Menstrual Cycle Influences on Acute Alcohol Intoxication (Estradiol, Progesterone, Blood Alcohol Level).

Alan Russell King

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MENSTRUAL CYCLE INFLUENCES ON ACUTE ALCOHOL INTOXICATION

The Louisiana State University and Agricultural and Mechanical Col. PH.D. 1984

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Menstrual Cycle Influences on Acute Alcohol Intoxication

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in The Department of Psychology

by Alan Russell King
B.A., Nicholls State University, 1977
M.S., University of Southwestern Louisiana, 1979
May 1984
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Completion of the requirements for this Ph.D. degree has required nine years of hard work, involving contributions from so many individuals along the long and challenging course. My interest in higher education began in high school under the subtle influences of Brother Alfred and Sister Rosalyn and the not-so-subtle promptings of Gail Salvatore. The road toward my terminal degree began in earnest with my introduction to Lavada Baggett at Nicholls State University back in year one. At once the ambition was clear, though the course was, at best, uncharted and uncertain. I reflect on my days at U.S.L. and the impact of Drs. McWhirter, Hotard, Leblanc, and Aurich. I remember my first year at L.S.U. and excitement of working with Drs. Riopelle and Hill in the primate lab. Earl K. Long Hospital followed, and the experiences accumulated during that time are certainly too numerous to recall in one sitting. There was my internship year at the V. A. Hospital in New Orleans and the memories elicited by the experience. And then, of course, there was Sam, and Melinda, and Alan, and Elson, and Bill, and Mark, and Dave, and all of my other friends who were so important along the way. An acknowledgment section really is inadequate to express the appreciation I feel for so many, but a few individuals must be given formal recognition.

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ABSTRACT

Recent studies suggest that the course of acute alcohol intoxication fluctuates as a function of the menstrual cycle. Attenuated behavioral effects of alcohol at descending, as opposed to corresponding ascending, phases of elimination and absorption further suggest that acute alcohol tolerance develops over the course of intoxication. The present study was designed to examine the course of acute alcohol intoxication at different points within the menstrual cycle and to analyze relationships among sex hormone levels and blood alcohol dependent measures. Acute alcohol absorption and elimination was investigated in 12 adult, normally cycling women administered a moderate dose (0.66 ml/kg) of 95% alcohol ingested over a 15 minute period. Women were tested in a repeated measures design on Days 2, 14 and 22 of their menstrual cycles. Plasma levels of estradiol and progesterone were collected prior to each session to measure changes in sex hormone levels associated with the menstrual cycle. Breath analyses of alcohol content were conducted at five minute intervals throughout the course of absorption and elimination. Measures of eye-hand coordination and standing steadiness were administered at baseline, at peak blood alcohol concentration, and at predetermined times on the absorption and elimination limbs of the acute alcohol intoxication curve. Self-ratings of intoxication levels were requested every 20 minutes until ratings of "completely sober" were achieved.

Women did not differ significantly in peak blood alcohol concentrations or in absorption times across phases of the cycle. Women eliminated alcohol more quickly on Day 22 of their cycles (p<.05),
although differences occurred only at low blood alcohol concentrations. Correlations between sex hormone levels and elimination times were inadequate to account for the findings. Likewise, body water percentage changes across the menstrual cycle were unrelated to differences in elimination times. It was suggested that the alcohol dose administered was too low to allow an adequate test of acute tolerance effects on the behavioral measure of hand-eye coordination. The standing steadiness measure proved unreliable, and the self-ratings indicated that subjects reported feeling "totally sober" when blood alcohol concentrations averaged about 30 mg%. Suggestions for future research are offered.
Menstrual Cycle Influences on Acute Alcohol Intoxication

Heightened public awareness of the deleterious effects of alcohol intoxication has become a distinguishing characteristic of the early 1980's. Attention has focused on automobile accidents since alcohol intoxication is linked closely to 50% of the nation's 50,000 annual automobile fatalities (Seixas, 1981). Estimates of the number of drinkers in the United States have remained constant at around 100 to 145 million people, with about 9% of this group thought to have serious drinking problems (Farris, 1974; Rosenberg, 1971). Psychological research has examined extensively etiological factors which influence alcohol consumption in problem drinkers. The present study instead examined the course of acute alcohol intoxication in average or normal drinkers.

It is a misconception to assume that the factors influencing alcohol are understood completely. A number of variables have been isolated such as ingestion rate, dose concentration, amount of food in the digestive tract, time of day, and others, but significant variance still remains in absorption and elimination data after such factors are experimentally controlled. Women have shown greater variability than men in response to alcohol ingestion, and speculations of hormonal influences have been supported by convergent lines of animal and human findings (Goldberg & Stortebecker, 1943; Jones & Jones, 1976; Kask, 1929; Klotz, 1937; Stortebecker, 1939). Women often are excluded from alcohol studies in an attempt to control for possible sex-specific influences. Studies examining specific factors in female alcohol metabolism are few in number.
The introduction of this study begins with an examination of the biological processes involved in alcohol metabolism, followed by a discussion of the menstrual cycle. A literature review will be used to isolate key response correlates of acute alcohol intoxication. This review is intended to provide a rationale for the proposed research objectives and methodology.

**Human Alcohol Metabolism**

Ethanol is one of a class of organic aliphatic hydrocarbon compounds containing an hydroxyl group which has come to be known as "alcohols". Other alcohols such as methyl alcohol, butanol, and octanol are either toxic in small quantities or found in such small amounts in naturally fermented beverages to be of minimal social significance. Ethanol is the principle active ingredient in all alcoholic beverages which are produced through fermentation of organic compounds such as grapes, wheat, barley, corn, potatoes, or honey with yeast (Seixas, 1981). The terms ethanol and alcohol commonly are used interchangeably.

The metabolism rate of ethanol involves interacting processes which have been elusive to identify and understand completely. For purposes of the present research, alcohol absorption and elimination are conceptualized as discrete and independent processes. Alcohol absorption refers to infiltration of ethanol from the mouth, stomach, and small intestine into the bloodstream. Elimination refers to the oxidation of alcohol in the liver and the 5% release in unchanged form in urine, breath, perspiration, and other mediums. This model oversimplifies the interactive nature of the metabolic processes but does have descriptive value. Ascending and descending limbs of the blood
alcohol curves can be conceptualized as representing the phases of absorption and elimination of alcohol respectively.

Absorption of ethanol occurs through mucous membranes in the mouth, through the stomach, and most rapidly through the duodenum, with absorption so complete that feces alcohol content essentially is zero (Seixas, 1981). Since approximately 80% of ingested alcohol is absorbed by the small intestine as quickly as it leaves the stomach, food ingestion significantly slows the time to peak blood alcohol levels and the time for total elimination by delaying gastric emptying (Becker, 1970; Ritchie, 1965).

Alcohol is absorbed directly into the bloodstream and circulates throughout the body. About 5% of alcohol is excreted unchanged in urine, breath, bile, tears, and perspiration (Becker, 1970; Isselbacher & Greenberger, 1964). Metabolism by the liver proceeds by the following pathway: ethanol + alcohol dehydrogenase (ADH) → acetaldehyde + acetaldehyde dehydrogenase → acetate + acetate thiokinase → acetyl CoA. Ethanol first is converted to acetaldehyde through the enzymatic action of alcohol dehydrogenase (ADH). Acetaldehyde is converted to acetate through the action of acetaldehyde dehydrogenase. Acetate is converted to acetyl CoA through acetate thiokinase activity. The concentration of acetate thiokinase is relatively low in the liver, and the final steps in the metabolism process occur in other sites in the body where this enzyme is present in sufficient quantities. The breakdown of ethanol to acetaldehyde is recognized as the rate limiting step in metabolism. This rate limiting step results essentially from a slower formation than subsequent removal of acetaldehyde in the body. Increased alcohol intake which
exceeds this oxidation rate will result in linear increases in blood alcohol levels and associated inebriated states.

The alcohol metabolism rate traditionally has been considered to be constant throughout elimination, following zero order kinetics (Makoid, Sieg & Robinson, 1976; Widmark, 1937), though recent disagreement should be noted (Sutker, Tabakoff, Goist & Randall, 1983). The zero order kinetics model predicts that the rate of alcohol elimination is constant throughout the entire elimination period despite the blood alcohol level in the body. This rate of oxidation is estimated at 15 mg% (Haggard & Greenberg, 1934) or about 3/4 ounces of alcohol per hour (Goldberg, 1950). The popular Widmark (1933) equation utilizes a zero order kinetics model and has been used extensively to predict the course of absorption and elimination in the human body.

**Measurement Considerations.** Alcohol concentrations can be measured in numerous mediums including blood, breath and urine. Prior to the sophistication in breath analysis achieved over the past 20 years, heavy reliance was placed on blood samples which were cumbersome and expensive to collect on the repetitive basis necessary for research. Breath analysis represents an important research advance by offering investigators a simple, quick and easily administered measure of blood alcohol levels (BALs). Breath concentrations of alcohol are estimated to be 1/2300 of that in blood (Jones & Jones, 1976), and correlations between blood alcohol estimates derived from blood and breath analysis range from about +0.95 to +0.96 (Dubowski, 1970).
Alcohol levels are calculated in terms of the ratio of alcohol to blood volume and are expressed as blood alcohol concentrations or levels. A BAL of 0.10% indicates that there are 100 mg of ethanol for every 100 ml of blood or that alcohol composes 1/10 of 1% of the blood. BALs are referred to commonly by mg%, a convention utilized in the present study. Legal intoxication has been defined operationally as BALs above 100 mg% (or 0.10%) in most localities. The term "intoxication" will be used in this study to indicate measurable BALs of any level.

The alcohol concentration of beverages is designated by its proof. A 200 proof alcohol rating denotes pure 100% ethanol. A mixture of 100 proof contains 50% ethanol. A rough estimate is that BALs may increase approximately 0.02% to 0.04% in a 150 pound individual for every ounce of ethanol consumed. According to this estimate, it would require approximately six to eight ounces of 100 proof alcohol ingested over a one hour period to produce BALs over the legal intoxication limit. Continued ingestion exceeding 3/4 ounces of alcohol per hour thereafter would lead to increased inebriation.

Parameters of Clinical Significance. Alcohol metabolism generates a characteristic absorption and elimination curve which is distinguished by quick initial BAL increases, a peak BAL, and a progressive decrease in BALs. Jones and Jones (1976) illustrated the classic curve for three different dosages in a single male subject (see Figure 1). Several clinical variables can be derived from this curve. The peak BAL is of most importance since it represents the highest degree of intoxication experienced during the entire absorption-elimination
process. Under certain conditions, the time period from initial alcohol consumption to peak BAL (absorption time) also is important. Some individuals may judge their level of inebriation partially by the time periods which have ensued since consumption. A person may feel capable of driving since drinking was initiated "only" 30 minutes before. In actuality, their peak BAL may occur around this same time. The time period from peak BAL to complete elimination (elimination time) may have similar importance. An individual may feel capable of driving because cessation of drinking and sleep onset occurred five hours before (e.g., person goes to sleep at 2:00 a.m. and awakens at 7:00 a.m. to drive to work). An individual could be intoxicated upon awakening if their BAL at sleep onset was 18 mg%. Thus, the dependent variables of clinical interest are absorption time, peak, BAL, and elimination time.

The Menstrual Cycle

The female menstrual cycle is the product of cyclical hormonal secretions and associated morphological changes which are precipitated and regulated by the hypothalamic-pituitary-ovarian axis. Estrous cycles are seen in other vertebrate groups while the menstrual cycle characterizes the primate female reproductive system. The two types of cycles differ essentially in the duration of sexual receptivity observed during the period. While the endocrinology is often similar, primates are receptive to male advances at virtually all points during the cycle rather than at those circumscribed periods of estrus where estrogen activity is elevated. The cycle lengths and durations of estrus differ sharply among species. The length of the human menstrual cycle also varies significantly among women with a mean of 28 days and
a standard deviation of about one week (March, 1979). Flow duration shows little variability with the mean flow lasting about four days.

The hormonal events responsible for the menstrual cycle involve primarily the gonadotrophic release of follicle-stimulating hormone (FSH) and lutenizing hormone (LH) along with the associated secretions of the estrogen and progesten sex hormones. These four endocrine factors serve as the principal agents and major focus of research attention. The role of the hypothalamic releasing factor for LH (LH-RH) and putative releasing hormone for FSH (FSH-RH) should be noted also, but the actions of both of these are not completely understood at this time and will not be discussed further.

Substances which elicit reproductive proliferative changes such as follicular and endometrial development have come to be known as estrogens. The three major estrogens thus far isolated in the human body include estriol, estrone, and most importantly, estradiol. Estradiol has emerged as the primary naturally active estrogen in the body and receives the majority of research attention.

Substances which prepare the sex organs for implantation and nourishment of the blastocyst in the uterine mucosa are known as progestens. Progestens help to maintain pregnancy. A variety of synthetic progestens have been developed though the number of naturally occurring ones is low. As estradiol is the primary estrogen in human primates, progesterone is the essential progesten.

Sequential analysis of major hormonal and physiological events constituting the menstrual cycle now follows. Appendices present a more complete delineation of sex hormone and gonadotrophin effects (Appendix A: Estrogens; Appendix B: Progestens; Appendix C: Gonadotrophins). Figure 2 presents a summary of the hormonal changes.
The ovaries, fallopian tubes, and uterus serve as the primary organs responsible for the female reproductive cycle. Of most importance are the ovaries, small glands of ovoid shape approximately 1 X 2 X 1 cm in size which reach maximum size during puberty and decline thereafter in a slow, progressive manner. The number of follicles contained in the ovary is estimated at between 300,000 and 450,000 (Watzka, 1957). Primordial follicles is a term given to follicles containing oocytes which have not yet begun to develop. A minute fraction of the total number of follicles begin maturation each cycle but only one will eventually ovulate while all of the others will become atretic. Approximately 99.9 percent of the oocytes present at birth will deteriorate eventually prior to maturation (Botella-Llusia, 1973).

The follicle continues to grow or ripen during the first two weeks of the menstrual cycle. The Graafian follicle is a term reserved for mature follicles primed for impending rupture at ovulation in response to an LH surge. At ovulation the follicle releases a single ovum into the fallopian tubes for its path to the uterus. Ovulation forces a marked reduction in the internal pressure of the follicle which causes it to fold up, shrink, and retract. The stoma of the ruptured follicle becomes occluded ultimately leading to additional structural and biochemical changes which produce what is known as the corpus luteum. The corpus luteum then proliferates as an essential entity in itself, synthesizing and secreting both progesterone and estrogen sex hormones. The corpus luteum also degenerates during the latter part of the cycle.
The ovary is therefore the most essential contributor to the reproductive cycle through initial development of a mature follicle which eventually will rupture at ovulation liberating the ovum for potential fertilization. The follicle then undergoes substantial morphological changes and transforms at post-ovulation to the corpus luteum which has significant hormonal ramifications which will be discussed shortly. A number of excellent comprehensive sources can be consulted for a clearer understanding of basic menstrual cycle physiology and endocrinology (Botella-Llusia, 1973; Guyton, 1976; Mishell & Davajan, 1979).

Menstruation and ovulation provide distinctive events during the cycle and are useful in determining important points in the menstrual sequence. Menstrual flow has been arbitrarily and consensually agreed upon to serve as day 1 of the cycle since it is the most overtly recognizable event in the entire sequence. At the point of menstruation the circulating estrogen level is at its lowest point and progesterone activity virtually is absent. Low progesterone and estrogen levels allow the release of FSH which stimulates follicular development and preparation for ovulation. Menstruation ends at approximately day 4 of the cycle. From onset of menstrual flow to ovulation at approximately day 14, FSH continues to decline in response to increasing estrogen secretion by the ovarian follicle. Around day 14 a sharp LH surge is triggered by the rapidly increasing estrogen levels which stimulates the rupture of the single, most mature follicle in the cohort and the release of an ovum into the fallopian tube entrance for possible fertilization. Just prior to ovulation, progesterone release is stimulated with the origin probably being the Graafian
follicle. An FSH and/or LH surge probably is responsible for the sudden drop in basal body temperature (about .5 degrees Fahrenheit) observed prior to ovulation. Ovulation generally occurs within 24 hours of the temperature drop and FSH/LH surge. The period from day 1 to ovulation is known as the proliferative or follicular phase of the cycle. During this phase, increasing estrogen secretions prime the fallopian tubes, uterus, and vagina for the subsequent effects of progesterone which is essential for successful implantation of the blastocyst.

At ovulation the follicle is transformed to the corpus luteum. Both LH and FSH are inhibited by high estrogen and increasing progesterone levels. Estrogen production takes an initial post-ovulatory drop since the primary origin of estrogen synthesis, the follicle, is in the process of transformation. Functioning of the corpus luteum is forthcoming, leading to progressive increases in both progesterone and estrogen synthesis and release. The addition of progesterone to the bloodstream finalizes uteran preparation for blastocyst implantation in the endometrium. The individual shows a .5 to 1 degree Fahrenheit increase in basal body temperature in response to increasing progesterone levels during this phase.

Progesterone levels reach a maximum about day 22 of the cycle, and estrogen levels also are elevated markedly at this time. The corpus luteum will regress progressively thereafter if successful blastocyst implantation does not occur. Decreased estrogen and progesterone levels associated with the demise of the corpus luteum results in a deterioration and sloughing of the endometrial lining which occurs at the end of the cycle. Low levels of both sex hormones
trigger FSH release just prior to menstruation which reinitiates the cycle. The portion of the cycle from ovulation to menstruation is known as the luteal or progestational phase. If pregnancy ensues, the functional integrity of the corpus luteum will persist for a number of months though the responsibility for estrogen and progesterone synthesis and secretion will be transferred gradually to the placenta.

**Literature Review**

It is logical to speculate that the hormonal changes occurring within the menstrual cycle could influence possibly the course of acute intoxication in women. Metabolic effects of the sex hormones would account for increased variability in women's responses to alcohol. Interestingly, a small body of human and animal research was isolated for the present review which suggests that significant within-cycle differences do exist. This data will be examined at the outset followed by a discussion of possible mechanisms of hormonal effects. An examination of the behavioral literature on acute alcohol intoxication is included also, in an attempt to isolate several behavioral measures of intoxication which would complement major physiological indices such as peak BAL and absorption and elimination times. Finally, subjects' ability to discriminate levels of intoxication will be discussed. Of interest is the correspondence between perceived and actual levels of intoxication during absorption and elimination.

**Menstrual Cycle Effects on Blood Alcohol Curves.** Scientific recognition of the potential influence of female sex hormones on alcohol absorption and elimination can be traced back to the early animal studies of Kask (1929) and Klotz (1937) which demonstrated
that castration of female rats exacerbated the behavioral effects which resulted from acute alcohol administration. Stortebecker's (1939) later report offered further evidence that castrated female mice and rabbits were more sensitive than intact female controls to the effects of alcohol administration as measured by simple reflex losses and lethality. In this study, exogenous estrogen injections were found to reverse largely the depressant effects of the alcohol dosage on performance. A follow-up study by the same research team (Goldberg & Stortebecker, 1943) implicated a direct antagonistic effect of estrogen rather than a secondary effect on performance through alterations in alcohol metabolism. Though these early studies elevated awareness of possible gender differences, the scientific community generally avoided direct examination of this potential source of variance and instead controlled for it by utilizing male subjects in their investigations of alcohol metabolism (Corrigan, 1974; Jones, 1975; Jones & Jones, 1976).

A minimal amount of information was obtained regarding estrogen and progesterone influences on alcohol metabolism until the 1970's. A number of studies appeared at this time which claimed to demonstrate a variety of behavioral, emotional, cognitive and physiological alterations which were associated with menstrual cycle changes (Jones & Jones, 1977; Jones & Vega, 1973; Linnoila, Erwin, Ramm, Cleveland & Brenole, 1980; Little & Zahn, 1974). Jones and Jones can be credited with pioneering a body of recent research which focused attention specifically on human gender differences in alcohol metabolism. Their studies of alcohol metabolism in women were summarized in a far-reaching 1976 book chapter which left many unanswered questions about menstrual
cycle influences. Their conclusions now will be reviewed, followed by a critical assessment of their supportive evidence.

In an initial study by Jones and Jones (1976), 20 female and 10 male social drinkers between the ages of 21 and 35 were examined. Female subjects were tested at two of three points in the cycle including day 1 (initiation of menstrual flow), day 14 (around ovulation), and day 28 (premenstrum). Male subjects were tested twice, two weeks apart. Each subject was administered .66 ml of 95% USP ethanol per kilogram (kg) of body weight mixed with orange juice in a 20% concentration. Breath estimates were collected every five to ten minutes until elimination was complete. The female sample obtained higher mean peak levels (0.072%) than their male counterparts (0.063%), with this difference found to be statistically significant at the p < .05 level. The female sample generated mean peaks of approximately 0.064%, 0.068%, and 0.080% at days 1, 14, and 28 respectively while males produced mean peaks of 0.063% at both points of data collection.

A replication of this study was completed later, utilizing 22 women and 11 men. The women were again found to have a significantly higher (p < .01) mean peak BAL of 0.072% while the men showed an even lower mean peak 3AL of 0.059%. The authors concluded that females become more intoxicated than males at all points within the menstrual cycle when given identical doses of alcohol.

Further experimentation was undertaken to determine if the obtained results could be generalized to different alcohol doses. With this objective in mind, two men and two women were administered three different alcohol doses (0.33 ml/kg, 0.66 ml/kg, and 1.32 ml/kg), with sessions separated by two day intervals. Both female subjects were
tested during the inter-menstrual period around ovulation. The findings once again demonstrated consistently higher female BAL peaks over all three dosages (low dosage: males = 0.03%, females = 0.04%; medium dosage: males = 0.06%, females = 0.08%; high dosage: males = 0.11%, females = 0.16%). Women were found also to absorb alcohol faster (reach peak sooner) and these gender differences in metabolism were accentuated by higher dosages.

Jones and Jones (1976) extended their investigation of sex hormone effects in women by examining a group of 11 oral contraceptive women in addition to groups of 11 men and 11 normally cycling women. The oral contraceptive group had been taking the pill for an average of 20.2 months (range of 2 to 48 months). A variety of pill brands were used by these 11 women including Ovulen, Oracon, Ortho-Novum, Norlestrin, Demulen, and Ovral. The women were administered moderate alcohol dosages at three points within the cycle including menstrual flow (days 1 to 3), ovulation (days 13 to 15) and premenstrually (days 26 to 28). The women on oral contraceptives were found to metabolize alcohol slower than the normal cycling women, indicating that the former group remains sensitive to alcohol for longer durations after ingestion. There were no differences between oral contraceptive and normally cycling women in mean peak BALs (about 0.072%), however, both female groups were significantly higher than the males (about 0.059%).

A complementary study by Jones and Jones (1976) compared three women who had natural decreases in estrogens as a result of hysterectomies with three normally cycling women. Unfortunately, two out of the three hysterectomized women were taking hormonal supplements which largely confounds the results of the study. The metabolism rate of
these two subjects was similar to that of women taking oral contraceptives while the one hysterectomized woman without hormonal supplements was found to have a similar metabolism rate as that of the three normally cycling subjects. One subject quit taking her hormones for one week, and further testing demonstrated predictable increases in alcohol metabolism rates, further implicating the role of the sex hormones in somehow slowing the rate of alcohol metabolism.

An offshoot of the present series of alcohol studies was conducted by Jones and Jones in which they administered 0.66 ml/kg of alcohol to three female subjects on a daily basis throughout an entire monthly cycle. The mean peaks for these three women (0.073%, 0.069% and 0.076%) were comparable to the results previously presented. Of more interest to the authors, however, were large peak BAL variations seen in all three subjects throughout the cycle. One subject, for example, was reported to generate peak BALs which ranged from 0.04% to 0.10%!

Highest BALs for these three subjects were found around premenstrum (day 28) and ovulation (day 14), although they noted that the trend is most clear for the former period.

It also is interesting to note reports of increased alcohol consumption associated with the premenstrual-menstrual point in the cycle. Premenstrual consumption increases have been reported with alcoholic women (Belfer, Shader, Carroll & Harmatz, 1971; Podolsky, 1963), and rats have been shown to voluntarily consume less alcohol around estrus (Aschkenasy-Lelu, 1960 a,b), after exogenous estrogen injections (Aschkenasy-Lelu, 1958; 1960 a,b; Mardones, 1960; Wallgren & Barry, 1970), and after oral contraceptive administration (Eriksson, 1969). Jones and Jones (1976) have reported also that women on oral contra-
ceptives consume less alcohol than their normally cycling counterparts. A recent study by Sutker, Libet, Allain and Randall (1983), however, failed to find significant differences in alcohol consumption during the cycle among normally cycling women.

From their series of investigations Jones and Jones arrived at three major conclusions about alcohol metabolism in women. First, they stated that women will obtain consistently higher peak BALs than men given dosages of alcohol at all points in the cycle. Second, women's peak BALs will have greater variability than that of men in response to alcohol ingestion. Third, fluctuations in sex hormones probably serve to mediate these blood alcohol effects.

The potential mechanisms by which estrogen and progesterone fluctuations might affect alcohol metabolism are numerous and limited primarily by one's knowledge of the underlying biochemical reactions involved. Proposed mechanisms are difficult to find in the literature at this time, which is probably not surprising since the occurrence of within cycle differences has yet to be established firmly. Nevertheless, these three potential mechanisms can be mentioned.

Differences between men and women in body water content have been examined closely and offer a possible explanation for gender differences in acute intoxication data. Water occupies approximately 65 to 70% of the adult male and 50 to 55% of the adult female body weight (Bell, Emslie-Smith & Patterson, 1976). Water content variations between individuals are largely the result of fat content differences since water percentages in lipid-free areas of the body remain essentially constant. Adipose tissue contains approximately 2.3% water in comparison to muscle tissue's 51% water content. Adipose tissue is water
insoluble, and thus, increased body fat means decreased body water. More adipose tissue is found in women than men which reduces body space for water molecules in the former group. Men are found to have more muscle tissue. In particularly obese individuals, water content may fall below 40% of the total body weight. It is assumed that alcohol is distributed uniformly throughout the water in the body (Lovell, 1972), and alcohol can be assumed to be more diluted in males than females. Such a body water dilution factor has been demonstrated recently in a study which accounted significantly for observed gender differences in alcohol metabolism through an analysis of body water percentages (Sutker, Tabakoff, Goist & Randall, 1983). Therefore, hormonal fluctuations are not necessary to account for gender differences in major alcohol metabolism parameters.

Differences within women at various points of their menstrual cycles are considerably more difficult to explain through body water composition differences. Water retention is a common complaint (as frequent as 80%) of women at the premenstrual and menstrual points in the cycle (Brooks, Ruble & Clark, 1977; Moos, Kopell, Melges, Yalom, Lunde, Clayton & Hamberg, 1969). It is conceivable that the sex hormones could lead to water retention which could mediate within cycle differences in peak BALs via a dilution effect, but various lines of evidence argue against this hypothesis. Water retention is difficult to quantify and measure reliably. Weight gains, however, show negligible changes throughout the cycle, leading one to question the significance of within cycle body water percentage changes. Further, Mattsson and Schoultz (1974) found that a placebo was equally effective in reducing "feelings of swelling" at premenstrum as a diuretic. Bell,
et al. (1976) studied fluid retention in pregnant women and found little change in retention until at least 20 to 30 weeks after fertilization. Hormone levels are much higher during the first trimester of pregnancy then those reached at any point during a normal menstrual cycle. Therefore, female complaints of water retention stimulate interest but are largely inadequate to account for significant intra-subject differences.

Estradiol levels and ADH activity have been linked. Estradiol administration to female rats has been found to increase ADH activity by increasing liver weight (Mezey, Potter & Tsitouras, 1981). In the rat, however, such changes are not accompanied by significant changes in elimination rates. Further, no evidence could be found which shows cyclical changes in ADH synthesis activity as a function of the menstrual cycle.

Glucocorticoids are reported to accelerate the elimination of alcohol (Goldstein, 1983), thus giving rise to speculation that increased hormone levels might elicit hyperadrenocortical activity. Progesterone is related chemically to steroid hormones and can be converted to corticosteroids (Botella-Llusia, 1973). Thus, a possible mechanism for menstrual cycle effects involves the adrenal-pituitary-hypothalamic axis. Nevertheless, such notions will remain speculation until within cycle differences are firmly established, and proposed mechanisms become the focus of research inquiry.

Although Jones and Jones findings support their notions about menstrual cycle effects, examination of the data base upon which the writers relied suggests that these conclusions may be premature. A number of fundamental and persistent problems detract from the overall significance of their work. A central problem is lack of biochemical
confirmation of stages within the menstrual cycle. Sharp hormonal fluctuations characterize the very nature of the cycle, yet Jones and Jones reported data collection from women "around" days 1-3, 13-15 and 26-28 of the cycle. The day of the cycle gives important indications of hormonal correlates but largely is inconclusive without direct biochemical confirmation. Progesterone levels may vary substantially from day 26 to 28, and subjects tested prior to ovulation will be experiencing estrogen surges while those tested post-ovulation will be influenced by slight decreases in estrogen levels. Even more important than this methodological shortcoming is the total lack of verification of ovulation. Anovulatory cycles have been reported to be a "relatively common occurrence" in normal women (Botella-Llusia, 1973) with estimated incidences found to vary widely depending on the methodology employed to make this determination. This problem of anovulatory cycles can cause significant problems since female endocrinology is characterized by an absence of progesterone in the luteal phase rather than the post-ovulatory surge anticipated during normal cycles. A natural question also arises concerning the wisdom of testing subjects at both the premenstrual and menstrual points within the cycle. Jones and Jones were attempting apparently to demonstrate the influence of sex hormone changes on alcohol metabolism in women. Surprisingly, however, they selected two points within the cycle for data collection which typically coincide in their hormonal levels of progesterone and estradiol. Examination of the sex hormone curves (see Figure 2) indicates that the three most dissimilar points in the cycle are days 1, 14 and 22 rather than 28. This testing procedure allows for the assessment of three unique combinations of estradiol and progesterone levels (day 1:
estrogen low, progesterone low; day 14: estrogen high, progesterone low; day 22: estrogen high, progesterone high). Instead, the selection of day 1 as well as day 28 by Jones and Jones was influenced possibly by literature pointing to significant psychological effects of the pre-menstrum such as depression, tension and anxiety.

The data presentation of Jones and Jones leads to interpretive difficulties. For example, when reporting the results of the critical study of 11 women on the pill, 11 normal cycling women, and 11 men, they neglect to present group differences at the various points within the cycle. Instead, they presented group means for each sample from the three different testing points taken together. Finally, the extreme degree of effects reported by the authors are probably best viewed with skepticism. One subject is reported to show peak BALs which span a wide range from 0.04% to 0.10% for peak BALs. Similar reports of such extreme effects could not be isolated in the literature.

A number of additional studies have emerged recently to further question the Jones and Jones conclusions. Linnoila, et al. (1980) administered different dosages of alcohol (0.5, 0.8, 1.2 ml/kg and a placebo condition) to 10 ovulating women at days 9 and 23 of their cycle. These researchers found no significant differences in peak BALs between the follicular and luteal points in the cycle for any of the four dosage conditions. Sutker, et al. (1982) studied 32 male and 32 normally cycling females for gender differences in blood alcohol levels at days 26 to 29 of the cycle. Each female subject also submitted blood samples on day 22 to confirm ovulation for all subjects through radioimmunoassays for plasma progesterone concentrations. No significant differences in peak BALs were found between men and women at days
26 to 29 of the cycle which is contrary to Jones and Jones conclusions. It also is interesting to note that these same authors found anovulatory cycles in approximately 25% of their normal cycling female sample (personal communication). Finally, Randall, Lochry, Moseley and Sutker (1981) conducted a recent animal study of 20 control, 40 ovariectomized, and 40 sham control female mice. In this study ovariectomized female mice failed to differ from their normal and sham control counterparts in peak BALs, a finding which is directly contrary to the early animal work (Goldberg & Stortebecker, 1943; Kask, 1929; Klotz, 1937) which offered a sound rationale for sex hormone experimentation in human subjects. It is clear that fundamental questions about the influence of the menstrual cycle on alcohol metabolism remain.

**Behavioral Effects of Acute Intoxication.** Relationships between BALs and functional impairment have been investigated extensively over the years in an effort to isolate observable performance correlates of intoxication. A range of dependent measures have emerged with relationships between BALs and impairment generally found to be dose dependent past pivotal blood alcohol thresholds. Evidence suggests greater alcohol impairment on the ascending as opposed to descending limb of the absorption-elimination curve (Eggleton, 1941; Jones, 1973; Jones & Vega, 1972; Meerloo, 1947; Mirsky, Piker, Rosenbaum & Lederer, 1941; Young, 1970). What follows is a review of popular behavioral correlates and evidence for gender differences and ascending/descending limb differentials. Experimental sessions in alcohol research last for long periods of time and can prove challenging if too many dependent measures are required. A primary objective of this review of behavioral correlates is selection of a small number of maximally sensitive and easily administered overt indicators of intoxication.
1. Standing Steadiness. Stability of stance has been a commonly used measure of intoxication. The apparatus used varies among research labs but all are similar in measuring durations and degrees of angular deviation from the subject's center of gravity as he or she stands on a stationary or, in some cases, vibrating platform (Goldberg, 1966; Idestrom & Cadenius, 1968; Shipley & Harley, 1971). The term Romberg is frequently used to indicate standing steadiness with both feet planted on a stationary platform while the subjects eyes are closed. A modified Romberg test measures sway while standing on one foot with eyes closed.

Research reviewed by Carpenter (1962) suggested that body sway is an "exceedingly sensitive" measure of intoxication. Goldberg (1966) studied 160 subjects and concluded that standing steadiness shows a good correlation with blood alcohol, coinciding with regard to peak BAL and general course. Likewise, Idestrom and Cadenius (1968) examined standing steadiness in response to mean peak BALs of 0.015%, 0.03%, 0.05%, 0.07% and 0.00% (placebo). Placebos had no effect on measures which were markedly impaired about one hour after ingestion for subjects who actually ingested alcohol. Slight and variable effects were produced by BALs of 0.03% and 0.05%. Evans, Martz, Rodda, Kiplinger and Forney (1973) similarly reported a dose dependent relationship between BALs and body sway. Literature on gender effects and ascending-descending limb differentials could not be isolated.

2. Reaction Time. Early critiques of reaction time research (Jellinek & McFarland, 1940; Teichner, 1954) are still valid today in their emphasis on subtle sources of error variance such as alterations in procedures, failure to control for boredom, fatigue, distractions, and other potential problem areas. Put simply, reaction time measure-
ments require precision and rigorous control of the testing environment if the data are to be reliable.

Virtually all researchers who have used reaction time as a dependent measure have found impaired reactivity to stimuli in intoxicated subjects (Carpenter, 1962; Huntley, 1972; Jones & Jones, 1976; King, 1975; Linnoila, et al., 1978; Taberner, 1980). Impairment is found to begin at BALs of 0.05% (Shillito, King & Cameron, 1974) and to follow a direct linear course (Rentoul, Smith & Beavers, 1962). There are also suggestions that alcohol dosages below the necessary threshold for significant reaction time impairment may nevertheless increase response errors in tasks (Moskowitz, 1971; Shillito, et al., 1974; Tharp, Rundell, Lester & Williams, 1974; Vuchinick & Sobell, 1978).

The association between reaction time impairment and intoxication level is not as clear during elimination, with evidence suggesting a weaker relationship on the descending limb of the curve (Eggleston, 1941; Meerloo, 1947; Young, 1970). Young (1970) concluded that it is now fairly well established that the relationship between simple reaction time and BALs becomes increasingly tenuous with the passage of time on the descending limb of the elimination curve. Reports of specific correlations between BALs and reaction time could not be found.

3. Hand-Eye Speed and Coordination. The most promising class of behavioral measures probably involves hand-eye speed and coordination. Idelstrom and Cadenius (1968) examined 31 male subjects on tapping speed and hand-eye coordination as measured by an apparatus employing a stylus which must be moved along an S-shaped slit without touching the edges. Five different dosages were administered to subjects:
<table>
<thead>
<tr>
<th>Dose</th>
<th>Concentration</th>
<th>Peak BAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>placebo</td>
<td>0.000%</td>
</tr>
<tr>
<td>B</td>
<td>0.2 g/kg</td>
<td>0.015%</td>
</tr>
<tr>
<td>C</td>
<td>0.4 g/kg</td>
<td>0.030%</td>
</tr>
<tr>
<td>D</td>
<td>0.6 g/kg</td>
<td>0.050%</td>
</tr>
<tr>
<td>E</td>
<td>0.8 g/kg</td>
<td>0.070%</td>
</tr>
</tbody>
</table>

The results demonstrated that coordination was effected by doses as low as 0.4 g/kg while tapping speed was unaltered until doses of as high as 0.8 g/kg were administered. Peak BALs of 0.070, however, are not that high and these results demonstrated the sensitivity of the coordination task to the alcohol. Figure 3 shows the relationship between hand-eye coordination as measured by the stylus task and intoxication.

Sidell and Pless (1971) examined 24 male subjects for deficits in hand-eye coordination as measured by a tracking task (apparatus requires subject to keep a light ray spotted over a moving target) in response to alcohol dosages which yielded peak BALs of approximately 0.14, 0.17, 0.18 and 0.0% (placebo). Absorption data analysis generated a simple correlation of 0.61 between BALs and impairment over all of the doses. The correlation for the highest dosage was 0.95. For the elimination limb of the curve the correlation was 0.52.

4. Driving Skills. Proficient driving ability requires the skillful combination of a multitude of skills including hand-eye speed and coordination, standing steadiness, and reaction time. The literature is essentially unanimous in predicting that driving skills deteriorate at relatively low BALs (sometimes less than 0.05%). Both actual driving courses and driving simulators have been utilized with measures collected on tasks involving a wide range a behaviors, from the delicate to the crude (e.g., time around course, number of stanchions hit, turning
ability in a limited space, number of bricks hit with front wheels, braking to a red light, release of pressure on accelerator at an amber light, simple braking, braking at different speeds, braking with judgment, etc.) with remarkable methodological sophistication achieved in driving studies. Drew, Colquhoun and Long (1958) found that both tracking error and steering wheel movement were linearly related to BALs while Loomis and West (1958) reported that time off the road followed the blood alcohol curve closely. Newman and Fletcher (1940) found a correlation between a tracking-braking task and crude steering and BALs to be 0.485 and 0.576 respectively. A number of additional studies are reported implicating similar relationships between alcohol and driving impairment (Bjerver & Goldberg, 1950; Coldwell, Penner, Smith, Lucas, Rodgers & Darboch, 1958; Gelin & Wretmark, 1951; Huber, 1955; Marquis, Kelly, Miller, Gerard & Rapaport, 1957), and deficits are often found at BALs as low as 0.032% (Gelin & Wretmark, 1951) and 0.04% (Bjerver & Goldberg, 1950). Many writers also note that psychomotor impairment often precedes overt behavioral signs of intoxication.

Self Estimation of Intoxication Levels. Measures of the accuracy of personal estimates of intoxication levels and degrees of associated impairment provide an additional, more subtle measure of intoxication. Individual estimations of BALs and associated impairment can have important consequences in regard to crucial decisions such as driving while intoxicated. Self-ratings of perceived intoxication and impairment are obtained easily and quickly from intoxicated subjects.

Ekman, Frankenhaeuser, Goldberg, Hagdahl and Myrsten (1964) studied subjective ratings of self intoxication in a sample of eight males. They used a score of 10 to represent minimal detectable levels of intoxication
and scores of 0 to denote complete sobriety. In most respects, these subjective estimates were found to coincide with the blood alcohol curves for the three different dosages which produced mean BAL peaks of 0.035, 0.045 and 0.072. Figure 4 shows the subjective ratings and actual blood alcohol curves. In both curves the ascent is seen to be rapid, with peaks coinciding in time and descent approximately in a linear fashion for the two measures of intoxication. One important point is that subjective rates of decline are much faster than actual blood alcohol elimination, leading to sober estimates when mean BALs were actually 0.02% and 0.04% for the two lowest (0.33 and 0.44 g/kg) and one highest dose (0.66 g/kg) respectively. Subjects were asked to rate their desire and energy for completing arithmetic testing. These ratings showed a significant discrepancy between subjects' estimates of work capacity and their actual performance ability. Subjects were most prepared and motivated to work when their BALs were highest and performance thus maximally impaired.

Goldberg (1966) reported similar findings in his study of 160 subjects at alcohol doses of 0.33, 0.44, 0.55 and 0.66 g/kg. The same basic Ekman, et al. (1964) rating scale was utilized in this study. The subjective ratings and actual BALs were again found to coincide largely, but significant differences in the appearance and disappearance thresholds were found. Subjects on low doses did not change appreciably their self-ratings until an ascending threshold of 0.022%, with the highest dose raising this threshold to 0.057%. Descending limb thresholds were also dose dependent with values for the four doses found to be 0.021, 0.026, 0.035 and 0.044% respectively. Self-ratings are correlated most highly with actual BALs within the curve. Relationships tend to be
lower on initial ascent and late elimination. Goldberg also found minimal correlation between subjective estimates of reaction time and actual performance. He noted that this discrepancy has been reported by others (Ekman, et al., 1964; Froberg, 1963). Further support for this contention is offered by Sidell and Pless's (1971) findings that 33% of subjects overestimated their performance on a measure of hand-eye coordination and motor dexterity at low levels of intoxication.

The Present Research

The interrelationship between sex hormone levels, blood alcohol variables and behavioral correlates of intoxication will be examined in the present study. Emphasis will be placed on analysis of within cycle differences among women. Evidence will be generated in regard to a number of fundamental questions about menstrual cycle effects on alcohol metabolism. The following questions are of most importance:

1. Are there differences in women's peak BALs, times to peak, and elimination times which are associated with points within the menstrual cycle?

2. Is there a significant relationship between estradiol and/or progesterone levels and the three major blood alcohol variables?

3. Are behavioral measures of intoxication sensitive to changes in blood alcohol concentrations?

4. Do behavioral measures of intoxication change as a function of the menstrual cycle? Are women equally impaired at different times within their cycles?

5. Are subjects equally impaired by the same blood alcohol concentrations experienced on the ascending and descending limbs of the curve?
Subjects

A total of 12 female volunteer subjects participated in the present investigation of acute alcohol intoxication. Participants were recruited primarily from hospitals and universities in the New Orleans area. An effort was expended to maximize sample homogeneity on variables of potential importance. Eligibility criteria were as follows:

1. All subjects must be between 21 and 35 years of age. Subjects had a mean age of $26 \pm 2.5$ years.

2. Subjects were all female, white Americans. Reed, Kalant, Gibbins, Kapur and Rankin (1976) reviewed a number of studies which suggested possible racial differences in alcohol metabolism.

3. Subjects were all moderate drinkers as defined by responses to the self-report Khavari Alcohol Test (KAT: Khavari & Farber, 1978) which estimates quantity and frequency of drinking. Subjects all reported drinking a minimum of 2 times or 4 drinks a week for a mean consumption rate of $0.88 \pm 0.34$ oz/day. The national drinking average is reported to be $0.94$ oz/day (Noble, 1978).

4. Subjects did not use oral contraceptives or
prescription drugs which may have influenced alcohol metabolism.

5. All subjects had a history of menstrual regularity.

6. All subjects scored above 100 on the Shipley Institute of Living Intelligence Test (Shipley, 1967).

7. Subjects with apparent weight problems were not considered for inclusion in the study. The final 12 subjects' mean weight was $129 \pm 17$ pounds. Body water percentages averaged to $52.0 \pm 2.86\%$. The national average has been estimated at 50 to 55\% in women (Bell, et al., 1976).

**Apparatus and Psychometric Instruments**

BALs were determined from breath samples using an Intoximeter Model 3000. This instrument operates on the principle of infrared absorption and incorporates an internal standard of known concentration (100 mg percent) and a blank of (0 mg percent). The standard and blank are analyzed after every three breath samples to confirm continued instrument accuracy. Basal temperature oral thermometers were used to record daily temperatures of subjects.

A standing steadiness device was used to measure gross balance disturbance. The device consisted of two pulleys suspended from walls at 90 angles to one another, approximately 4 feet from the floor. Photoelectric cells detected rotation of the pulleys, and filament attached the pulleys to the waist of the subject so that movement in any direction resulted in pulley rotation and pulse counter alterations.
Subjects were administered various psychometric measures during the initial screening interview. This battery of tests included the Shipley Institute of Living Scale (Shipley, 1967), Khavari Alcohol Test (KAT: Khavari & Farber, 1978), the Health History Questionnaire (see Appendix D), the Menstrual Distress Questionnaire (MDQ: Moos, 1968), and the Menstrual History Questionnaire.(see Appendix E).

The grooved pegboard test was used to measure hand-eye speed and coordination. This psychomotor test is produced by Lafayette Instrument Company and consists of a wooden block containing 25 randomly positioned slots or holes. Metal "keys" or pegs were positioned in a tray next to the device, and subjects were instructed to place individually all of the pegs into the slots as quickly as possible. Trials were given with alternating dominant and nondominant hands.

Independent Variables

The day of the menstrual cycle served as the primary independent variable examined in the present study. The three levels of the independent variable corresponded with data collection on days 2, 14 and 22 of the menstrual cycle. Subjects were counterbalanced on the trial order of their data collection to control for possible practice effects, each subject being assigned randomly to one of three possible trial orders (order one: day 2, day 14, day 22; order two: day 14, day 22, day 2; order three: day 22, day 14, day 2).

A second independent variable was the phase point of the blood alcohol absorption-elimination curve during the test session. Behavioral measures were taken at baseline, ascending limb, peak, and descending limb. Thus, there were four levels of phase for each behavioral measure.
Dependent Measures

Radioimmunoassays (RIAs) for estradiol and progesterone, blood alcohol levels, grooved pegboard performance, standing steadiness, and self ratings of intoxication all served as dependent measures.

Estradiol and Progesterone. Radioimmunoassays of these two hormone levels were conducted by the Tulane Medical School RIA laboratory under the direction of A. K. Arimura, M.D., Ph.D. An RIA kit produced by Pantax Corporation was utilized to measure estradiol levels in units of pg/ml. Abraham, Chiamor, Ferrandex, Stevenson, Worlikar and Washington (1981) delineated the specific procedures involved in these RIA analyses of plasma estradiol. The Pantex Corporation presents evidence of high reliability of the measurement procedure in their manual which accompanies the RIA kit. Expected value ranges of estradiol are listed as follows:

- Early follicular stage: 30-100 pg/ml
- Late follicular stage: 100-400 pg/ml
- Luteal stage: 50-150 pg/ml
- Adult males: 10-60 pg/ml

Progesterone levels were measured with the use of a Nuclear Medical Systems Inc. RIA kit. Specific information on the technical procedures implemented in these measurements is offered by Youssefnejadian, Florensa, Collins and Somercille (1972). The accompanying RIA manual assures high reliability of the measurement and offers evidence of such (Malvano, Trojsi, Gandolfi, Altanorio & Crargnani, 1974). Expected value ranges for progesterone are:

- Follicular stage: 1.0 - 2.6 ng/ml
- Luteal stage: 5.3 - 29.2 ng/ml
**Blood Alcohol Levels.** All BAL measurements were made through the use of the Intoximeter Model 3000. The reliability of breath analysis in the determination of BALs has been established, with correlations between the two commonly reported in the +0.95 to +0.96 range (Dubowski, 1970). Peak BAL, time to reach peak BAL (absorption time), and time from peak until elimination (< 0.015) served as the three dependent measures classified under the heading of blood alcohol analyses.

**Grooved Pegboard Performance.** Previous research reports have indicated that psychomotor measures can provide a simple, easily administered, yet sensitive overt measures of intoxication. The grooved pegboard test is such a measure of hand-eye speed and coordination. The test has been found useful in discriminating between brain damaged and normal control subjects and is incorporated into the Trites Clinical Neuropsychological Test Battery (Trites, 1977). No data could be found on pegboard sensitivity to intoxication, but the nature of the task and the previous literature on behavioral correlates of intoxication suggest its utility for this purpose. Pilot subjects were administered the test under the influence of elevated BALs and appreciable differences were found, supporting its usage as a behavioral measure of intoxication for the present study.

Reliability data related specifically to the grooved pegboard could not be isolated, but extensive information is available on the Purdue Pegboard test which is similar in its essential features. In fact, both pegboards were developed by the same researchers (Tiffin & Asher, 1948), and both are distributed by Lafayette Instrument Company. Purdue Pegboard reliability coefficients of +0.85 to +0.90 are common
(Tiffin, 1968), and a variety of validity studies are presented in
the manual.

Standing Steadiness. Measurement of standing steadiness provided
an indicator of gross motor and balance impairment. This measure comple­
mented the grooved pegboard which assessed fine hand-eye coordination.
Research has shown the sensitivity of similar measures in detecting
intoxication levels as low as 65 mg%.

Self-Ratings. A 10 point rating scale was used for subjective
self intoxication ratings. Subjects were asked to define a score of
1 as completely sober and a score of 10 as severely intoxicated. An
anchored scale was provided to assist subjects in making this deter­
mination (see Appendix F).

Summary of Dependent Measures. The following list of dependent
measures will be examined in the course of the present study:

1. Estradiol and Progesterone levels
2. Blood Alcohol Analyses: Peak BAL, Absorption Time,
   Elimination Time
3. Grooved Pegboard: Dominant Hand, Nondominant Hand
4. Standing Steadiness
5. Self-Ratings

Blood samples were drawn from subjects prior to alcohol ingestion
in each of the three experimental sessions. BALs were taken at five
minute intervals until elimination was completed. The grooved
pegboard and standing steadiness measures were taken at baseline, peak
BAL, and approximately 60 mg% on both the ascending and descending
limbs of the curve. BAL self-ratings were taken every 20 minutes
until a rating of 1, completely sober, was obtained.
Procedure

All eligible subjects were required to complete an initial screening interview which involved the administration of the Shipley Institute of Living Scale, Khavari Alcohol Test, and Health History, Menstrual Distress and Menstrual History Questionnaires. Subjects were told that the objective of the study was to explore the course of acute alcohol intoxication in women. It was stated that moderate, though not physically harmful, doses of alcohol had to be ingested during the study, and that a blood sample would be drawn at the start of each experimental session. An agreement was made during the initial interview to pay subjects $50 for each of the experimental sessions and $20 for the self-monitoring of alcohol consumption and basal body temperature. In addition, subjects were told that they may acquire information regarding their alcohol metabolism and menstrual cycle upon completion of the study.

During the initial interview, subjects were asked to chart daily basal body temperature and alcohol intake for the entire study. This self-monitoring procedure was to be initiated on day 1 (beginning of menstruation) of each subject's next menstrual cycle. A basal temperature oral thermometer was provided for each subject along with Alcohol Log Sheets (see Appendix G) and Basal Body Temperature Forms (see Appendix H) to assist in their monitoring of the target responses. Subjects were questioned to insure that there was no misunderstanding about the recording procedure. They were told that experimental sessions would be scheduled only after they had completed one full month of body temperature and alcohol consumption recordings. A consent form (see Appendix I) was signed by both the subject and the
experimenter at the conclusion of the initial interview, and the subject was asked to contact the lab upon the first day of their upcoming cycle (beginning of self-monitoring).

Subjects were called at random points during their first month of self-monitoring to help maximize compliance with the temperature and alcohol consumption measurements. Within one to two weeks before the end of this first month of the study, subjects were assigned randomly by computer to one of three counterbalanced orders of trial sequencing.

Subjects assigned to order one were scheduled to complete their first experimental session on day 2 of their next cycle. Some subjects had difficulty scheduling a session specifically on day 2, and some allowances were made to accommodate subjects as best as possible (two subjects scheduled sessions as late as day 7). Subsequently, subjects in order one would be scheduled for a second session around day 14 (ovulation) of this same cycle, approximately two weeks later than their first session. Subjects were contacted daily by telephone on the days immediately preceding ovulation to obtain daily temperature readings. Ovulation was inferred by a temperature dip around the middle of the menstrual cycle of about .5 degree centigrade. Subjects would be asked to come into the lab for a session on the day after the temperature dip. Subjects were scheduled immediately if a temperature dip did not occur by day 15. The temperature charts from the first month of self-monitoring were useful in helping to estimate when ovulation was occurring in the later cycle since women often show consistency in their menstrual cycle patterns. Subjects assigned to order one would complete their third session approximately one week after ovulation, around day 22. This third session often could be scheduled a week in
advance at the day 14 experimental session. Flexibility in scheduling was essential for maintaining some subjects in the study. Five subjects were not able to complete all three sessions within a sequential menstrual cycle and had to be scheduled with a one cycle interval interposed between two of the experimental sessions.

Subjects randomly assigned to order two of the counterbalancing sequence would complete their first session at ovulation of the cycle which followed the first month of self-monitoring of basal body temperature and alcohol consumption. This first session was followed by data collection on days 22 and 2 respectively. Likewise, subjects assigned to the third order began their first experimental session on day 22 of the menstrual cycle which followed the self-monitoring initial month. This session was followed by testing on days 2 and 14 with scheduling always following the basic procedure discussed above. Three subjects were included in order three, with one final subject being tested in the sequence of day 2, day 22 and day 14. This violation of the third order trial sequence was essential to maintain this last subject in the study.

Subjects were given preparatory instructions sometime before coming in for their first experimental session. They were told not to consume alcohol or other drugs on the day prior to the session. They also were asked to avoid consuming food or beverages, with the exception of water, after 10:00 p.m. on the night before. Subjects reported to the lab at 8:00 a.m. on testing mornings. The subject's weight, baseline BAL and blood sample were taken, followed by a rest period of approximately five minutes duration. During this time, subjects were questioned about dietary compliance on the day prior to the session, despite
previous reminders. Subjects were then given the grooved pegboard and standing steadiness measures. Following these baseline measures, 0.66 ml alcohol/kg body weight was administered in a concentration of four parts decarbonated tonic water to one part alcohol with a slice of lime. Subjects were given 15 minutes to consume the alcohol dose which was given sequentially in three separate cups, each containing a third of the total mixture. Each cup of alcohol mixture was consumed in five minutes.

    After drinking the alcohol, subjects were instructed to gargle and rinse their mouths thoroughly for five minutes. This procedure was useful in removing ambient alcohol from the mouth. Breath samples provided valid estimates of BALs only after ambient alcohol was removed from the mouth. Breath samples were taken every five minutes until elimination virtually was complete (<.015%). Subjects were tested five minutes after ingestion on the grooved pegboard and standing steadiness measures. This point on the absorption-elimination curve generally corresponded with BALs of about 0.05 to 0.06%. These same behavioral measures also were given after the first BAL reading which demonstrated a drop in BAL (peak BAL point of the curve). The final testing on the grooved pegboard and standing steadiness measures occurred on the descending limb of the blood alcohol curve at a point which corresponded with the point at which the ascending measures were taken. Self-ratings of intoxication levels were taken every 20 minutes until subjects rated their intoxication level as 1 (sober).
Research Design and Data Analysis Strategy

A single factor, within-subjects design with three levels of the independent variable was utilized for the analysis of the blood alcohol measurements. All 12 subjects were tested at each of the three different points of the menstrual cycle with counterbalancing used to control for practice effects.

A Subjects X Hands X Day of cycle X Phase of blood alcohol curve repeated measures analysis was used to analyze the grooved pegboard data. All subjects were tested at the three different points within the menstrual cycle. In addition, subjects were tested at four different points or phases of the blood alcohol absorption/elimination curve during sessions. Testing was conducted for both the grooved pegboard and the standing steadiness measures at baseline, ascent, peak and descent. Subjects were tested individually with both their dominant and nondominant hands.

A Subjects X Day of cycle X Phase of blood alcohol curve repeated measures analysis was used to analyze the standing steadiness data. Subjects were measured at all levels of both the day of cycle as well as the phase of the blood alcohol curve (baseline, ascending, peak, descending limbs).

Hormonal data was analyzed through simple Pearson produce moment correlations and multiple correlational analyses utilizing estradiol and progesterone as predictors of the three major blood alcohol dependent measures. Difference scores between hormone levels at various points within the menstrual cycle, and difference scores between dependent measure times at different times within the cycle were used to obtain estimates of the magnitude of treatment effects.
RESULTS

Estradiol, progesterone, weight and body water percentages all were found to vary significantly across the course of the menstrual cycle. Mean estradiol levels were found to be 52.4 ± 20.6 pg/ml, 189.6 ± 112.6 pg/ml and 150.4 ± 73.9 pg/ml for days 2, 14 and 22 of the cycle respectively (F 2,22 = 11.4, p<.01). Changes in weight and body water percentages just reached statistical significance. Mean weights of 58.1 ± 8.3 kg, 58.5 ± 7.6 kg and 59.2 ± 8.1 kg (F 2,22 = 5.54, p<.05) and mean body water percentages of 52.2 ± 3.1%, 52.0 ± 2.7% and 51.8 ± 2.8% (F 2,22 = 3.1, p<.05) were found for days 2, 14 and 22 of the cycle respectively.

An overall one-way analysis of variance generated no significant menstrual cycle effects on either peak BALs (F 2,22 = 3.22, p>.05) or absorption times (F 2,22 = 2.04, p>.05). Cell values for the peak BAL data were 81.0 ± 11.0 mg%, 76.0 ± 9.0 mg% and 78.0 ± 10.0 mg% for days 2, 14 and 22 of the cycle respectively. Absorption time cell means were 22.1 ± 8.1, 31.2 ± 17.2 and 27.9 ± 14.7 minutes for days 2, 14 and 22 respectively. Newman-Keuls analysis found no significant pairwise differences among the peak BAL or absorption time data (p<.05).

A main effect of the menstrual cycle on alcohol elimination time was found (F 2,22 = 6.12, p<.01), with Newman-Keuls analysis indicating significant differences between day 2 (X̄ = 264.8 ± 39 minutes) and day 22 (X̄ = 229.6 ± 46 minutes) at the p<.01 level. Day 14 sessions had a mean elimination time of 249.0 ± 43 minutes which did not differ significantly from either day 2 or day 22 elimination.
times (p>.05). Seventy-five percent of the subjects produced their slowest and fastest elimination times of days 2 and 22 respectively. A summary of the overall blood alcohol findings is presented in Figure 5. Subjects' individual elimination time scores are presented in Figures 6, 7 and 8 which show the patterns of cell means for subjects assigned randomly to orders one, two and three respectively.

The course of subjects' alcohol elimination is shown in Figure 9. Subjects were found to eliminate alcohol significantly slower when drinking on day 22 of the menstrual cycle. Differences in elimination times, however, were found primarily at the lower end of the descending limb of the elimination curve. Elimination scores calculated using 50 mg% as the final BAL reading, i.e., time from peak BAL to 50 mg%, generated cell means of 78.3 ± 28.7, 65.0 ± 25.8 and 65.4 ± 26.3 minutes for days 2, 14 and 22 respectively (F 2,22 = 2.78, p>.05). Differences in elimination times thus occurred after 50 mg% was reached on the descending limb of the curve. Inspection of figure 9 suggests that differences in elimination times occurred when BALs were at their lower points (<25 mg%).

Three subjects deviated from the general pattern of faster elimination time on day 22 and slower time on day 2 of the cycle. These three subjects were compared to the remaining subjects on a number of variables which may have accounted for their elimination time differences. These three subjects were within ± one standard deviation from the sample mean on the variables of age, body water percentage, Khavari alcohol test scores and estradiol/progesterone levels on days 2, 14 and 22 of the menstrual cycle.
One subject (#127) failed to ovulate during the one menstrual cycle in which she participated in this study. She was atypical since her progesterone level at day 22 was significantly lower than that of ovulatory women at this same time. Examination of her pattern of elimination times (see Figure 7) showed no significant deviation from the general pattern observed for other subjects in the study. Analysis of variance was completed, eliminating this one anovulatory subject, and the same conclusions were reached for the blood alcohol measures of peak BAL (F 2,20 = 0.48, p > .05), absorption time (F 2,20 = 2.07, p > .05) and elimination time (F 2,20 = 4.6, p < .05).

Simple and multiple correlations were calculated between hormonal levels of estradiol and progesterone and the three blood alcohol measures at each of the three target points within the menstrual cycle. Only one significant simple correlation (r = 0.58) between estradiol levels and absorption time, and one significant multiple correlation (R = 0.72) between both estradiol and progesterone and absorption time was generated, with both significant correlations found only during day 14 of the cycle. Table 1 presents the entire matrix of the simple and multiple correlational analyses between the hormonal and blood alcohol measures.

Body water percentages did vary significantly across the menstrual cycle. Analysis of covariance was calculated for each of the blood alcohol measures using body water percentage as a single covariate. None of the conclusions reached in the initial analyses were altered by covarying for body water percentage; peak BAL (F 2,21 = 2.58, p > .05) and absorption time (F 2,22 = 1.72, p > .05) remained
nonsignificant whereas elimination time remained significant (F 2,21 = 4.45, p<.05).

Analyses were conducted to test for the presence of differential practice effects on the blood alcohol measures. Overall practice effects were not detected by Subjects X Trials single factor analysis of variance for the elimination time (F 2,22 = 1.02, p>.05), peak BAL (F 2,22 = .00001, p>.05) and absorption time (F 2,22 = 0.53, p>.05) dependent measures. Examination of the individual counterbalanced trial sequences likewise indicated an absence of significant practice effects for individual orders of trial sequencing for the peak BAL (order one: F 2,6 = 0.007, p>.05; order two: F 2,6 = 0.0004, p>.05; order three: F 2,4 = 1.0, p>.05) as well as the absorption time data (order one: F 2,6 = 2.34, p>.05; order two: F 2,6 = 3.79, p>.05; order three: F 2,4 = 3.0, p>.05).

For the elimination data, orders one (F 2,6 = 0.53, p>.05) and three (F 2,4 = 0.59, p>.05) showed no evidence of a practice effect, but the order two trial effect was significant (F 2,6 = 10.4, p<.05). Examination of order two subjects (see Figure 10), however, indicated that only one subject demonstrated substantial differences over trials. Further, all subjects in the study had a minimum time interval between sessions of six days, and the number of days since the previous session was unrelated to the three blood alcohol measures at the three different points within the menstrual cycle. Specifically, the number of days since the previous session was not correlated significantly (p<.05) with elimination times on days 2 (r = -0.44), 14 (r = 0.05) or 22 (r = 0.04) of the menstrual cycle.
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The grooved pegboard data were analyzed using a Subjects X Hands X Day of cycle X Phase of blood alcohol curve repeated measures analysis of variance. Significant differences were found between performance using the dominant and nondominant hands (F 1,11 = 39.51, p<.01); the cell means and standard deviations were 52.58 ± 7.54 seconds and 57.17 ± 6.96 seconds respectively. A significant effect also was found for the phase of the blood alcohol curve (F 3,33 = 22.64, p<.01); the cell means and standard deviations were 51.07 ± 5.57, 55.68 ± 8.08, 56.85 ± 7.13, and 55.89 ± 7.95 seconds for baseline, ascending, peak, and descending readings respectively. Newman-Keuls analysis of these differences indicated that baseline readings were significantly faster than those obtained at the ascending (p<.05), peak (p<.05), or descending (p<.05) limbs of the absorption-elimination curve, but the ascending-descending limb differentials failed to reach statistical significance.

The standing steadiness data were analyzed using a Subjects X Day of cycle X Phase of blood alcohol curve repeated measures design. Neither day of cycle, phase of blood alcohol curve, or the interaction of the two proved significant.

Correlations between self-ratings of intoxication and actual BALs were statistically significant for most subjects. The mean levels at which subjects ceased reporting sensations of intoxication (self-ratings of 1) were 29 mg%, 32 mg% and 32 mg% for days 2, 14 and 22 respectively.
DISCUSSION

The present findings failed to support previous claims, especially that of Jones and Jones (1976), that peak BALs are effected by changes in the menstrual cycle, and instead bolsters recent studies indicating that early speculations about peak BAL within cycle differences were premature (Linnoila, et al., 1980; Sutker, et al., 1983; Randall, et al., 1981). Jones and Jones (1976) reported mean peak BAL of about 72 mg% for their female subjects who were given the same alcohol dose of 0.66 ml/kg was discrepant from the present experimental findings of mean peak BALs of 81 mg%, 76 mg% and 78 mg% for days 2, 14 and 22 of the cycle respectively. Proced­ural differences between the two studies may account for these differences, but unfortunately, many details are missing from the Jones and Jones reports. For example, it is not stated whether or not food restrictions prior to sessions were monitored closely. Jones and Jones did report that their subjects ingested the alcohol in five minutes, and that it was necessary to wait 15 minutes to obtain initial valid breath readings. The present procedure generated valid readings five minutes after consumption which was completed over a 15 minute ingestion period. Some of Jones and Jones subjects may have been on the descending limb of the absorption-elimination curve prior to their initial breath reading. Reported differences in peak BALs as large as 100 mg% among women at different points within their cycles are especially puzzling. The largest between session difference observed for a subject in the present study was 22 mg%. Thus, Jones and Jones results warrent skepticism.
Reports of differences in elimination times across the menstrual cycle could not be isolated. Jones and Jones found that women taking oral contraceptives metabolized alcohol significantly slower than normal cycling women, but within cycle elimination time differences for the latter group were not reported. Seventy-five percent of the women in the present study eliminated alcohol significantly faster on day 22 of their cycles, but these differences were not observed until descending blood alcohol levels of 50 mg% and lower were achieved. Women metabolized the alcohol from their peak BAL to 50 mg% in about the same amount of time on days 2, 14 and 22 of their cycles. Significant differences occurred at points on the descending limb when blood alcohol concentrations were much lower than those achieved at peak (see Figure 9). Deficits on some behavioral measures can occur with BALs as low as 40 mg% to 30 mg% (Bjerver & Goldberg, 1950; Evans, et al., 1973; Gelin & Wretmark, 1951; Idestrom & Cadenius, 1968; Sidell & Pless, 1971), but the observable effects of alcohol probably do not extend below these BALs. Thus, subjects in the present study who drank on day 22 of their cycles probably showed only minimal and temporary behavioral advantage, with deficits in functioning below the 30 mg% mark being difficult to demonstrate empirically.

Hormonal fluctuations are commonly hypothesized to account for within cycle alcohol metabolic differences. Both estradiol and progesterone levels for subjects in the present study were found to vary predictably over the course of the menstrual cycle (see Figure 2). The unique combination of estradiol and progesterone levels corresponding with day 22 of the cycle would appear to be the most logical mediator of the observed elimination time effects, but
correlational analyses failed to support such an hypothesis. Only two significant correlations between hormone levels and blood alcohol measures were found (see Table 1), and these relationships were not found for the elimination time measures. These two isolated findings for absorption times may well be spurious and not reproducible. Therefore, hormonal fluctuations in women participating in the present study did not account significantly for the within cycle differences observed in the elimination time measures. The small sample size analyzed, however, necessitates future research to assure that subtle hormonal effects actually are not present.

Body water percentages are important also in alcohol metabolism. Body water percentages were found to fluctuate significantly across the menstrual cycle for subjects in the present study, but significant treatment effects on elimination times were found after body water percentage effects were removed through analysis of covariance. Body water percentage changes were inadequate, therefore, in accounting for the observed within cycle elimination time differences. The role of body water percentage in accounting for inter-subject effects is much clearer. Sutker, et al. (1983) have demonstrated body water percentage differences account completely for gender differences in peak BALs. Thus, the association between intra-subject variability in body water percentages and within cycle alcohol metabolic differences remains inconclusively demonstrated.

The possibility that differential practice effects accounted for the observed differences in elimination times was considered, but the possibility was refuted by the findings. Nine subjects demonstrated a tendency to eliminate faster on day 22 of their
cycles (see Figures 6, 7 and 8), and differential practice effects on the order three subjects would not account for this same general pattern in the other five subjects. Figure 10 shows that one subject in order three contributed inordinately to the practice effect observed for this trial sequence. The nature of these speculative practice effects is especially odd, with subjects observed to eliminate faster on trial two followed by slower rates on trial three. No data could be found in the literature of a similar practice effect pattern. There is evidence, however, that a six day intersession time interval should be satisfactory to minimize practice effects (Tabakoff & Rothstein, 1983), and subjects usually had longer intertrial periods. Finally, correlational analyses indicated that the intertrial period was unpredictive of dependent measure scores. These various lines of evidence argue strongly against differential practice confounding of the research design utilized in the present study.

Examination of the subjects who failed to exhibit the elimination pattern observed in 75% of the sample was undertaken to determine if differences existed on any one particular potentially important characteristic. In fact, the three atypical subjects were found to be similar to the overall group on the variables of age, body water percentage, alcohol consumption in general, and hormonal fluctuations within the menstrual cycle. The entire sample also appeared to reflect the "normal" population on variables such as body water percentage, alcohol consumption in general, and alcohol elimination rates. Sample body water percentages averaged around 52.0%, with
estimates of the average adult female body water percentage being from 50% to 55% (Bell, et al., 1976). Women in the study reported drinking an average of 0.88 ounces of alcohol a day while the national average was reported to be 0.94 ounces per day (Noble, 1978). Also, elimination rates generally corresponded with the commonly-cited estimate of 15 mg% per hour (Haggard & Greenberg, 1934).

Therefore, future research will be essential to verify the elimination time differences observed in the present study and to isolate the precise mechanisms by which such effects may occur. Investigations of additional potentially important variables such as corticosteroids, ADH and prostaglandins may prove fruitful.

Significant ascending-descending grooved pegboard performance differentials were not found, failing to support previous findings of an acute alcohol tolerance effect. Subjects were no more disabled on this particular behavioral measure on the ascent as they were on the descent of the absorption-elimination curve, suggesting that grooved pegboard performance did not show improvement (on descent) after the initial exposure (on ascent) to the alcohol dosage. The grooved pegboard measure did prove to be a sensitive measure of the presence of elevated levels of alcohol, but was unable to discriminate between ascending/descending and baseline BALs. Thus, the alcohol dosage selected for this study was probably too low to assess adequately for acute tolerance effects on the grooved pegboard measure. As expected, subjects performed significantly better with their dominant as opposed to their nondominant hands, and an absence of a significant interaction between handedness and phase of absorption/elimination curve indicated that the subject's
nondominant hand was not effected more adversely by intoxication than the nondominant hand.

The standing steadiness measure failed to detect alcohol intoxication for subjects in the present study. Other researchers have demonstrated the sensitivity of similar standing steadiness devices (Evans, et al., 1973; Idestrom & Cadenius, 1968), and limitations in this particular apparatus rather than the measure in general are suspected. Reliability and validity data on this particular device were not obtained, unfortunately, prior to the initiation of the study.

Self-ratings of intoxication demonstrated that subjects claimed to be "completely sober" prior to complete alcohol elimination. Self-reports of sobriety were recorded with BALs generally around 31 mg%. These findings agree with the previous reports of other researchers (Ekman, et al., 1964; Goldberg, 1966). Behavioral deficits are difficult to demonstrate in subjects under the influence of BALs of below the 30 mg% point. Thus, perceptions of "completely sober", though physiologically incorrect, may result from the return to behavioral competency experienced by the subject.

The present research represents an advance over previous studies in this area as a result of several methodological distinctions. No previous study could be found in which subjects were tested in a repeated measures design over all three points within the menstrual cycle when women are known to experience maximal differences in estradiol/progesterone level combinations. In fact, studies of acute alcohol intoxication in women on day 22 of their cycles could not be found. This design distinction, accompanied by
blood samples and hormonal assays collected from each subject on each session day, allowed a unique opportunity to assess the relationships between hormonal changes and metabolic and behavioral correlates of acute alcohol intoxication. The analysis of within cycle fluctuations of body water percentage as they relate to blood alcohol dependent measures also is distinctive. Thus, menstrual cycle treatment effects were examined in addition to the most important potential mediators of such effects if they indeed were found to exist. Unfortunately, the small sample size examined made it possible that subtle treatment effects went undetected in the present study. The strictness of the inclusion criteria, time commitment involved, and general aversive nature of participation made research subjects difficult to secure. Subsequently, small sample sizes are the rule rather than the exception for research in this area.

Future research should place high priority on obtaining large, representative samples. Relationships between fluctuations in hormonal and blood alcohol variables are of particular interest, and such studies would provide critical data regarding the nature of estradiol and progesterone effects. Body water percentage also needs further attention. Possibly, alcohol dosages calculated on the basis of body water percentage could be administered at various points within the menstrual cycle to determine if within cycle differences in blood alcohol measures remained. Additional control groups could be included in research designs such as menopausal women and/or women taking various types of oral contraceptives which alter estradiol and progesterone differentially. To be certain, considerable ingenuity is still required to demonstrate conclusively menstrual cycle treatment effects and to tease out their underlying mechanisms.
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Figure 1. Absorption and Elimination Curves for Three Different Dosages for a Single Subject (Taken from Jones, B.M. & Jones, M.K., Women and Alcohol: Intoxication, Metabolism, and the Menstrual Cycle. In M. Greenblatt & M.A. Schuckit (Eds.), Alcoholism Problems in Women and Children, 1976, N.Y.: Grune and Stratton, Inc., p. 110).
Figure 2. Hormonal levels during the menstrual cycle (Taken from Thiel, D. H. and Gavaler, B.S., Alcoholism: Clinical and Experimental Research, 1982, 6(2), 182)
Figure 3. Mean Changes from Base Values on Coordination Test After Placebo (dose A), high (dose E), and low (dose C) Alcohol Doses (Taken from Idestrom, C. M. & Cadenius, B., Psychopharmacologia, 1968, 13, 195).
Figure 4. Means for all subjects of blood alcohol concentrations (diagram A) and self-estimated degrees of subjective intoxication (diagram B) (Taken from Ekman, G., Frankenhaeuser, L.G., Hagdahl, R. & Myrsten, A., Psychopharmacologia, 1964, 6, 405).
Figure 5. Graph of Mean Blood Alcohol Dependent Measures Within the Menstrual Cycle
Figure 6. Elimination time scores for subjects assigned to order one (trial sequence of day 2, 14, 22).
Figure 7. Elimination time scores for subjects assigned to order two (trial sequence of day 14, 22, 2).
Figure 8. Elimination time scores for subjects assigned to order three (trial sequence of day 22, 2, 14).
Figure 9. Mean absorption-elimination curves on days 2, 14 and 22 of the menstrual cycle.
Figure 10. Elimination time scores plotted by trials for subjects assigned to order two (trial sequence of day 14, 22, 2).
Table 1. Hormonal Relationships with the Blood Alcohol Dependent Measures

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<th>Cycle Day</th>
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<th>Progesterone</th>
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*p < .05 level of statistical significance*
APPENDIX A

Estrogens

The estrogens have been shown to exert a wide range of activity involving their essential role in all phases of stimulation and maintenance of normal reproductive capacity. Some of the more important effects of the estrogens are summarized below:

1. Estrogens act on the ovary to sensitize granulosa cells to the effects of FSH. This response may serve to multiply the number of follicles which initiate development, thereby maximizing the probability of successful maturation and ovulation of a single follicle. Normal follicular maturation is not seen in the absence of estradiol production in human females.

2. Optimal estrogen levels influence the fallopian tubes by increasing tubal motility and therefore maximizing the probability of successful ovum fertilization and blastocyst implantation in the endometrium. Too much estrogen leads to accelerated tubal motility causing premature entry into the uterine cavity prior to endometrial readiness.

3. The most important estrogenic activity is seen in the uterine endometrium. Proliferative changes characterized by increased thickness and chemical composition of all three mucosa constituent elements (the glands, stoma, and vessels) are predictably elicited in mammals exposed to adequate dosages of estrogens. These marked histochemical changes in the endometrium are essential for implantation.
and nourishment of the blastocyst. Menstruation is the periodic hemorrhage which occurs with shedding of the endometrium mucosa as a result of an abrupt diminution in the level of circulating estrogens and progestens.

4. Estrogens have effects on the myometrium as well, producing significantly enhanced muscle contractibility.

The estrogens are seen to have a multiplicity of morphological and biochemical effects on the female reproductive organs in addition to the major ones listed above. All of these effects are designed to maximize the probability of fertilization, implantation, and development of the ovum. Estrogenic activity in one sense elicits initial preparation for later pregnancy.

Estrogens are synthesized in the ovaries, adrenals, testes, and placenta. The ovarian follicle is one of the two primary sources of estrogen release with the quantity of secretion closely associated with the follicular maturation rate. The second source is the corpus luteum which proliferates after ovulation from the hemoraged follicle. Plasma and urinary estrogen curves show parallel patterns of release with increases found during the first preovulatory half followed by a post ovulatory dip and a subsequent recovery concomitant with corpus luteum development in the luteal phase of the cycle. Estrogen release is therefore largely secondary to follicular and corpus luteum functioning.

Estrogen receptors have been isolated in high concentration in the hypothalamic median eminence. Experimental studies indicate that elevated blood concentrations of estrogens stimulate release of LH by the anterior pituitary via the secretion of LH releasing factor
(variously labelled LH-RF, LH-RH, Gn-RH) into the hypothalamic hypophyseal portal system.

The precise events responsible for ovulation have been difficult to isolate. There is virtual consensus that the LH surge observed at ovulation is responsible for follicle rupture which occurs approximately 12 to 36 hours thereafter. Increasing estrogen levels apparently stimulate this surge in the follicular phase with LH inhibited during the luteal phase when both the estrogens and progestens are elevated. Estradiol levels have already begun to drop when the LH surge is at its highest point. This effect may result indirectly from ovulation and follicle rupture or perhaps more direct effects are present. Estrogens may be seen to have a biphasic effect on LH secretion. Small amounts are thought to stimulate the LH surge while direct and potent inhibition is observed with elevated levels of both the estrogens and progestens. This well known fact has led to a proliferation of birth control pills which prevent pregnancy by elevating levels of the sex hormones high enough to inhibit LH and FSH secretions, reliably preventing follicular growth and ovulation.
APPENDIX B

Progestens

Only recently have scientists been able to isolate and measure progesterone in the blood of human females. Prior to this breakthrough only the indirect method of measuring the progesterone urinary metabolite pregnanediol was available. Progesterone is synthesized in the adrenals, placenta, and most importantly, the ovary. The principle ovarian site of synthesis and secretion is the granulosa cells of the corpus luteum. Progesterone levels therefore are directly related to corpus luteum functioning. Minute levels of progesterone have been found just prior to ovulation and the origin is unknown but believed to be follicular in nature.

The effects of progesterone on the reproductive organs of the human female are widespread. Progestens lead to the most substantial changes in the endometrium. While estrogens begin uterine preparatory activity through proliferation, the progestens are necessary to complete the process. These endometrial effects are extensive and summarized by Botella-Llusia (1973) as involving glandular dilatation, decreased height of gland epithelium with parabasal arrangement of nuclei, festooned configuration of the glandular basement membrane with formation of infolding connective tissue spurs, vast development of the vascular supply with distinct outlining of the spiral anterioles, the appearance of glycogen in the endometrial glandular epithelium, changes in the alkaline phosphatase distribution, and increased carbonic anhydrase activity. Progesten activity is seen as indispensable for blastocyst implantation and nourishment in the uterine mucosa. At the same time, estrogen priming is essential for progesterone to have an adequate functional response.
Menstruation is the result of decomposition and sloughing of this endometrial buildup which is directly associated with an abrupt fall in circulating estrogens resultant from corpus luteum demise. Progesten declines are not thought to affect the initiation of menstruation directly, however, if the high luteal levels are maintained the sloughing will be delayed though nevertheless inevitable as a result of estrogen withdrawal. A very interesting and clinically useful effect of progesterone is offered by its thermogenic influences. Progesterone raises basal body temperature by .5 to 1 degree centigrade through the stimulation of hypothalamic thermoregulatory centers. This temperature increase occurs just after ovulation when progesterone levels are increasing, and it serves as a useful and noninvasive indicator that ovulation has occurred.

Progesterone is also a common component of oral contraceptives. High levels of progesterone has clear suppressant effects on LH and FSH which prevents ovulation. Most birth control pills now use both progesterone and estrogens to closely mimic the actual reproductive endocrinology. Menstrual flow is typically allowed through a cessation of birth control pills once a month.
APPENDIX C

Gonadotrophins

FSH and LH are known to be synthesized and released by the anterior pituitary and to play critical roles in the reproductive process. The factors governing release remain largely unknown despite substantial data describing their secretion curves. The important role of the hypothalamus and its releasing factors is noted.

FSH increases are seen early in the cycle and serve to stimulate follicle development and preparation for ovulation. The FSH increase in the proliferative phase results from low estrogen and progesterone in the bloodstream. A hypothalamic releasing factor similar to LH-RF is suspected to mediate FSH release, but this has not yet been proven. Significant evidence points to an FSH surge at ovulation though the validity, significance, and/or cause of such activity is unknown. Without FSH, however, there would be no ripened follicle from which an ovum could be ovulated.

The pattern of release of LH is better understood. LH shows a dramatic preovulatory peak followed by an equally marked return to lower pre-ovulatory baseline levels. This peak has been shown to initiate ovulation. The rapidly rising estrogen levels associated with follicular growth are thought to initiate the midcycle LH surge. Human female ovulation occurs 12 to 36 hours after this peak in LH.
APPENDIX D
HEALTH HISTORY QUESTIONNAIRE

<table>
<thead>
<tr>
<th>Subject Number:</th>
<th>Age:</th>
<th>Sex:</th>
<th>Race:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight:</td>
<td>Height:</td>
<td>Date:</td>
<td>Examiner:</td>
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</tbody>
</table>

Check all of the following problems which you experience:

<table>
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<tr>
<th>PROBLEM</th>
<th>CURRENT</th>
<th>HISTORY OF</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>Chest pain</td>
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<td>Cirrhosis</td>
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<td>Diabetes</td>
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<td>Emphysema</td>
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<td>Gastritis</td>
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<td>Gonorrhea</td>
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<td>Hepatitis</td>
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<td>Hyperglycemia</td>
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<td>Hypotension</td>
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<tr>
<td>Indigestion pain</td>
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<tr>
<td>Irregular heart rate</td>
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<td>Irregular menses</td>
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<td>Jaundice</td>
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<td>Kidney infections</td>
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<td>Vitamin deficiency</td>
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<td>Weight gain</td>
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<td>Weight loss</td>
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<tr>
<td>Other</td>
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</table>

Medications (List all current):
APPENDIX E

MENSTRUAL HISTORY QUESTIONNAIRE

Name: ______________________'  Age: _____________

Age of menarche: ___________ Average duration of flow: ___

Date of last menstrual flow: ___________ to ___________

Average length of menstrual cycle: ___________

Amount of flow: Heavy _____ Average _____ Light ______

Dysmenorrhea ______ Spotting ______ Irregularity ______

Edema ______ Swelling breasts ______ Headache ______

Vaginal Discharge ______ Pap Smear results ______

Current contraceptive method: ____________________________

History of oral contraceptives:

Current use: Yes _____ No _____

Name of pill: ______________________

Number of months continuous use: ________

Name of other pills used: _____________________________

History of pregnancies:

Number of pregnancies: ________

Number of living children: ________

Number of abortions: ________

Number of miscarriages: ________

List all current prescription and over the counter medications in use:

________________________________________________________________________

Additional remarks:
APPENDIX F

SELF-REPORTED INTOXICATION SCALE

Subject Number: _____ Age: _____ Sex: _____ Date: _____

Please estimate your level of alcohol intoxication at this moment. Please circle the number of the scale item which best describes your present condition (1 = completely sober; 10 = severely and completely intoxicated).

1. Completely sober - no evidence of alcohol consumption.

2. Aware alcohol has been consumed - but no detectable evidence of alcohol effects.

3. Relaxed - feel calm and contented.

4. Light-headed - initial signs of alcohol impairment.

5. Tipsy - conscious of changes in speech patterns; initial evidence of awkwardness in movements.

6. Tight - definite evidence of slurred speech; mild unsteadiness in motion and balance; mind beginning to seem slower, less alert.

7. Initial stages of intoxication - speech, coordination, and thinking mildly but definitely impaired.

8. Moderately intoxicated - speech, coordination, and thinking markedly impaired; notable difficulties in maintaining attention and concentration and in controlling movements and posture.

9. Highly intoxicated - speech, coordination, and thinking markedly impaired; notable difficulties in controlling movement and posture.

10. Severely and completely intoxicated - all motor and cognitive functions severely impaired.
<table>
<thead>
<tr>
<th>Day of Cycle</th>
<th>Date</th>
<th>BEVERAGE TYPE and QUANTITY CONSUMED</th>
<th>Hours of Intake</th>
<th>With Whom/Where</th>
<th>Intox. Rating</th>
<th>Medications</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Beer ____ # ____; size: ____</td>
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<td>Wine ____ # ____; size: ____</td>
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<td>Liquor ____ # ____; ounces: ____</td>
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<td>Liquor ____ # ____; ounces: ____</td>
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</table>
APPENDIX H

Basal Body Temperature Log

BASAL BODY TEMPERATURE (°F)

DAYS OF THE MENSTRUAL CYCLE

96.5 97.0 97.5 98.0 98.5 99.0 99.5 100.0

1 5 10 15 20 25 30
APPENDIX I

INFORMED CONSENT AGREEMENT

I, __________________________, for valuable compensation, do hereby consent to participate in a research study conducted for the purpose of learning the differential effects of alcohol consumption among women and men. I have been informed that the possible benefits from this study include greater understanding of the physiological and emotional effects of alcohol which may lead to the development of more productive strategies for the prevention and treatment of problems related to alcohol use and abuse.

Dr. Patricia B. Sutker and/or her associate have explained to me the details and reasons for this study. I understand that I may be asked to consume substances which may contain alcohol. However, the dosages of alcohol to be used are such that the possibility of untoward consequences is extremely remote, and every assurance has been taken to prevent the occurrence of any such unpleasant effects.

I understand that the design and procedures of this study require that pregnant females be excluded from participation and have been requested to inform Dr. Sutker, and/or her associates if I am pregnant or think that I may possibly be pregnant. As an added precaution, I understand that routine pregnancy tests will be administered which will require collection of a urine sample.

I further understand that routine hormonal assays will be performed which will require collection of blood samples (approximately 10 cc or 1/3 oz. each) obtained through a needle from a vein in my arm (venipuncture). In addition, I am requested to record my basal body temperature for the duration of the study and my alcohol consumption for a period of approximately 4 weeks.

I am aware that I will be asked to divulge personal information. I have been informed that all information received from me will be kept confidential, and at no time will any of my replies or responses be associated with my name.

I have been informed that the following coding system will be employed to insure confidentiality:

Each participant will be assigned a subject number which will be recorded on the Informed Consent Agreement. All records pertaining to subject responses will be identified and filed by number only. Informed Consent Agreements will be maintained in a separate file.

RISKS/DISCOMFORTS: There is no risk/discomfort involved in collection of urine samples.
Blood samples (venipuncture) will be obtained through a needle from a vein in my arm. There may be a slight pain when the arm is stuck with the needle. A bruise may be left temporarily at the spot where the arm is stuck. There is a slight change of inflammation of the vein and/or blood clot formation; this is extremely rare.

I understand that if I have any questions regarding this study or this form, they will be answered so that I satisfactorily and completely understand.

I understand that in the event of physical injury resulting from the research procedures, no medical treatment for injuries or illness is available and financial compensation for wages lost because of injury or illness is not available. I understand that full information concerning the availability of compensation or treatment can be obtained from the Office of the Dean, 1430 Tulane Avenue, New Orleans, Louisiana 70112, (504) 588-5462 (phone).

I have been informed of and fully understand the procedures and purposes of this investigation as well as the possible risks involved and safeguards employed. I voluntarily agree to participate in this investigation. In addition, I realize that I will receive $50 per session for my participation in this investigation.

I understand that I am free to withdraw my consent and discontinue participation at any time. Discontinuation will in no way jeopardize my ability to receive services.

WITNESS ___________________________ SIGNATURE OF PARTICIPANT

DATE ___________________________
Name: Alan R. King, Ph.D.

Date of Birth: August 25, 1956
Place of Birth: New Orleans, Louisiana
Marital Status: Single
Present Position: Assistant Professor of Psychology, Southern University in New Orleans

EDUCATION: Vandebilt Catholic High School
Houma, Louisiana
1970 - 1974
Graduation in May, 1974

Nicholls State University
Thibodaux, Louisiana
1974 - 1977
Graduation in May, 1977
B.A. degree in psychology

University of Southwestern Louisiana
Lafayette, Louisiana
1977 - 1979
Graduation in May, 1979
M.S. degree in experimental psychology

Louisiana State University
Baton Rouge, Louisiana
1979 - 1984
Graduation in May, 1984
Ph.D. in clinical psychology
minor area: medical psychology

RESEARCH: Master's Thesis: The Effects of a Court-Probated Alcoholics Anonymous Program for Driving While Intoxicated Offenders on Seven Self-Report Indicators of Life Adjustment (winner of the 1979 Louisiana Psychological Association's annual Graduate Research Award)

Secondary Research Requirement: The Efficacy of a Computerized Simulation Program to Teach Research Methodology

Dissertation: Menstrual Cycle Influences on Acute Alcohol Intoxication


EXAMINATION AND THESIS REPORT

Candidate: Alan Russell King
Major Field: Psychology
Title of Thesis: Menstrual Cycle Influences on Acute Alcohol Intoxication

Approved:

[Signatures]

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Date of Examination: March 2, 1984