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Experimental Induction of Hangover

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THE CLUSTER of unpleasant aftereffects which commonly follows ingestion of relatively large amounts of alcoholic beverages when the alcohol concentration within the body declines has received surprisingly little formal study. Yet prevention and treatment are obviously of great practical interest even for moderate or occasional drinkers, and this late phase is of fundamental importance as a major element in the sequence of events which comprise the total episode of alcohol intoxication.

Hangover also appears to be critically relevant to alcoholism. Reinitiation of drinking during hangover in order to moderate or terminate it is a conspicuous feature of the drinking behavior of many alcoholics, and psychodynamic mechanisms, perhaps associated with guilt and shame, may give the punishment represented by the hangover a key role in sustaining the pattern of excessive alcohol consumption (1). Similarly, a significant proportion of the incapacity to fulfill work responsibilities which results from heavy drinking is attributed to changes in mental, physical and motivational factors associated with hangover (2).

Furthermore, hangover is a topic of potentially broad significance for the study of psychobiological factors in health and disease, since its occurrence and severity are related not only to the specific chemical agents (ethanol and beverage congeners) ingested, but also are greatly influenced by complex personality, behavioral, social and environmental factors (3, 4). It is of specific interest for its potential usefulness as a method of experimentally inducing headache (5, 6, 7).

Symptomatology of Hangover

Most of the familiar components of the hangover were described more than 2500 years ago by a Hindu Ayurvedic medical writer²

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² Quoted in Leake and Silverman (8).

who included "vomiting, loss of appetite, heartburn, lassitude, continued thirst, tremors of head and limbs, palpitation, weakness of joints, respiratory difficulties, sleeplessness, giddiness, and a feeling as if one were wrapped in a sheet." Headache, fatigue, sweating, disturbance of balance and gait, pallor, tremor, nystagmus, general malaise, and disturbances of mood, with anxiety and depression, must be added to extend the list of common symptoms in non-alcoholics.

In alcoholics this symptomatology is usually both intensified and more complex. On the basis of interviews with 106 alcoholic patients, Tuominen (9) found that in early alcoholism, headache, general indisposition and vomiting dominated. With moderately advanced alcoholism, symptoms of tension, irritability, restlessness, stomach disturbances and guilt feelings were prominent; in long-standing severe alcoholism, cardiac disturbances, hallucinations, sleeplessness, severe depression, and delirium were also present. Despite the severity of physiological symptoms (which may often include exacerbation of pain from preexisting disease such as gastric ulcer) in the hangover of the alcoholic, psychological distress is often so intense that it overshadows physical suffering. Feelings of hopelessness and despair, self-deprecation, anxiety and depression combine to result in a severe or even profound dysphoria: "The general psychological picture in hangover is that of a person saying, 'the world doesn't offer me anything, I have lost everything, I am worth nothing'" (10). The complex topic of the hangover in the alcoholic is beyond the scope of this presentation, which will be limited to hangover symptomatology in nonalcoholics.

Pathophysiological Mechanisms

The underlying physiological mechanisms responsible for the symptoms of hangover remain little studied (11). Himwich (12), reviewing the pathophysiological factors which are probably relevant to hangover, listed overactivity of the vestibular system, accumulation of acetaldehyde, retention of potassium, lactic acidemia, disturbed fluid balance and gastrointestinal irritation. In addition to the role of alcohol itself, Birch (13) concluded on the basis of clinical observations that "smoking, bright lights, noise, and dehydration from diuresis and the sweating of exercise and dancing all play a part. . . . There is also the personal constitutional or psy-

chological factor. . . . The prime action of all the factors is on the nervous system" (13).

Some clinicians have concluded that transient liver dysfunction (14) or cerebral edema (15) can be induced by a single episode of alcohol intoxication and are important pathophysiological mechanisms in hangover. However, others believe that unless there is preexisting disease of these organs, such mechanisms in the liver (13) or brain (5) are unlikely to be pertinent in most instances. Recently, however, Di Luzio (16) and Mallov and Bloch (17) have shown that a single severe intoxication in healthy animals could cause appreciable accumulation of fat in the liver.

In view of the well-known drying action of alcohol on tissues, thirst—perhaps the most common symptom in hangover—may be related to a shift of intracellular water to the extracellular spaces. In 1938, Nicholson and Taylor (18) reported that alcohol induces a water diuresis and decreased blood pH levels. Lolli, Rubin and Greenberg (19) demonstrated that body water is shifted to extracellular compartments. Specifically, a mechanism related to inhibition of antidiuretic hypophyseal factors with decreased tubular reabsorption of water in the kidney has received experimental support (20, 21). Strauss, Rosenbaum and Nelson (22) reported that urine output was greatly increased after ingestion of whisky, while the rate of glomerular filtration remained constant. While Flynn (23) in a carefully controlled study found no constant relationship between general hangover symptomatology and alterations of water-electrolyte balance, the specific symptom of thirst may be more directly related. There are osmoreceptors in the hypothalamus which appear to regulate neurohypophyseal secretion of antidiuretic hormone (24). The sensation of thirst in hangover could represent both the consequence of water loss through the hypophyseally mediated diuresis and also through an action on osmoreceptors in the "drinking center" of the hypothalamus which have been shown to be responsive to shifts in extra-intracellular water balance (25).

Nicholson and Taylor (18) drew attention to the possible role of electrolyte shifts in the pathophysiological mechanisms of hangover and specifically suggested that potassium retention might be of special significance. Rubini, Kleeman and Lamdin (20) also have furnished experimental evidence to indicate that there are relatively long-lasting changes in electrolyte excretion following

alcohol ingestion. They observed a consistent fall in the excretion of sodium, chlorides and potassium.

Attention has also been directed to changes in blood sugar levels induced by alcohol (26, 27). Vartia, Forsander and Krusius (27) studied blood sugar values in 53 subjects who had been arrested for drunkenness the previous evening. They observed significant decreases in blood glucose levels in subjects with hangover and concluded that hypoglycemia is an important contributing factor in its genesis.

Wolff (5) inferred that most hangover headache probably results from painful dilatation of the intra- and extracranial blood vessels. Such headache often "throbs" or intensifies with each heart beat, and is relieved by carotid artery compression or vasoconstrictor agents (indicating its vascular nature) and is usually intensified by sudden head movements (indicating the participation of an intracranial component). Ethanol does dilate cerebral vessels (28) but maximum headache occurs in the hangover phase when the alcohol concentration is low. Wolff concluded that headache resulted not only from the action of alcohol and associated "impurities" but was dependent also on environmental and psychological factors related to the drinking episode. Since alcohol has rather dramatic effects on the vascular system—including peripheral vasodilatation—it seems likely that an episode of alcohol intoxication might induce disturbances in the balance of complex constrictor and dilator influences on the cranial vasculature which could outlast the period of elevated blood alcohol levels. A mechanism of "undamping" normal swings in craniovascular tonus may be pertinent to vascular headache of the migraine type (29).

One cluster of symptoms—dizziness, nystagmus, motor incoordination, visual disturbances, difficulties with balance and walking, headache, and nausea—suggests a common disturbance in the cerebellar-vestibular-visual system during hangover. Nystagmus has received special attention in recent years. It was reported in the first half of the 19th century that alcohol could induce nystagmus in animals (30). In 1941 Goldberg and Störtebecker (31), using modern recording techniques, observed an orderly relationship between positional nystagmus and level of blood alcohol. Goldberg (32) in 1961 showed that one type of positional nystagmus (PAN II), which can be recorded objectively, was predictably present during hangover and apparently was related to symptoms of dizzi-

ness, vertigo, nausea and vomiting. Murphree, Price and Greenberg (33) directed interest to the role of congeners in nystagmus induction by showing that fortification of relatively small amounts of vodka with congeners present in a large amount of whisky resulted in a dramatic increase in nystagmus as compared with vodka alone.

Disturbances of sleep during hangover have begun to receive experimental attention (34, 35), with results suggesting that alcohol may induce changes in the sleep-regulating mechanisms of the central nervous system which outlast the period of elevated alcohol levels in the body. For example, it is intriguing to note that the paradoxical or rapid-eye-movement phase of sleep was markedly inhibited during the second half of a night following ingestion of moderate amounts of alcohol (35).

Gastric and intestinal symptoms are apparently related to the mild irritating action of alcohol when present in strong solutions, and to such factors as stimulation of gastric juices, slowing of gastric motility, and pyloric spasm. Along with tremor, fatigue, cardiovascular phenomena, respiration changes, increased perspiration, and complex disturbances of mood, thought and behavior, they have received relatively little experimental study as components of the hangover.

Ingestion of moderately large amounts of alcohol results in a decrease of blood bicarbonate levels, due to elevated lactic acid. This lactacidemia has been found to persist into the hangover phase, and has been suggested as a pathophysiological mechanism in hangover (36).

Finally to be mentioned among the possible mechanisms of hangover is acetaldehyde, the first intermediate substance produced in the metabolic oxidation of alcohol (alcohol to acetaldehyde to acetate to carbon dioxide and water). Tetraethylthiuram disulfide (disulfiram) slows the speed of oxidation of acetaldehyde, permitting its accumulation (37). Jacobsen and his associates (37, 38) showed that disulfiram administered simultaneously with ethanol (in amounts that were innocuous when administered alone) resulted in many of the signs and symptoms of hangover, thereby suggesting that elevated acetaldehyde levels may be critically relevant to hangover pathophysiology.

A few studies have been directed to the question of whether or not hangover is accompanied by measurable changes in higher level brain functions (39). In 1901 Kürz and Kraepelin (40) re-

ported that concentration, memory and arithmetical computation were significantly impaired when testing was done on the day following evening ingestion of 2 liters of beer (80 g of alcohol). Similar results were reported in other older studies; however, recent studies (39, 41) with improved understanding of the complexities involved have failed to support such unequivocal results. Walther (41) reported improvement on test scores with repeated alcohol administration on successive days, and Takala, Siro and Toivainen (39), in a well-controlled study with a large series of subjects, failed to observe statistically significant impairment on behavioral tests the day following ingestion of 1.4 g of alcohol per kg (in beer or brandy). These studies, however, did reveal somewhat poorer performance in those who had received beer as contrasted with those who had brandy: "No significant impairment of the intellectual functions occurred as an aftereffect of brandy, whilst at least a tendency toward poorer results on the difficult intelligence tests was observable during beer hangover" (39). Tests administered during intoxication did not reveal any definite differences between the beverages.

With a concern for the role of hangover in disturbing the capacity for occupational work, Karvinen, Miettinen and Ahlman (2) studied physical performance (bicycle ergometer, hand grip strength, maximum jumping height) in firemen and policemen during the morning following ingestion of cognac-ethanol-water (33% alcohol) mixtures in amounts from 1.0 to 2.4 (mean 1.67 g) of alcohol per kg. Of the 30 subjects, 9 had severe hangovers. The remaining 21 were described as having slight or no hangover. The environmental setting was a dormitory at the Helsinki Institute of Occupational Health.

Possible Role of Congeners

Defined broadly, congeners are substances which appear in alcoholic beverages in addition to ethanol and water (8, 42). The conventional listing of congeners includes methanol, higher alcohols, low molecular weight organic acids, esters, phenols, aldehydes and other carbonyl compounds, tannins, solids, and a relatively large number of additional organic and inorganic compounds, usually in trace amounts. In addition, beers, wines and distilled spirits also contain significant amounts of sugar, maltodextrins, botanicals, nitrogen compounds, pigments, polyphenols, vitamins, histamine,

miscellaneous organic and inorganic compounds, etc. Any comprehensive listing of possible congeneric substances in beverage alcohols would be lengthy and would have important omissions. Trace amounts of a substance that altered enzyme kinetics in the metabolism of ethanol with resulting build-up of intermediate metabolites, for example, could be of major relevance to hangover, and yet not be among the group of "major" congeneric substances usually considered.

Certain of the congeners contribute to the taste, flavor and aroma of a beverage, but although the total congener content of the beverages usually consumed in the United States is low, the obvious toxicity of some of these compounds has made them suspect of being implicated in the production of hangover (43, 44, 45). Vodka is of special interest in this regard because of its low congener content; it is essentially neutral spirits and water filtered through charcoal (8). Its congener content can be assumed to be the lowest of all alcoholic beverages.

There is widespread lay belief that various kinds of alcoholic beverages differ greatly in their hangover-inducing properties (threshold, qualitative features, severity, etc.). Brewed beverages are widely held to induce more severe hangover than distilled spirits, certain wines are singled out as inducing special kinds of hangover. Some clinicians have concluded that specific allergies to the grains from which alcoholic beverages are prepared are pertinent (46). Because of its low level of congeners, vodka is commonly believed to be less likely to induce hangover (47, 48, 49).

Pharmacological and toxicological studies of some of the major congeners have been made in a few experimental animals and isolated tissues (43, 50, 51), but these observations are difficult to interpret with regard to possible adverse effects in man when administered in the small amounts present in the usual quantity of alcoholic beverage consumed. Similarly, studies of differences in the toxicity of various beverages in laboratory animals have been of little value in assessing the possible role of congeners in hangover.

A few studies specifically focused on the effects of congeners in human subjects have been published. In 1935 Muehlberger (52) reported that when equated in terms of ethanol content, equivalent amounts of low-congener-water-synthetic-ethanol mixtures and relatively high-congener-blended-whisky mixtures resulted in apparently identical degrees of behavioral change during the period of

intoxication. More recently, several studies (47, 48, 49, 53) have reported that a low-congener distilled spirit (vodka) results in less-frequent hangover when compared with high-congener distilled spirits. The observations of Damrau and Liddy (48) concern only low amounts (2 oz) of alcoholic beverage and mild, infrequent hangover, while methodological considerations of the observations of Brusch et al. (53) sharply limit the inferences which can be drawn, but these reports of a much lower incidence of hangover symptoms in subjects receiving vodka as contrasted with other distilled beverages add to the desirability of further studies of the role of congeners in hangover induction.

Purpose of the Present Study

The primary goal of the present experiments was to establish a useful method which would predictably induce hangover for experimental studies. A number of investigators have noted the difficulty of inducing hangover when synthetic nonbeverage alcohol is administered under the usual laboratory circumstances. Among others, Wolff (5) and his co-workers at the New York Hospital reported that attempts to induce headache and other hangover symptomatology by experimental administration of 60 to 90 cc of ethanol in the setting of the clinical laboratory were surprisingly unsuccessful. Emphasizing that "the taking of alcohol under laboratory conditions is quite different from social drinking," Wolff concluded that hangover headache "results not alone from the pharmacodynamic action of alcohol and 'impurities' on cranial vessels, but also results from the effects on the subject of late hours, loss of sleep, excitement of social intercourse (talking, singing, laughing), sustained effort and exhaustion, loss of restraint, and perhaps some remorse."

A few investigators (24) have taken advantage of "spontaneous" hangover by studies of volunteers from persons who had been identified as intoxicated the previous night by the police. Since reliable information on the environmental circumstances, amount of food ingested, etc., is lacking in these subjects, the usefulness of this category of subject is severely limited.

Recently several studies (2, 39, 54) have utilized with encouraging results a supervised but somewhat less restrained environment than the usual disciplined "laboratory" setting and mood which is necessary for many experimental studies. This approach

obviously presents special challenges for appropriate supervision, and sharply restricts the kind and range of observations that can be made, but it may be essential in duplicating the antecedent circumstances for optimal incidence of hangover.

A second major concern was the selection of the specific form of alcohol to be administered. Older attempts to induce hangover experimentally, such as those reported by Wolff (5), often used reagent or USP grade synthetic alcohol. More recent studies which have been successful in inducing a useful incidence of hangover symptomatology (2) have employed various commercially available alcoholic beverages. In the present series we selected two distilled beverages (bourbon and vodka) which would allow us to examine the effect of high versus low congener content.

METHODS

In general, we attempted to reproduce the circumstances under which hangover in nonalcoholics appears in our culture: (a) a party atmosphere, with encouragement of talking, singing and dancing; (b) a period of ingestion during the hours between 8 PM and 2 AM; (c) use of a beverage rather than "lab" alcohol; and (d) a bare minimum of scientific or medical procedures during the period of study. In addition, we attempted to (1) define and standardize the environmental and social setting; (2) control the amounts of food and drink ingested prior to, during, and after drinking; (3) control the type, rate, dilution and amount of the specific alcoholic beverages to be consumed; (4) control the setting after drinking has stopped; and (5) assess hangover symptomatology in a standard "blind" manner at a fixed interval after drinking.

For the purposes of the present study, assessment of hangover intensity and symptomatology was limited to the subjects' subjective verbal report. Several objective indicators, such as positional alcohol nystagmus (33), blood sugar levels (27), recordings of temporal artery pulsations (28), appear to be consistently altered during hangover and may prove useful as objective indicators, but as yet hangover remains a subjective phenomenon. Therefore, as a first step, we sought to induce hangover by replicating the components of its natural history; further, we limited our assessment of its presence and severity to the terms in which it is now defined, i.e., a group of characteristic subjective complaints.

The subjects were paid volunteers of both sexes between the ages of 21 and 35. All subjects were interviewed and weighed in a preliminary session. None were obese or grossly underweight. All were in good health; candidates with chronic diseases or other health abnormalities that might confound the results were excluded. All were occasional or moderate drinkers. Candidates who never drank as well as heavy drinkers and alcoholics were excluded, as were subjects who regularly re-

ceived medications or drugs. Almost all were residents of a large city in the western United States. Many were college or graduate students, but a number of occupations were represented.

The subjects were picked up by automobile from their homes between 6 and 7 PM and brought to the private house where drinking would take place. At the conclusion of observations (approximately 2 AM) they were returned by automobile individually to their homes.

The purpose of the experiment was explained to the subjects as being "to study the effect of measured amounts of alcoholic beverage" on several simple behavioral tasks such as serial subtraction of numbers, touching tip of nose with finger while eyes were closed and maintaining balance with eyes closed (i.e., the kinds of tests that law-enforcement officials might use in evaluating automobile drivers suspected of intoxication). They were told that they would be required to take a Breathalyzer test during the evening, and that someone would call on them the next morning to "see that they were all right." The subjects' attention was not directed to the hangover phase at this time. All subjects understood that the amount of alcohol to be administered would vary from subject to subject and that they might receive a relatively large amount. They were specifically told that hangovers could result. All subjects had to agree to drink both vodka and bourbon, since the choice would be determined by random selection. (A few potential subjects withdrew because of this requirement, presumably because of personal dislike of one beverage or the other.)

All subjects were requested to abstain from drinking alcohol or taking medication (aspirin, antacids, etc.) for 24 hours prior to the experimental session, and to eat a light lunch, and no food after lunch, on the day of the session. After arriving at the "party" house where the experimental sessions were conducted, the subjects were interviewed in a "testing room" regarding their intake of food and drink on that day. They then completed a brief (10 minutes) control series of simple behavioral tests including spoken serial subtraction of 7 from 100, number of errors in repeating 3 "tongue twister" sentences, procedure for eliciting Romberg sign, and rapid nose touching with alternate fingers (eyes closed).

The size of groups for individual sessions ranged from 4 to 10. In most sessions, an approximately equal number of men and women participated. For the sessions in which the largest amount of ethanol was administered (1.75 ml per kg) only men were used. In other sessions the amounts ranged from 1.0 ml per kg to 1.50. The 1.0 ml per kg dose was administered to 5 subjects as vodka and to 5 as bourbon; the 1.25 ml per kg dose to 5 as vodka and 4 as bourbon; the 1.50 ml per kg dose to 30 for each beverage; and the 1.75 ml per kg dose to 5 as vodka and 6 as bourbon.

In order to standardize the stomach contents and to minimize gastric irritation, each subject drank $\frac{1}{2}$ pint of milk approximately 15 min before beginning alcohol ingestion.

Each subject received a "punch" (55) consisting of chilled bourbon

or vodka diluted with chilled water and served in thermally insulated plastic mugs. The final solution contained 200 ml of ethanol per liter (i.e., a 20% solution by volume). The congener contents of the specific vodka (80 U.S. proof = 40% ethanol) and bourbon (86 U.S. proof = 43% ethanol) used were, respectively, as follows (in g per 100 liters): Acetaldehyde, 0.35 and 1.70; ethyl formate, 0.40 and 2.70; ethyl acetate, 0 and 82.50; methanol, 0.39 and 2.60; *n*-propanol, 0 and 11; isobutanol, 1.08 and 25; isoamyl alcohol, 0.42 and 120; fusel oil, 1.50 and 156; total, 2.64 and 245.50. These values were determined by gas chromatography.⁸ Free acids did not appear, probably because of esterification; the method was not appropriate for furfural. The total major congener contents, corrected to equal ethanol concentration, were 1 g per 100 liters in grain neutral spirits (base), 1.02 in vodka and 88.40 in bourbon.

The subjects were then directed to the "party" room with instructions to ingest a container of punch ($\frac{1}{2}$ the calculated amount) in a 30-min period. They were instructed to return for a second portion at that time, and to finish this in an additional 30 min. Most of the subjects were successful in accomplishing this; a few required from 15 to 30 min more to finish the second portion.

Each subject began to drink approximately 10 min (the time required for interview and behavioral testing) after the preceding subject. The time of beginning drinking was noted and the subject was returned to the testing room 15 min after completing drinking. At this time breath alcohol was determined (by Breathalyzer) and the behavioral tests were repeated. The subject then returned to the "party." A party atmosphere was encouraged by furnishing an appropriate party setting (private home, adequate space for dancing, music for dancing, etc.). The subjects represented a mixture of previously known friends and strangers. In all sessions a "party" atmosphere was soon established, with loud talking, singing, dancing, etc. The investigators remained outside the party area unless arguments or other problems developed. In each session a paid nonsubject "host" remained in the party area for the purpose of making introductions, encouraging a party atmosphere, and alerting the investigators about arguments or other potential problems. He drank small amounts (up to 1.0 ml per kg) of either bourbon or vodka during the evening.

At 1 AM each subject received a sandwich and $\frac{1}{2}$ pint of milk. At 2 AM they were returned by automobile to their homes with instructions to go to sleep as soon as possible.

At 10 AM the next morning (all sessions were conducted on Friday or Saturday nights, when the following day was a holiday for the subjects), the subjects were interviewed concerning hangover symptomatology. They were first asked by a participant who did not know how much or which beverage the subject had ingested the previous evening

⁸ We are grateful to the Center of Alcohol Studies, Rutgers University, for furnishing the analysis.

to rate any hangover they might have on a 0 to 7 scale (0 for no hangover at all, 7 for the most severe hangover possible). Next a check list of symptoms was read to them; they were asked to state whether or not they had experienced the listed symptom during the night or morning (thirst, fatigue, drowsiness, trouble in sleeping, general malaise, nausea, loss of appetite, dizziness or feelings of faintness, headache, depression, anxiety).

RESULTS

The simple behavioral tests administered before drinking and during the period of maximal blood alcohol levels were selected for their brevity, in order not to interfere with the "party" atmosphere developed, and are of only limited value in assessing degree of behavioral impairment. Table 1 contrasts performance on these procedures in the groups receiving vodka and bourbon. No significant differences were apparent.

Only 1 of 10 subjects who received 1 ml of ethanol per kg received a hangover rating of 2 or higher, 2 of 10 who received the 1.25 ml per kg dose, 33 of 60 who received 1.50 ml per kg, and 6 of 11 who received 1.75 ml per kg. Thus 1.5 ml of ethanol per kg or more, in these beverages, induced definite hangover in approximately 50% of the subjects. Lesser amounts only occasionally induced definite hangover.

Table 2 compares the incidence and severity of hangover after bourbon and vodka. In the group that received the 1.50 ml per kg dose, 20 of the 30 subjects who received bourbon reported definite (rating of 2 or more) hangover, as contrasted with 13 of the 30 who received vodka. It is noteworthy that severe hangover (ratings greater than 3) was reported by 10 of the 30 who received bourbon, but by only 1 of the 30 who received vodka. Ratings of the severity

TABLE 1.—Behavioral Assessment during Maximal Blood Alcohol Level*

	Bourbon	Vodka
<i>Series of Subtraction:</i> Mean increase in errors	1.7	1.2
<i>Digit Span:</i> Subjects with digit span less than control number	15	17
<i>Speech Defects:</i> Subjects with more errors than control trial	6	5
<i>Rhomberg Sign:</i> Subjects falling in 30 sec	9	7

* Ethanol dose in bourbon or vodka = 1.5 ml per kg. Thirty subjects received each beverage. None of the differences are significant.