolerance.

Racial differences were not consistently the same with regard to various parameters of sobriety. Black males had a considerably lower incidence of slurred speech (19.2%) as compared with whites (35.5%), and a lower incidence of incoordination, as defined by the study. Whites fared better than blacks in verbal comprehension, gait, and ability to undress (Fig. 2).

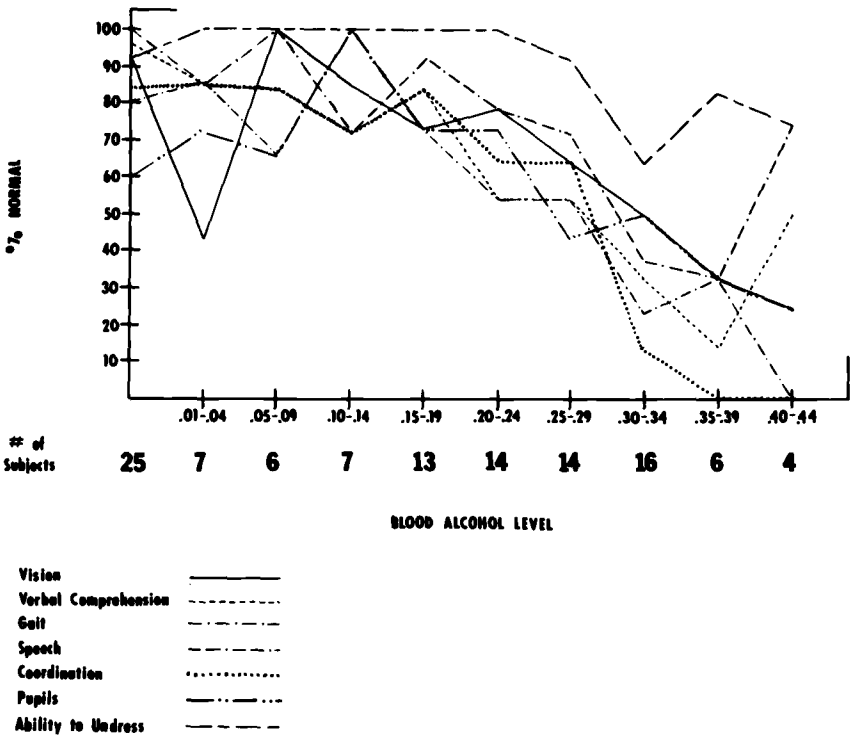

FIG. 2—*Sobriety tests and blood alcohol concentrations.*

The capabilities that were most affected by alcohol and less well protected by tolerance were the coordination and the verbal comprehension (Fig. 2). One should also emphasize that the impairment in the majority of cases was slight rather than moderate or severe. Only three subjects showed diplopia, a reputed sign of alcoholic intoxication, and two out of three had BACs in excess of 0.3 g/dL.

When the patients were examined after four days of total abstinence, a few showed signs which could have been interpreted as part of the general picture of acute intoxication in the presence of a positive blood alcohol. A total of seven subjects fell into this category. Interestingly, three of the subjects exhibited impairments in verbal comprehension, coordination, and gait four days after admission, when sober, although they were documented as being normal in these respects while intoxicated at BACs of 0.15, 0.19, and 0.22%, respectively.

In other areas, these subjects, together with the remaining four, exhibited similar impairments both while sober and while having BACs ranging from 0.02 to 0.42. Obviously, such manifestations were caused by chronic alcohol damage or preexistent personality characteristics.

Discussion

The factors that affect the severity of alcohol intoxication have been extensively studied. The available data clearly indicate that the extent of clinical intoxication is not related only to the blood alcohol concentration, but also to how rapidly the concentration is achieved and whether the individual is on the ascending (absorbing) or the descending (clearing) limb with regard to changes in blood alcohol level [*10,11*]. Demographic characteristics such as race, sex, and age are clearly important in this regard. Asians, for example, were shown to be more susceptible with regard to both physiological and behavioral effects of alcohol [*12–14*]. Our study, while showing some differences between blacks and whites with regard to some types of alcoholic impairment, failed to reveal a consistent difference in all parameters evaluated. Sex-related differences with regard to sensitivity to alcohol intoxication have also been reported, with women not only developing higher blood alcohol concentration than men under identical conditions (because of their reduced water compartment), but also showing more cognitive impairment than men at similar blood alcohol concentrations [*15*].

Age is an important factor in infancy and childhood. Children were shown to be more sensitive than adults to the hypoglycemia effect of acute alcoholic intoxication [*16*]. Coma and fatalities associated with alcohol induced hypoglycemia were reported in very young children at ethanol levels below 0.1 g/dL and as low as 0.02 g/dL [*17–19*].

Circadian variations in the effects of alcohol intoxication have also been reported, with individuals performing more poorly in nonverbal cognitive tasks in the afternoon than in the evening [*20–21*].

Most of the studies on the physiological effects of alcohol deal with blood alcohol concentrations within the "social drinking" experience (that is, ranging between 0.075 and 0.120%) [*22*]. Within this range it has often been emphasized that alcohol drinking experiences produce a considerable degree of tolerance to clinical intoxication, which may extend even to higher blood alcohol concentrations [*23*].

As a matter of fact, Paredes and Hood make the paradoxical statement that "drunkenness is not a necessary sequel of intoxication" [*24*]. Put in more precise, though less colorful terms, the presence of high ethanol levels in the blood does not necessarily result in observable clinical manifestations of drunkenness.

Survival at high blood alcohol levels which should have resulted in death have been generally reported in the literature as a curiosity. Hammond [*25*] reported a patient, who had been arrested for drunken driving, became comatose at 0.78 g/dL, and, following treatment, reversed to full consciousness at a BAC of 0.52 g/dL. A number of additional cases have been published which relate incidents of individuals surviving blood alcohol concentrations varying from 0.65

to 1.5 g/dL [*26–32*]. Interestingly, a number of these individuals were conscious and able to converse; and some did not appear to be intoxicated (Table 2).

In recent years a few reports indicate that a significant number of emergency room patients who were admitted for minor medical problems and who appeared clinically not intoxicated had, in fact, high blood alcohol concentrations [*33*]. Our study clearly indicates that the tolerance of alcoholics to alcohol extends well into the high blood alcohol concentrations, above 0.3 g/dL and including the potentially fatal blood concentrations (above 0.35 g/dL).

It should be pointed out, however, that our study population consisted of alcoholics who recognized their problems and came voluntarily to seek treatment. It is possible, therefore, that they were on the descending limb of their blood alcohol curve where tolerance is more pronounced [*11*].

Our data do not support the contention that women are more susceptible than men to alcohol intoxication at similar blood alcohol levels. However, all our patients were chronic alcoholics and it is possible that chronic alcohol addiction reverses the natural sensitivity observed in naive female drinkers.

We conclude that, in chronic alcoholics, apparent sobriety or slight intoxication is not necessarily predictive of relatively low or normal blood alcohol concentrations. Therefore, in instances of emergency admission of alcoholics, one may very easily miss the diagnosis of high blood alcohol levels. In such circumstances, alcohol analgesia may dangerously mask severe trauma; and the high BAC may create a substantial risk for the administration of other central nervous depressants in spite of clinical sobriety. It seems, therefore, that, in such cases, determinations of blood alcohol concentration are always indicated to orient properly the medical care.

From a medico-legal point of view, the interpretation of a high blood alcohol concentration as an indicator of incapacitation, manifest drunkenness, or as an exclusive cause of death is unreliable. Therefore, for example, a bartender who serves a "chemically intoxicated" person, (that is, having ipso facto a high BAC) should not be accused of serving alcohol to an obviously "clinically intoxicated" individual.

One should not, however, conclude that apparent clinical sobriety in chemically intoxicated alcoholics reflects safe or acceptable driving capabilities. Driving combines a complex array of physical and mental activities that require anticipatory judgments, estimates of distance, peripheral vision, and short reaction time to unexpected hazards, all of which are known to be adversely affected by alcohol.

This is not to say that driving skills are totally exempt from the tolerance effect. A number of researchers [*34*], while reconfirming the well-known impairment associated with driving while intoxicated, found, under controlled experimental conditions, that some individuals show a similar tolerance as described above in relation to many required driving skills.

The mechanism of tolerance, with resultant apparent sobriety in spite of marked chemical intoxication, raises many interesting questions. The great disparity in toxic and lethal blood ethanol levels between alcoholics and inexperienced drinkers confirms the trend of thinking expressed in the literature, that is, the major factor responsible for it is biological in nature and not psychological and adaptational [*35–37*].

It has been demonstrated that chronic drinkers develop a more efficient process of detoxification and clearance of alcohol. The rate of detoxification has been shown to increase with the duration of alcohol intake and the amount ingested. The more effective elimination rate of ethanol is apparently related, not only to the chronic ingestion, but also to the magnitude of blood alcohol concentration. It has been experimentally demonstrated that the elimination of alcohol in heavy drinkers at high blood alcohol concentrations is about 40% higher than the elimination rate at lower blood alcohol levels in the same individuals [*38*]. This phenomenon is associated with an increase in both alcoholic dehydrogenase and microsomal enzymes oxidating system (MEOS) levels [*39*]. While these mechanisms explain the capability of experienced drinkers to show lower levels of blood alcohol after drinking the same amounts as nonexperi-

TABLE 2—*Tolerance at high blood alcohol concentrations.*

Authors	*N*	Age/Sex	BAC, mg/L	Circumstances	Alcohol Intake, mL[a]	Activity[b]	Recovery/Release
Hammond et al [*25*]	1	23/F	7 800	hit and run driver	390	coma in jail Class 1A	y/"sober" (at 1900 mg/L) in 12 h
Linblad and Olsson [*28*]	16	40.2 ± 13 (range 24-63 14M/2F	6 320 + 680 (range 5 220-7 730)	unspecified E.R. admissions	?	Coma O-A:8 Coma IA:6 Coma IIA:2	y/"sober" in 12 h
Poklis and Pearson [*26*]	1	52/M	6 500	unconscious in bar	430-530	coma	y/"sober" in 12 h
Berild [*29*]	1	59/M	11 270	suicide attempt	750[c]	coma	y/release after 1 month
Linblad et al [*33*]	65	28.6 ± 32 (range 16-48) 47M/18F	2 680 + 100[a] (range 1 200-5 400)	minor trauma minor medical/surgical complaints		appearing sober, ambulatory, oriented, followed commands, and so forth	
Johnson et al [*30*]	1	24/F	15 100	abdominal pain	750[c]	agitated, alert, slight confusion, responsive	y/"sober" in 12 h
Kobayashi [*27*]	1	59/M	7 300	suicide attempt	230	coma	y/?

[a]Calculated as absolute alcohol.

[b]Coma grades: O-A—asleep, can be roused, answers questions, sits, drinks, and so forth;
IA—comatose, withdrawal from painful stimuli, and all reflexes present; and
IIA—coma, no withdrawal from painful stimuli—most or all reflexes present, no circulation, and respiratory embarrassment.

[c]Equivalent to 2½ fifths of 80 proof whiskey.

enced drinkers, they cannot account for the ability of alcoholics to withstand intoxication at similar blood levels as naive drinkers.

Tolerance to high blood alcohol concentrations obviously implies a mechanism of central nervous system adaptation to the intoxicating action of alcohol. The ability of alcoholics to withstand the intoxicating effects of alcohol has been ascribed to a number of mechanisms. The capability of certain individuals to withstand high blood alcohol concentrations with little or no clinical evidence of intoxication appears to be a tolerance phenomenon similar to that seen in narcotic addicts [*40–42*].

Alcohol has been shown to intercalate into membrane lipids and produce an increased fluidity of the cell membrane and an inhibition of the (Na^+, K^+) activated adenosine triphosphatase (ATPase) [*43*]. The inhibitory action of ethanol on neurotransmitters at neural synapsal sites has been related to either reduced entry or increased removal of free intracellular calcium ions from the synapse [*44*]. It has been surmised that tolerance to alcohol develops as a result of a reversal of these processes which has been shown to occur with prolonged consumption. Experimental studies indicate that chronic administration of ethanol results in an increased saturation of the phospholipid component of mitochondrial and synaptosomal membranes, which results in increased rigidity of the structure and reduced binding of ethanol [*45*]. Concomitantly, there is apparently an increase in synaptic sensitivity to the influx of Ca^{2+} which counterbalances the ethanol effect.

The tolerance phenomenon is also related to the kinetics of the blood alcohol curve. The intoxicating effect of the same blood alcohol levels is considerably less on the descending slope of the alcohol curve than on its ascending limb, and maintaining constant blood alcohol concentration for a certain period of time is followed by a progressive recovery of coordinating skills [*46*]. The phenomenon of tolerance to alcohol may also be influenced by acetaldehyde.

Japanese, who demonstrate a much higher sensitivity to both vasomotor and circulatory actions of ethanol, as well as to its general intoxicating effect, have been shown to be less effective in the metabolism of acetaldehyde. Hormonal factors are also influential to some extent.

Our study confirms that the phenomenon of tolerance to alcohol is multifactorial in nature, with chronic ingestion of alcohol being a central factor. The recognition of the significant magnitude of tolerance in chronic alcohol users carries important medical and legal implications.

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Address requests for reprints or additional information to
Joshua A. Perper, M.D.
Allegheny County Coroner's Office
542 Fourth Ave.
Pittsburgh, PA 15219