THE INCIDENCE OF ACUTE MOUNTAIN SICKNESS
AS AFFECTED BY THE USE OF HORMONAL CONTRACEPTIVES

By

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A clinical research project submitted in partial fulfillment of
the requirements for the degree of

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To the faculty of Whitworth College:

The members of the Committee appointed to examine the clinical research project of SHARON ELIZABETH REYNOLDS find it satisfactory and recommend that it be accepted.

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Acknowledgments

An internationally renowned climber said, "It's not what you climb, but whom you climb with." How true! These guides and companions have made this journey a real joy, and I thank them for their generosity of time, acumen, and encouragement along the route.

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Dedication

For Steve and Danielle,

who have lovingly belayed me over life's crevasses

and onto its pinnacles.
THE INCIDENCE OF ACUTE MOUNTAIN SICKNESS
AS AFFECTED BY THE USE OF HORMONAL CONTRACEPTIVES

Abstract

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May 1996

CHAIR: Margaret Auld Bruya

OBJECTIVE: To describe and compare the incidence of acute mountain sickness (AMS): a) between the genders; b) between women who are using hormonal types of contraception as contrasted with those who are not; and c) to compare the incidence of AMS between stages of the female menstrual cycle.

DESIGN: Descriptive correlational survey.

SETTING: Camp Muir, elevation 3,072 meters, on Mt. Rainier (4,392 m) in Washington State, during the summer climbing season, June through August 1995.

PARTICIPANTS: 44 recreational climbers (35 men and 9 women) between the ages of 18 through 52, who had attempted the summit of Mt. Rainier.

MAIN OUTCOME MEASURES: Participants completed the Lake Louise Consensus Questionnaire and a demographic questionnaire, plus underwent a brief physical exam, to quantify the occurrence of acute mountain sickness. In addition, women answered several
questions regarding the use of hormonal contraceptives, and timing of menstrual cycles. An attempt to correlate menstrual cycle phases to AMS susceptibility was also made.

RESULTS: Although this study attempted to investigate if hormonal contraceptive use or the menstrual cycle stage is correlated with AMS incidence, the results did not support any difference between genders and the incidence of AMS, given the sample size of nine women. Neither was the use of hormonal contraception nor the menstrual cycle stage associated with increased or decreased AMS rates. Further elucidation of the effects of either endogenous or exogenous progesterone on AMS was not obtained.

CONCLUSIONS: A more adequate sample size of women is needed to determine accurately whether hormonal contraception affects AMS incidence. Investigation is needed to determine the accuracy of the method used in this study to extrapolate menstrual cycle phases. Additional research controlling for menstrual cycle phases, plus the type of hormonal contraception and the effect of progesterone on AMS, is also suggested.
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Chapter 1

Introduction and Background

People residing at low altitude who rapidly ascend to elevations above 2,500 meters (8,200 ft) may develop unpleasant symptoms such as headache, anorexia, nausea, vomiting, dyspnea, lassitude, and insomnia between 6 and 96 hours after arrival at high altitudes (Ward, Milledge, & West, 1994). Termed acute mountain sickness (AMS), these symptoms range on a continuum from the uncomfortable symptoms mentioned previously, to fulminating fatal illness (high altitude pulmonary edema and high altitude cerebral edema).

Hypoxia, directly related to rapid ascent to high altitudes, is the underlying critical mechanism triggering the development of AMS (Ward et al., 1994; Rathat, Richalet, Herry, & Larmignat, 1992; Edelman, Santiago, & Neubauer, 1984). Several different pathways are postulated, involving alteration of fluid or electrolyte homeostasis, with either water retention and/or shifts of water from intracellular to extracellular compartments (Krasney, 1994; Ward et al., 1994). Apparently, hypoxia's immediate effect is to stimulate the HVR (hypoxic ventilatory response) in either the central nervous system or the peripheral chemoreceptors in the carotid bodies; there is some dissention about the site (Coote, 1995; Krasney, 1994; Ward et al., 1994). Respiratory rate and volume then increase, augmenting minute ventilation. Decreased partial pressure of carbon dioxide (pCO₂) and increased pH results, inhibiting the central chemoreceptors in the choroid plexus. Subsequently, minute ventilation decreases. This fluctuation and balance between the peripheral and central chemoreceptors ultimately determines the rate of renal bicarbonate excretion. As acclimatization continues over the next few days and weeks, renal bicarbonate excretion improves, resulting in a decrease in serum pH. This mild
metabolic acidosis is believed then to stimulate respiration at the level of the central chemoreceptors of the choroid plexus, increasing minute ventilation (McMurray, 1994; Coote, 1991). Multiple studies have shown that individuals with a strong (or brisk) HVR, which is inherent, are not as likely to become as hypoxic upon ascent to altitude, with the subsequent development of AMS (Rathat et al., 1992; Moore et al., 1986; Schoene, 1984).

The briskness of the HVR, a characteristic that varies among individuals, may be modified to some extent by both endogenous and exogenous factors, including the hormone progesterone (Regensteiner et al., 1989; Schoene, 1984). Progesterone peaks during the mid-luteal phase of a woman's menstrual cycle. It is also an active ingredient of hormonal contraception (oral contraceptives; implantable Norplant®; injectable Depo-Provera®).

Besides individual susceptibility, the incidence and severity of AMS is highly dependent upon the rate of ascent and the ultimate altitude achieved (Hackett, Rennie, & Levine, 1976). AMS does not seem to be associated with physical fitness (Ward et al., 1994). Some evidence suggests that younger people may be more susceptible than older individuals (Hackett et al., 1976).

For healthy individuals at sea level, maintaining ventilation is non-problematic. The partial pressure of carbon dioxide (PCO₂) is the primary regulator, with hypoxia acting as a safeguard mechanism. However in disease states such as chronic obstructive pulmonary disease (COPD), where gas exchange and oxygenation are impaired, the HVR becomes increasingly important. At high altitudes, where ambient PO₂ drops precariously low, the HVR plays an integral role in the survival of even healthy individuals (Schoene, 1984).
AMS affects millions of climbers, skiers, trekkers, soldiers, and tourists yearly (Bezruchka, 1992). As adventure travel to high altitude destinations continues to increase in ease and popularity, identifying at-risk populations for AMS will help in decreasing the morbidity and mortality of this preventable illness through prophylaxis, diagnosis, treatment, and education.

Statement of the Problem

Studies conflict regarding the incidence of gender susceptibility to AMS (Hackett et al., 1976; Honigman et al., 1993; Houston, 1987; Maggiorini, Buhler, Walter, & Oelz, 1990; Sutton & Lazarus, 1973 as cited in Pigman, 1991; Harris, Shields, & Hannon, 1966). Charles Houston MD (personal communication, February 5, 1995) believes this is partially due to the absence of data on age and menstrual cycles.

Progestins and estrogens have long been linked to augmentation of the HVR, which is inherent and closely linked to susceptibility to AMS (Regensteiner et al., 1989; Schoene, Robertson, Pierson, & Peterson, 1981). Despite this link, Hackett & Roach in 1987 commented that, to their knowledge, the effect of progesterone had not yet been studied in climbers. This investigator could find only one study (Bradwell, Wright, Imray, Fletcher, & BMRES, 1995) dealing with the effect of progesterone on AMS incidence. No studies were available in the literature describing or linking the incidence of acute mountain sickness to the use of hormonal contraceptives.
Statement of the Purpose

The purposes of this study were to investigate: a) if there is a gender difference in AMS incidence; b) if the use of any available hormonal contraception (oral, injectable, or implantable) affects the incidence of AMS in women; and c) if the menstrual cycle stage affects the incidence of acute mountain sickness in women.

Conceptual Framework

Acute mountain sickness is preventable by slow ascent, allowing adequate time for acclimatization to occur. If AMS does develop, it is treated by halting ascent until symptoms subside. If no improvement results, descent is the primary treatment. Reflecting the movement proposed by Dorthea Orem (1991), self-care is pivotal in the acclimatization process. The individual can affect and control the primary risk factor, rapid ascent. The concept of "expedition behavior" is the climber's version of Orem's self-care constructs (Petzoldt, 1974).

First postulated by Paul Petzoldt (1974), a pioneer in North American mountaineering, expedition behavior consists of preventive actions aimed toward reducing risks to both the self, other climbing party members, and potential rescuers. For example, the self-care behavior of consuming adequate fluids during a climb decreases the risk of thrombophlebitis to the individual, thus sparing team members and potential rescuers from having to participate in a risky evacuation of the affected member. Another example of expedition behavior (or Orem's self-care) is the individual promptly reporting to other party members the development of symptoms of AMS, so that ascent can be temporarily halted to forestall the development of high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE) (Cashel, 1994).
Review of the Literature

Review of literature addresses the physiology of the female menstrual cycle, gender differences in the acclimatization process and the HVR, plus the incidence of AMS. Progesterone's effect upon respiratory chemosensitivity is also explored.

The two types of ovarian sex hormones are the estrogens and the progestins. The most significant of the estrogens is the estradiol; the most important progestin is progesterone. They are secreted in varying amounts during the female menstrual cycle (Figure 1). Hormonal contraceptives, such as oral contraceptive pills ("the Pill," Ortho-Novum®, Desogen®, Triphasil®, Ortho-Cept®, etc.), levonorgestrel implant (Norplant®), and medroxyprogesterone acetate injections (Depo-Provera®), contain varying degrees of estrogens or progestins (or both). Selectively inhibiting pituitary function, they result in a hormonal mimicking of pregnancy, thus preventing ovum release and possible subsequent pregnancy (Katzung, 1992).
Figure 1. Approximate plasma concentrations of the ovarian hormones during the normal female menstrual (sexual) cycle. Adapted from Guyton (1991)
Mabel FitzGerald (1913), an associate of J. S. Haldane, first suggested gender differences in the process of acclimatization. Unfortunately, due to the era and her gender, her work was dismissed by her scientific contemporaries and only recently rediscovered. Schoene (1984) remarked that exogenous or endogenous manipulation of chemosensitivity can substantiate the relationship between resting HVR and exercise hyperpnea. For example, exogenous progesterone (medroxyprogesterone acetate) augments ventilatory drives (Tatsumi, Hannhart, Pickett, Weil, & Moore, 1991). Higher ventilatory drives and exercise ventilation were noted by Schoene (1984) during the luteal phase of the menstrual cycle, when endogenous progesterone is highest.

Tatsumi et al. (1991) explored gender differences in HVR. They observed that progesterone, particularly when combined with estrogen, raised ventilatory rates and HVR in humans and experimental animals of either gender. Their studies on cats also suggested that female and male hormones acted to raise HVR sensitivity. Also, the effects of female gender, unrelated to levels of circulating sex hormones, acted to enhance HVR. Lawrence Mohr and colleagues, in a 1985 study conducted on Mt. Rainier in Washington State, noted the decrease of testosterone and the increase of estradiol in a cohort of male Army Rangers. This seemed directly related to acclimatization and ability to perform at altitude. However, because the U.S. Army refused to allow investigators to administer female hormones to soldiers, further study was precluded (Lawrence Mohr MD, personal communication, February 17, 1995).

Most studies suggest there is no gender difference in AMS incidence, but the findings are muddied and inconclusive due to absence of age and menstrual phase data (Charles Houston MD, personal communication, February 5, 1995). Hackett et al., in the landmark 1976 study in
the Himalayan Range, found no difference in incidence between genders. Harris et al. (1966) remarked on the paucity of studies done, correlating women and AMS. Their observations of eight college-age females on the summit of Pikes Peak, Colorado (4,300 m/14,110 ft) seemed to agree with the only two observations available to them—which were done with Peruvian women in the Andes during 1913 and 1920. Harris concluded that the duration of AMS in his study's eight females appeared to be similar to the illness spectrum reported in males, but was possibly less severe. Although small changes were noted in the length and duration of the menstrual cycles of five of the eight females, no hormonal studies were conducted. Harris commented on the need for further investigation of the changes and hormonal levels, but apparently did not pursue further study of these findings.

Maggiorini et al. (1990) noted that men and women were equally affected by AMS in a study done in the Swiss Alps. Conversely, Honigman et al. (1993) reported a significant difference in AMS occurrence in a study of Colorado tourists (n = 3,158), ages 16 to 87. At moderate altitudes of 1,920 m to 3,000 m (6,300 to 9,700 ft), incidence in males was 23.6%, while females diagnosed with AMS had an incidence of 27.9% (p = 0.01); no information regarding menstrual cycle phases was gathered. In Colorado, Houston (1985) interviewed a general population of 3,906 men, women, and children during three winter months in six resorts ranging from 2,440 m to 2,900 m (8,000 to 9,500 ft) in altitude. Houston, extrapolating a 12% incidence of AMS at these modest altitudes, did not attempt to differentiate incidence rates between genders or age groups. A review of the medical records of 150 patients with HAPE seen over a 39-month period in a Colorado ski resort at 2,928 m (9,606 ft) revealed that 84% were
males, and suggested the higher incidence in men was due to comparative hypoventilation (Hultgren, Nicholas, Honigman, & Theis, 1995).

Kryger et al. (1978) postulated progesterone has a beneficial effect in decreasing oxygen desaturation during sleep. Schoene and his colleagues (1981) demonstrated that hormonal fluctuation during the luteal phase of the menstrual cycle augments chemosensitivity. Progestin, alone or with estrogen, increased resting ventilation and decreased end-tidal PCO$_2$, according to Regensteiner et al. (1989). Tatsumi et al. (1991) presented evidence that progesterone, especially when combined with estrogen, raises ventilatory rates and HVR in humans and experimental animals of either sex. Their study also argued that the female cats' higher HVRs, whether intact or spayed, were the effects of female gender unrelated to endogenous sex hormones, but also acting to enhance HVR.

The 1994 British Mt. Everest Medical Expedition noted the unexpected finding of blood gas differences between the genders: after acclimatization, females had a greater decrease in capillary CO$_2$ than males. The expedition's results suggest that ventilatory control changes in chronic hypoxia may be superior in women, validating Mabel FitzGerald's 1913 work (Barry, Mason, & Collier, 1995; David Collier MD, personal communication, February 17, 1995).

Beidleman et al. (1995) suggested that menstrual cycle phase does not affect work performance at sea level and 4,300 meters (14,108 ft). His study did determine that SaO$_2$ was significantly increased (3%) in the mid-luteal phase compared with the follicular phase of the menstrual cycle at acute altitude. An increase of approximately 40% in the six women's HVR during the luteal phase, as compared with the follicular phase, was reported by Weil, White, Douglas & Zwillich (1984). They reported this correlated with the findings of previous studies.
The effects of dexamethasone, furosemide, acetazolamide, spironolactone, antacids, and nifedipine on AMS have been studied to varying degrees (Parker, Hollingshead, Dietz, & Hackett, 1995; Maggiorini, Merki, Pallavicini, Bärtsch, & Oelz, 1995; Grissom, Roach, Sarnquist, & Hackett, 1992; Bezruchka, 1992; Bradwell, Wright, Winterborn, & Imray, 1992; Coote, 1991; Ellsworth, Meyer, & Larson, 1991; Beeckman & Buskirk, 1988; Hackett & Roach, 1987). These investigations have been constrained by sample size, gender mix, or the inclusion of males-only in the studies. Studies of progesterone have been even more limited.

Coote, in his 1991 review of the pharmacological control of AMS, noted the known respiratory stimulant effect of progesterone, speculating that susceptibility to AMS might be expected to vary in women depending on the stage of their menstrual cycle when they arrive at altitude. He also stated "there is little information on this point" (p. 455). Coote remarked that progesterone was believed to have a probable site of action in the respiratory neurons, and that despite intriguing respiratory stimulant effects, it had only been used in the prevention of sleep apneas at altitude up to that time.

Four years later, Coote (1995) again reviewed the medications and mechanisms of altitude sickness. His comments regarding progesterone were virtually identical to those he made in 1991, adding that the mechanism of progesterone's enhancement of respiratory drive was still unknown. The need for further study was remarked on yet again. Coote professed that, to his knowledge, there had been only one trial of the effect of progesterone in the prevention of AMS: Bradwell, Wright, Imray, Fletcher, & the Birmingham Research Expeditionary Society (1995). This was also the only investigation on this topic that this investigator could find. "Progesterone in acute mountain sickness" has been published only as an abstract, and given as a podium
presentation at Hypoxia '95: The Ninth International Hypoxia Symposium, held at Lake Louise, Canada, February 14 - 18, 1995.

In this study, Bradwell et al. (1995) compared progesterone, acetazolamide, progesterone/acetazolamide in combination, and placebo in the prevention of AMS. The small sample consisted of 22 men and only two women, ascending to 5,200 m (17,060 ft) over seven days. Conclusions were somewhat inconsistent and puzzling, but high doses of progesterone (60 mg daily) seemed to prevent AMS and appeared similar to acetazolamide in efficacy. The relationship between AMS incidence and hormonal contraceptives, such as Depo-Provera®, Norplant®, and various oral contraceptives ("the Pill") did not appear in the literature review, and has apparently never been examined.

Research Questions

a) Is there a gender difference in the incidence of AMS among persons climbing Mt. Rainier in Washington State?

b) Does the use of hormonal contraception affect the incidence of AMS in women?

c) Does the phase of the menstrual cycle affect the incidence of AMS in women?

Definition of Terms

Acclimatization - the process of bodily adaptation to the presence of decreased oxygenation associated with changes in elevation.
Hypoxia - the presence of a lower than normal quantity (< 95%) of oxygen in the blood or body tissues.

Acute mountain sickness (AMS) - a symptom complex commonly seen after ascent to altitudes above 2,500 meters (8,200 ft). It is characterized by headache, anorexia, nausea, insomnia, and malaise. AMS is usually self-limited but may progress to life-threatening high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE) if ascent is continued while symptoms are present. In this study, AMS was diagnosed by a score of 3 points or greater on the Lake Louise Consensus Questionnaire (LLCQ) (Roach, Bärtsch, Hackett, Oelz, & the Lake Louise AMS Scoring Consensus Committee, 1993).

High altitude pulmonary edema (HAPE) - a severe gradation of progressive AMS. Signs and symptoms may include any combination of dyspnea, marked fatigue, weakness, subjective feelings of chest tightness or impending suffocation, and productive cough with frothy watery white, pink, or bloody sputum. Resting heart rate is greater than 110 beats/minute; resting respiratory rate is greater than 16/minute. Crackles may be auscultated, and chest X-rays display infiltrates. HAPE is invariably fatal within hours if rapid and immediate descent is not undertaken, although supplemental oxygen, medications, and the use of a portable hyperbaric chamber may delay progression of symptoms.

High altitude cerebral edema (HACE) - a severe gradation of progressive AMS. Signs and symptoms may include any combination of worsening headache, ataxia, memory loss, confusion, hallucinations, impaired judgement, coma, and papilledema.
HACE may be associated with HAPE. It is invariably fatal within hours if rapid and immediate descent is not undertaken, although supplemental oxygen, medications, and the use of a portable hyperbaric chamber may delay progression of symptoms.

Female menstrual cycle - may also be termed the female sexual cycle. The average cyclic duration is 28 days. Days 5 - 14, the follicular (or secretory) phase, are marked by a cyclic increase in estradiol. Ovulation occurs approximately on Day 14, triggering an increase in progesterone and estrogen, secreted by the corpus luteum. Progesterone levels peak on Day 21 and rapidly decline as the corpus luteum degenerates in the absence of fertilization and subsequent pregnancy. Menstruation commences on Day 1, lasting for 5 days in the average cycle. For each woman who was not using hormonal contraception, the phases of her menstrual cycle were deduced from: a) her average cycle length; b) the first day of her last menstrual period (LMP); and c) the date the woman participated in the study.

Luteal phase - also known as the secretory phase, it extends from the day of ovulation to about three days before the next menstrual period: Days 14 - 25. Progesterone (and some estrogen) is secreted in increasing amounts by the corpus luteum.

Mid-luteal phase - Days 19 - 23 of the female menstrual cycle, when the corpus luteum is at peak production of progesterone. Estimation of the occurrence of the mid-luteal phase was extrapolated from each woman's average cycle length, LMP, and date of study participation.
Significance to Nursing

As adventure travel to high altitude destinations continues to increase in ease and popularity, identifying at-risk populations for AMS will help in decreasing the morbidity and mortality of this preventable illness through diagnosis, prophylaxis, treatment, and education. Lessons from high altitude illness also provide valuable insight into the problems sea-level patients with impaired oxygen transport face. Orem's self-care theory applied to acute mountain sickness suggests that nurses both in standard and advanced practice can educate patients to prevent and self-treat AMS.
Chapter 2

Methods of Study

Design

The study is of descriptive correlational design. Quantitative data were collected. The purpose was to describe and compare the incidence of acute mountain sickness: a) between the genders; b) between women who are using hormonal types of contraception as contrasted with those who are not; and c) to compare the incidence of AMS between stages of the female menstrual cycle.

Setting

This study was conducted at Camp Muir (3,072 m/10,080 ft), on Mt. Rainier (4,392 m/14,411 ft) in Washington State. Camp Muir serves as high camp for the most popular route on Mt. Rainier, Disappointment Cleaver. The route taken by study participants starts from the Paradise ranger station (1,647 m/5,400 ft). The vast majority of climbers then rest for 6 - 30 hours at Camp Muir before continuing up Disappointment Cleaver to the summit, then retracing the route back to Muir. While the route is strenuous, it is not complex. Disappointment Cleaver is considered a long plod, without technical rock or ice climbing. There is little seasonal variation in the "trail" (or more precisely, the trench!) worn into the glaciers by several thousand aspirants.

The Disappointment Cleaver route is notorious in the climbing community for the numbers of inexperienced and ill-prepared aspirants it attracts. According to statistics released by Mt. Rainier National Park (B. Ingle, personal communication, April 8, 1996), during 1995
there were 3,549 official summit attempts via the Disappointment Cleaver route (excluding professionally guided parties); 1,776 climbers (50.0%) reached the top. By comparison, on all of Rainier's other routes in 1995, 45.4% (n = 3,259) summited. Larson, Roach, and Schoene's 1982 study (as cited in Hackett & Roach, 1987) reported an approximate incidence of AMS on Mt. Rainier of 67%; mean ascent time to the summit was $33 \pm 1$ hours. Houston's studies on Mt. Rainier (as cited by Hackett et al., 1976) noted "50% with severe headache in 1972, and, in 1973, 60% with some symptom of AMS" (p. 1153).

**Population and Sample**

A convenience sample of 44 recreational climbers (35 male; 9 female) descending after a successful or unsuccessful summit bid was obtained at Camp Muir (3,072 m/10,080 ft). Climbers using any medications (other than hormonal contraceptives) were excluded from the study. This included medications used for acclimatization purposes, such as acetazolamide or dexamethasone. Also excluded were individuals who used tobacco in any form, or those diagnosed with chronic illnesses such as diabetes, asthma, or COPD. Length of time on hormonal contraception, if utilized, was three months or longer. An attempt to control the confounding factors of pre-menarcheal and menopausal states was done by limiting the ages of those participating in the study to between 18 and 52. The mean age of menarche in the United States is 12.7 years; the mean age of menopause is 51.4 years (Frederickson & Wilkins-Haug, 1991).

Group I contained 35 men. Group II included the three women who had not used any form of hormonal replacement or supplementation for the three months prior to the study. Group
III consisted of the six women who had used hormonal contraception for a minimum of three months prior to the study.

Data Collection Procedure

Upon descent to Camp Muir after a successful or unsuccessful summit attempt, mountaineers were surveyed on four random and separate weekends during the regular summer climbing season, June 16 through August 14, 1995. Data collection was done by the principal investigator on the first three weekends, and by a trained assistant (a neurosurgeon) the fourth weekend. Participant consent was obtained verbally; a written copy of the informed consent was given to each individual (Appendix A). Participants then completed the Lake Louise Consensus Questionnaire, 1995 revision (LLCQ). Demographic data were collected. In addition, women answered questions about the use of hormonal contraceptives and the timing of menstrual cycles. The investigator then requested that participants perform a simple heel-to-toe walking test for approximately 5 meters and completed the clinical assessment questions of the LLCQ (Appendix B). Only climbers who were not professionally guided participated in the study. Every climber who was approached, and met the criteria, agreed to participate. No one chose to withdraw from the study.

Data Gathering Instrumentation

According to the criteria of the LLCQ, "a diagnosis of AMS (was) based on a recent gain in altitude, at least several hours at the new altitude, and the presence of headache and at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), fatigue or
weakness, dizziness or lightheadedness and difficulty sleeping. A score of three points or greater on the AMS Self-report alone, or in combination with the Clinical Assessment score (constituted) AMS" (Roach et al., 1993).

**Validity and Reliability**

Content validity of the LLCQ has been established by several researchers who used it to measure acute mountain sickness: Ellsworth, Duncan, Goldberg, Johnson, & Hackett (1993); Atkins, Honigman, Houston & Roach (1993); Maggiorini, Muller, Bärtsch, & Oelz (1993). All reported the LLCQ compared favorably to the Environmental Symptoms Questionnaire III (ESQ III) for both sensitivity and specificity. The Birmingham Medical Research Expeditionary Society (BMRES) reported that the LLCQ correlated well with the BMRES questionnaire on validity and reliability (Wright et al., 1995). The LLCQ has the advantage of taking only several minutes to complete, as compared with the ESQ III that contains 67 items and takes proportionately longer to answer (Roach et al., 1993).

Determination of the menstrual cycle phase via extrapolation method used in this investigation has apparently never been tested for validity, sensitivity, or specificity. Estimating the stage of a woman's menstrual cycle through post-hoc analysis rather than serum testing leaves the inevitable possibility of a significant error. However, it was the only feasible method for this initial study.

Permission to use the LLCQ was granted via electronic mail by Charles S. Houston (Appendix C). The study questionnaire also contained demographic data, plus questions about physical fitness and the estimated highest altitude reached on the climb.
Data Analysis

Descriptive analysis (mean and standard deviation) was applied to demographic data and AMS incidence (determined by LLCQ scores). Groups were compared by chi-squared test; p values < 0.05 were considered significant. Systat® was used for computerized data analysis.

Human Rights Protection

Permission to conduct the study was obtained from the Institutional Review Board of Washington State University (Appendix D) and Mt. Rainier National Park (Appendix E) prior to beginning the investigation. Participants were given an informed consent form prior to the beginning of the study. To assure anonymity, participants did not reveal their names to the investigator. Completion of the questionnaire implied consent to participate.

This study did not contain any procedures that result in an increased risk to the participants. In recognition that some women might find questions regarding use of hormonal contraception or timing of menstrual cycles embarrassing, participants had the option of withdrawing from the study at any time.

Data collected were used by the investigator for research purposes only. The results of this investigation may appear in scientific journals, research symposia, or lay climbing publications. An abstract is on file with Mt. Rainier National Park as a condition of granting a research permit. However, any publication of the study results has included, or will include, group data only.
Chapter 3

Manuscript

The following is a manuscript prepared for the publication of findings of this study. The Journal of Wilderness Medicine is the target, and the format is set according to its guidelines. However, references have been left in American Psychological Association (APA) format, to be consistent with the clinical project guidelines for Whitworth College and the Intercollegiate Center for Nursing Education. References will be converted to Index Medicus format when the manuscript is submitted.
THE INCIDENCE OF ACUTE MOUNTAIN SICKNESS
AS AFFECTED BY HORMONAL CONTRACEPTIVES

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Abstract

OBJECTIVE: To describe and compare the incidence of acute mountain sickness (AMS): a) between the genders; b) between women who are using hormonal types of contraception as contrasted with those who are not; and c) to compare the incidence of AMS between stages of the female menstrual cycle.

DESIGN: Descriptive correlational survey.

SETTING: Camp Muir, elevation 3,072 meters, on Mt. Rainier (4,392 m) in Washington State, during the summer climbing season, June through August 1995.

PARTICIPANTS: 44 recreational climbers (35 men and 9 women) between the ages of 18 through 52, who had attempted the summit of Mt. Rainier.

MAIN OUTCOME MEASURES: Participants completed the Lake Louise Consensus Questionnaire and a demographic questionnaire, plus underwent a brief physical exam, to quantify the occurrence of acute mountain sickness. In addition, women answered several questions regarding the use of hormonal contraceptives, and timing of menstrual cycles. An attempt to correlate menstrual cycle phases to AMS susceptibility was also made.

RESULTS: Although this study attempted to investigate if hormonal contraceptive use or the menstrual cycle stage is correlated with AMS incidence, the results did not support any difference between genders and the incidence of AMS, given the sample size of nine women. Neither was the use of hormonal contraception nor the menstrual cycle stage was associated with increased or decreased AMS rates. Further elucidation of the effects of either endogenous or exogenous progesterone on AMS was not obtained.
CONCLUSIONS: A more adequate sample size of women is needed to determine accurately whether hormonal contraception affects AMS incidence. Investigation is needed to determine the accuracy of the method used in this study to extrapolate menstrual cycle phases. Additional research controlling for menstrual cycle phases, plus the type of hormonal contraception and the effect of progesterone on AMS, is also suggested.

Keywords: acute mountain sickness, mountaineering, hypoxia, hypoxic ventilatory response, progesterone, gender, women, contraceptives
Introduction

People residing at low altitude who rapidly ascend to altitudes above 2,500 meters (8,200 ft) may develop unpleasant symptoms such as headache, anorexia, nausea, vomiting, dyspnea, lassitude, and insomnia between 6 and 96 hours after arrival at high altitude (Ward, Milledge, & West, 1994). Termed acute mountain sickness (AMS), these symptoms range on a continuum from the uncomfortable symptoms mentioned previously, to fulminating fatal illness (high altitude pulmonary edema and high altitude cerebral edema).

Hypoxia, directly related to rapid ascent to high altitudes, is the underlying critical mechanism triggering the development of AMS (Ward et al., 1994; Rathat, Richalet, Herry, & Larmignat, 1992; Edelman, Santiago, & Neubauer, 1984). Several different pathways are postulated (Krasney, 1994; Ward et al., 1994), involving alteration of fluid or electrolyte homeostasis with either water retention and/or shifts of water from intracellular to extracellular compartments. Apparently, hypoxia's immediate effect is to stimulate the HVR (hypoxic ventilatory response) in either the central nervous system or the peripheral chemoreceptors in the carotid bodies; there is some dissention about the site (Coote, 1995; Krasney, 1994; Ward et al., 1994). Respiratory rate and volume then increase, augmenting minute ventilation. Decreased partial pressure of carbon dioxide (pCO₂) and increased pH results, inhibiting the central chemoreceptors in the choroid plexus. Subsequently, minute ventilation decreases. This fluctuation and balance between the peripheral and central chemoreceptors ultimately determine the rate of renal bicarbonate excretion. As acclimatization continues over the next few days and weeks, renal bicarbonate excretion improves, resulting in a decrease in serum pH. This mild metabolic acidosis is believed then to stimulate respiration at the level of the central
chemoreceptors of the choroid plexus, increasing minute ventilation (McMurray, 1994; Coote, 1991). Multiple studies have shown that individuals with a strong (or brisk) HVR, which is inherent, are not as likely to become as hypoxic upon ascent to altitude, with the subsequent development of AMS (Rathat et al., 1992; Moore et al., 1986; Schoene, 1984).

The briskness of the HVR, a characteristic that varies among individuals, may be modified to some extent by both endogenous and exogenous factors, including the hormone progesterone (Regensteiner et al., 1989; Schoene, 1984). Progesterone peaks during the mid-luteal phase of a woman's menstrual cycle. It is also an active ingredient of hormonal contraception (oral contraceptives; implantable Norplant®; injectable Depo-Provera®).

Besides individual susceptibility, the incidence and severity of AMS is highly dependent upon the rate of ascent and the ultimate altitude achieved (Hackett, Rennie, & Levine, 1976). AMS does not seem to be associated with physical fitness (Ward et al., 1994). There is some evidence that younger people may be more susceptible than older individuals (Hackett et al., 1976).

For healthy individuals at sea level, maintaining ventilation is non-problematic. The partial pressure of carbon dioxide (PCO₂) is the primary regulator, with hypoxia acting as a safeguard mechanism. However in disease states such as chronic obstructive pulmonary disease (COPD), in which gas exchange and oxygenation are impaired, the HVR becomes increasingly important. At high altitudes, where ambient PO₂ drops precariously low, the HVR plays an integral role in the survival of even healthy individuals (Schoene, 1984).

AMS affects millions of climbers, skiers, trekkers, soldiers, and tourists yearly (Bezruchka, 1992). As adventure travel to high altitude destinations continues to increase in ease
and popularity, identifying at-risk populations for AMS will help in decreasing the morbidity and mortality of this preventable illness through prophylaxis, diagnosis, treatment, and education.

Studies conflict regarding the incidence of gender susceptibility to AMS (Hackett et al., 1976; Honigman et al., 1993; Houston, 1987; Maggiorini, Buhler, Walter, & Oelz, 1990; Sutton & Lazarus, 1973 as cited in Pigman, 1991; Harris, Shields, & Hannon, 1966). Most reports suggest there is no gender difference in AMS incidence, but the findings are muddied and inconclusive due to absence of age and menstrual phase data (Charles Houston MD, personal communication, February 5, 1995). Hackett et al., in the landmark 1976 study in the Himalayan Range, found no difference in incidence between genders. Harris et al. (1966) remarked on the paucity of studies done correlating women and AMS. Their observations of eight college-age females on the summit of Pikes Peak, Colorado (4,300 m/14,110 ft) seemed to agree with the only two observations available to them—which were done with Peruvian women in the Andes during 1913 and 1920. Harris concluded that the duration of AMS in his study's eight females appeared to be somewhat similar to the illness spectrum reported in males, but was possibly less severe. Although small changes were noted in the length and duration of the menstrual cycles of five of the eight females, no hormonal studies were conducted. Harris commented on the need for further investigation of the changes and hormonal levels, but apparently did not pursue further study of these findings.

Maggiorini et al. (1990) noted that men and women were equally affected by AMS in a study done in the Swiss Alps. Conversely, Honigman et al. (1993) reported a significant difference in AMS occurrence in a study of Colorado tourists (n = 3,158), ages 16 to 87. At moderate altitudes of 1,920 m to 3,000 m (6,300 to 9,700 ft), incidence in males was 23.6%,
while females diagnosed with AMS had an incidence of 27.9% ($p = 0.01$). No information regarding menstrual cycle phases was gathered. In Colorado, Houston (1985) interviewed a general population of 3,906 men, women, and children during three winter months in six Colorado resorts ranging from 2,440 m to 2,900 m (8,000 to 9,500 ft) in altitude. Houston, extrapolating a 12% incidence of AMS at these modest altitudes, did not attempt to differentiate incidence rates between genders or age groups. A review of the medical records of 150 patients with high altitude pulmonary edema (HAPE) seen over a 39-month period in a Colorado ski resort at 2,928 m (9,606 ft) revealed that 84% were males, and suggested the higher incidence in men was due to comparative hypoventilation (Hultgren, Nicholas, Honigman, & Theis, 1995).

Mabel FitzGerald (1913), an associate of J. S. Haldane, first suggested gender differences in the process of acclimatization. Unfortunately, due to the era and her gender, her work was dismissed by her scientific contemporaries and only recently rediscovered. Schoene (1984) remarked that exogenous or endogenous manipulation of chemosensitivity can substantiate the relationship between resting HVR and exercise hyperpnea. For example, exogenous progesterone (medroxyprogesterone acetate) augments ventilatory drives (Tatsumi, Hannhart, Pickett, Weil, & Moore, 1991). Higher ventilatory drives and exercise ventilation were noted by Schoene (1984) during the luteal phase of the menstrual cycle, when endogenous progesterone is highest.

Tatsumi et al. (1991) explored gender differences in HVR. They observed that progesterone, particularly when combined with estrogen, raised ventilatory rates and HVR in humans and experimental animals of either gender. Their studies on cats also suggested that female and male hormones acted to raise HVR sensitivity. Also, the effects of female gender,
unrelated to levels of circulating sex hormones, acted to enhance HVR. Lawrence Mohr and colleagues, in a 1985 study conducted on Mt. Rainier in Washington State, noted the decrease of testosterone and the increase of estradiol in a cohort of male Army Rangers. This seemed directly related to acclimatization and ability to perform at altitude. However, because the U.S. Army refused to allow investigators to administer female hormones to soldiers, further study was precluded (Lawrence Mohr MD, personal communication, February 17, 1995).

Kryger et al. (1978) postulated progesterone has a beneficial effect in decreasing oxygen desaturation during sleep. Schoene, Robertson, Pierson, and Peterson (1981) demonstrated that hormonal fluctuation during the luteal phase of the menstrual cycle augments chemosensitivity. Progestin, alone or with estrogen, increased resting ventilation and decreased end-tidal PCO₂, according to Regensteiner et al. (1989). Tatsumi et al. (1991) presented evidence that progesterone, especially when combined with estrogen, raises ventilatory rates and HVR in humans and experimental animals of either sex. Their study also argued that the female cats' higher HVRs, whether intact or spayed, were the effects of female gender unrelated to endogenous sex hormones, but also acting to enhance HVR.

The 1994 British Mt. Everest Medical Expedition noted the unexpected finding of blood gas differences between the genders: after acclimatization, females had a greater decrease in capillary CO₂ than males. The expedition's results suggest that ventilatory control changes in chronic hypoxia may be superior in women, validating Mabel FitzGerald's 1913 work (Barry, Mason, & Collier, 1995; David Collier MD, personal communication, February 17, 1995).

Beidleman et al. (1995) suggested that menstrual cycle phase does not affect work performance at sea level and 4,300 meters (14,108 ft). His study did determine that SaO₂ was
significantly increased (3%) in the mid-luteal phase compared with the follicular phase of the menstrual cycle at acute altitude. An increase of approximately 40% in the six women's HVR during the luteal phase, as compared with the follicular phase, was reported by Weil, White, Douglas & Zwillich (1984). They reported this correlated with the findings of previous studies.

The effects of dexamethasone, furosemide, acetazolamide, spironolactone, antacids, and nifedipine on AMS have been studied to varying degrees (Parker, Hollingshead, Dietz, & Hackett, 1995; Maggiorini, Merki, Pallavicini, Bársch, & Oelz, 1995; Grissom, Roach, Sarnquist, & Hackett, 1992; Bezruchka, 1992; Bradwell, Wright, Winterborn, & Imray, 1992; Coote, 1991; Ellsworth, Meyer, & Larson, 1991; Beeckman & Buskirk, 1988; Hackett & Roach, 1987). These investigations have been constrained by sample size, gender mix, or the inclusion of males-only in the studies. Studies of progesterone have been even more limited. Although progestins and estrogens have long been linked to augmentation of the HVR, which is inherent and closely linked to susceptibility to AMS (Regensteiner et al., 1989; Schoene et al., 1981), Hackett & Roach in 1987 commented that, to their knowledge, the effect of progesterone had not yet been studied in climbers.

Coote, in his 1991 review of the pharmacological control of AMS, noted the known respiratory stimulant effect of progesterone, speculating that susceptibility to AMS might be expected to vary in women depending on the stage of their menstrual cycle when they arrive at altitude. He also stated "there is little information on this point" (p. 455). Coote remarked that progesterone was believed to have a probable site of action in the respiratory neurons, and that despite intriguing respiratory stimulant effects, it had only been used in the prevention of sleep apneas at altitude up to that time.
Four years later, Coote (1995) again reviewed the medications and mechanisms of altitude sickness. His comments regarding progesterone were virtually identical to those he made in 1991, adding that the mechanism of progesterone's enhancement of respiratory drive was still unknown. The need for further study was remarked on yet again. Coote professed that, to his knowledge, there had been only one trial of the effect of progesterone in the prevention of AMS: Bradwell (1995). This was also the only investigation on this topic that this investigator could find. "Progesterone in acute mountain sickness" has been published only as an abstract, and given as a podium presentation at Hypoxia '95: The Ninth International Hypoxia Symposium, held at Lake Louise, Canada, February 14 - 18, 1995.

In this study, Bradwell et al. (1995) compared progesterone, acetazolamide, progesterone/acetazolamide in combination, and placebo. The small sample consisted of 22 men and only two women. Conclusions were somewhat inconsistent and puzzling, but high doses of progesterone (60 mg daily) seemed to prevent AMS and appeared similar to acetazolamide in efficacy. As no studies were discovered in the literature describing or linking the incidence of acute mountain sickness to the use of hormonal contraceptives, this topic has apparently never been examined.

The purposes of this study were to investigate: a) if there is a gender difference in AMS incidence; b) if the use of any available hormonal contraception (oral, injectable, or implantable) affects the incidence of AMS in women; and c) if the menstrual cycle stage affects the incidence of acute mountain sickness in women.
Methods

The study is of descriptive correlational design. Quantitative data were collected. Research was conducted at Camp Muir (3,072 m/10,080 ft), on Mt. Rainier (4,392 m/14,411 ft) in Washington State. Muir serves as high camp for the most popular route on Mt. Rainier, Disappointment Cleaver. According to statistics released by Mt. Rainier National Park, during 1995 there were 3,549 official summit attempts via the Disappointment Cleaver route (excluding professionally guided parties); 1,776 climbers (50.00%) reached the top. By comparison, on all routes in 1995, 45.4% (n = 3,259) summited.

The route taken by study participants starts from the Paradise ranger station (1,647 m/5,400 ft). The vast majority of climbers then rest for 6 - 30 hours at Camp Muir before continuing up Disappointment Cleaver to the summit, then retracing the route back to Muir. While the route is strenuous, it is not complex. Disappointment Cleaver is considered a long plod, without technical rock or ice climbing. There is little seasonal variation in the "trail" (or more precisely, the trench!) worn into the glaciers by several thousand aspirants.

A convenience sample of recreational climbers (male and female) descending after a successful or unsuccessful summit bid was obtained at Camp Muir (3,072 m/10,080 ft) on four random and separate weekends during the regular summer climbing season, June 16 through August 14, 1995. Data collection was done by the principal investigator on the first three weekends, and by a trained assistant (a neurosurgeon) the fourth weekend. Recreational mountaineers were approached upon arrival back at Camp Muir and requested to complete the Lake Louise Consensus Questionnaire (LLCQ), 1995 revision. Demographic data were also collected. Women answered additional questions about the use of hormonal contraceptives and
the timing of menstrual cycles. Participants then performed a simple heel-to-toe walking test for approximately five meters and completed the clinical assessment questions of the Lake Louise questionnaire (Appendix B).

Excluded were mountaineers using any medications other than hormonal contraceptives. Medications used for acclimatization purposes, such as acetazolamide or dexamethasone were rigorously screened for. Also excluded were climbers who used tobacco in any form, or those diagnosed with chronic illnesses such as diabetes, asthma, or COPD. Length of time on hormonal contraception, if utilized, was three months or longer. Age of all participants was restricted to between the ages of 18 through 52.

According to the criteria of the LLCQ, "a diagnosis of AMS (was) based on a recent gain in altitude, at least several hours at the new altitude, and the presence of headache and at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), fatigue or weakness, dizziness or lightheadedness and difficulty sleeping. A score of three points or greater on the AMS Self-report alone, or in combination with the Clinical Assessment score (constituted) AMS" (Roach, Bärtsch, Hackett, Oelz, & the Lake Louise AMS Scoring Consensus Committee, 1993).

Content validity has been established by several researchers who used the LLCQ to measure acute mountain sickness: Ellsworth, Duncan, Goldberg, Johnson, & Hackett (1993), Atkins, Honigman, Roach, & Houston (1993), Maggiorini, Muller, Bärtsch, & Oelz (1993). They reported the LLCQ compared favorably to the Environmental Symptoms Questionnaire III (ESQ III) for both sensitivity and specificity. The Birmingham Medical Research Expeditionary Society (BMRES) reported that the LLCQ correlated well with the BMRES questionnaire on
validity and reliability (Wright et al., 1995). The LLCQ has the advantage of taking only several minutes to complete, as compared with the ESQ III that contains 67 items and takes proportionately longer to answer (Roach et al., 1993).

Determination of the menstrual cycle phase via extrapolation method used in this investigation has apparently never been tested for validity, sensitivity, and specificity. Estimating the stage of a woman's menstrual cycle through post-hoc analysis rather than serum testing leaves the inevitable possibility of a significant error. However, it was the only feasible method for this initial study.

An attempt to control the confounding factors of pre-menarcheal and menopausal states was done by limiting the ages of those participating in the study to between 18 and 52. The mean age of menarche in the United States is 12.7 years; the mean age of menopause is 51.4 years (Frederickson & Wilkins-Haug, 1991).

Ethics

Permission to conduct the study was obtained from the Institutional Review Board of Washington State University and Mt. Rainier National Park prior to beginning the investigation. Participants were given an informed consent form prior to the beginning of the study. To assure anonymity, participants did not reveal their names to the investigator. Completion of the questionnaire implied consent to participate.
Statistics

Descriptive analysis (mean and standard deviation) was applied to LLCQ scores. Groups were compared by chi-squared test; p values < 0.05 were considered significant. Systat® was used for computerized data analysis.

Results

A convenience sample of 44 recreational climbers (35 male; 9 female) descending after a successful or unsuccessful summit bid was obtained at Camp Muir (3,072 m/10,080 ft) on four random and separate weekends during the regular summer climbing season, June 16 through August 14, 1995. Only climbers who were not professionally guided participated in the study. Every climber who was approached, and met the criteria, agreed to participate. No one chose to withdraw from the study.

Age range of the climbers surveyed was between 18 and 52, with a mean of 33.8 (± SD 10.07) years. Participants had a wide range of previous exposure to altitude: from the summit of Mt. Everest (8,088 m/29,032 ft) to novices without previous mountaineering experience. Minimum altitude reached by participants during this study was approximately 3,353 m (11,000 ft). Overall summit success rate was 77% (34/44). According to statistics released by Mt. Rainier National Park (B. Ingle, personal communication, April 8, 1996), during 1995 there were 3,549 official summit attempts via the Disappointment Cleaver route (excluding professionally guided parties); 1,776 climbers (50.0%) reached the top. By comparison, on all routes in 1995, 45.4% (n = 3,259) summited.
Group I contained 35 men. Group II included the three women who had not used any form of hormonal replacement or supplementation for the three months prior to the study. Group III consisted of the six women who had been using hormonal contraception for a minimum of three months prior to the study.

Analyzed by gender, 80% of the men summited successfully, compared with 66% of the women. Overall, AMS occurred in 19 of 44 climbers (43%). Women were afflicted 5/9 (55%); men were afflicted 14/35 (40%). Of those summitting (both genders), 13/34 (38%) developed AMS. AMS afflicted 55% (5/9) of those not summitting. Skewing of any incidence rates that include women are possible due to the sample size.

An attempt was made to control the confounding factor of pre-menarcheal and menopausal states by restricting the age range of participants. Men's ages ranged from 18 to 52, while the age range for women was 19 to 41. Eight of the nine women reported having regular menstrual periods. The exception was the one who scribbled on her questionnaire, "8 months nonstop menses due to Norplant®." While the women were not specifically questioned regarding peri-menopausal signs and symptoms, this investigator concluded that none were approaching menopause, based the regularity of their menses and their age range of well below 51 years.

This study did not support any difference between genders and the incidence of AMS, given the limited sample size of nine women. Neither was the use of hormonal contraception associated with increased nor decreased AMS rates, given the sample size. Five women used oral contraceptives; one used Norplant®, none used Depo-Provera®, and three used no form of hormonal contraception. Interestingly, three of the five women using oral contraceptives reported they were taking Ortho-Cept® and one other was taking Desogen®. These brands are
identical: they are both monophasic, contain 0.03 mg ethinyl estradiol, and have identical forms of progestin (gonane-containing desogestrel; 0.15 mg). One woman utilized Demulen 1/50®, a monophasic containing 0.5 mg of ethinyl estradiol and 1.0 mg of the progesterone, ethynodiol diacetate. The woman taking Ortho-Novum® did not specify the type. During the study, one woman who was taking Demulen® was on Day 3 of her cycle, thus on a placebo.

An attempt was made to extrapolate the menstrual cycle phase by participants recalling the average number of days between menses and the date of the last menstrual period (LMP). The investigator then calculated the probable phases the women not using hormonal contraception were in during their sojourn on Rainier (Figure 2). Menstrual cycle distribution of the women not using hormonal contraception fell within the follicular phase (Days 5 through 14) for two of the three women. (Figure 2). The third woman's cycle phase was deduced to be early luteal. No women fell within the mid-luteal phase (Days 19 through 23). The sample size of this category (three women) prevented any insight into the incidence of AMS during these times, and particularly during the mid-luteal phase when progesterone levels are highest.
Figure 2. Extrapolated distribution of day of menstrual cycle and AMS occurrence in women not using hormonal contraceptives.
Discussion

As this is a study of incidence, the data were carefully examined for bias. While current symptoms or previous affliction with AMS would probably make susceptible individuals more likely to participate in the study compared with those who felt well, no one who was approached declined to participate. Therefore, self-selection must be eliminated as a source of bias. While the two investigators attempted to contact every potential participant returning to Muir, convenience sampling may still have led to error. The possibility of between-observer bias exists to some degree, as the second investigator (a neurosurgeon) surveyed climbers on one weekend. However, as the LLCQ depends mostly on self-report for the diagnosis of AMS, this source of error is proposed to be minimal.

The route taken by study participants starts from the Paradise ranger station (1,647 m/5,400 ft). The vast majority of climbers then rest for 6 - 30 hours at Camp Muir (3,072 m; 10,080 ft) before continuing up Disappointment Cleaver to the summit, then retracing the route back to Muir. While the route is strenuous, it is not complex. Disappointment Cleaver is considered a long plod, without technical rock or ice climbing. There is little seasonal variation in the trail worn into the glaciers by several thousand aspirants. The variables of alternative routes, with significantly different terrain, ascent times and concurrent exposure to altitude, were thus eliminated.

It has been suggested that seasonal variations of temperature and barometric pressure may affect AMS incidence (Reeves, Wagner, Zafren, Honigman, & Schoene, 1993). Due to inclement weather, data had to be collected over four separate weekends, possibly influencing the results: some climbers ascended in very cold and windy conditions; others sweltered under a
hot sun. Another role weather may have played was in the availability of study participants: women may have been more reluctant than men to attempt the summit when poor conditions prevailed. No data was collected on the numbers of aspirants who abandoned any summit attempt at Muir.

While limited demographic data was collected on previous exposure to altitude, no attempt was made to analyze it or incorporate it into study findings. It was not possible in this investigation to identify individuals who may thus have already been acclimated to at least some degree, thereby decreasing AMS rates. Another factor that may have affected AMS incidence is that the Disappointment Cleaver route is notorious in the climbing community for the numbers of inexperienced and ill-prepared aspirants it attracts. Although this route provided a broader cross-section of participants compared with other routes, the typical climber ascending the Disappointment Cleaver is probably less attuned to preventing or recognizing AMS.

Larson, Roach, and Schoene's 1982 study (as cited in Hackett & Roach, 1987) noted an approximate incidence of AMS on Mt. Rainier of 67%, with a mean ascent time to the summit of 33 ±1 hours. Houston (as cited in Hackett et al., 1976) noted on Mt. Rainier, "50% with severe headache in 1972 and, in 1973, 60% with some symptom of AMS" (p. 1153). Participants in this study had an overall incidence of 43%. However, as the LLCQ was not developed until 1991, different tools to quantify AMS were used by Larson and Houston. This may be a factor in the different rates of incidence. This study did not attempt to calculate ascent time. It is already well documented that rapidity of ascent is linked to increased AMS incidence (Ward et al., 1994). Confounding factors that may mimic AMS, such as dehydration, fatigue, hangovers, and
common illnesses unrelated to altitude exposure, cannot easily be controlled for in this or any other study, due to the nature of the AMS symptom complex.

Although this study attempted to investigate if hormonal contraceptive use or the menstrual cycle stage is correlated with AMS incidence, the results do not further elucidate the actions of either endogenous or exogenous progesterone. As no research is retrievable about the effects of hormonal contraceptives and AMS incidence, there is no data to compare these results with directly. Only one other study was available which examined the role of exogenous progesterone and its effect on AMS incidence (Bradwell et al., 1995). Limiting factors in that study included sample size and gender mix. Bradwell's study also used large doses of progesterone: 60 mg administered daily, commencing seven days before an ascent to 5,200 m (17,060 ft). Only one of the two women in his study ingested this amount. In comparison, women using oral contraceptives in this study ingested 0.15 - 1.0 mg of progesterone, 21 of every 28 days, and had done so for a minimum of three months prior to the investigation. While Bradwell concluded that progesterone was as efficacious as acetazolamide (Diamox®), other results in his study were mixed and need additional examination.

Dexamethasone, furosemide, acetazolamide, spironolactone, antacids, and nifedipine have been studied to varying degrees (Grissom et al., 1992; Bezruchka, 1992; Bradwell et al., 1992; Coote, 1991; Ellsworth et al., 1991; Beeckman & Buskirk, 1988; Hackett & Roach, 1987). These investigations, too, have been limited by sample size, gender mix, or the inclusion of males-only in the studies. This is a significant and ongoing problem with research of this type done at altitude.
Although there is inherent error when menstrual phases are deduced, as compared to precise determination of hormonal levels through blood samples, extrapolation was deemed the only suitable method given the scope and logistics of this study. Difficulty recalling LMP or cycle length with precision by women who suffered from the mental clouding of AMS threatens the external validity of this method.

Conclusions

Due to the importance of identifying factors that may reduce the incidence of AMS, this subject merits further study. A more adequate sample size of women is required to determine accurately whether hormonal contraception affects AMS rates. Despite progesterone's recognized effects as a ventilatory stimulant, its influence upon AMS has undergone only extremely limited investigation. Further research is needed to determine the accuracy of extrapolating menstrual cycle phases by the method used. Additional studies controlling for menstrual cycle phase and type of hormonal contraception are also suggested. Sub-grouping age, evaluation of the possibility of preexisting acclimatization, and screening for peri-menopausal symptomatology, might also clarify findings.
References


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Appendix A

Consent Form
The Incidence of Acute Mountain Sickness as Affected by Hormonal Contraceptives

CONSENT FORM

Introduction
You are being asked to participate in a study which examines how frequently acute mountain sickness occurs. It is being conducted by SHARON REYNOLDS R.N.-Certified, a graduate student at the Intercollegiate Center for Nursing Education, located in Spokane, Washington; telephone (509) 324-7360.

Purpose
Acute mountain sickness is a common illness suffered by many people who ascend above 8,500 feet. The purpose of this study is to determine if the incidence of acute mountain sickness is different between men and women. This study will also investigate whether the use of hormonal contraceptives ("the Pill", Depo-Provera, and Norplant) affects how frequently acute mountain sickness occurs. Lastly, it will examine whether the stage of a woman's menstrual cycle affects the incidence.

Procedures
A questionnaire, given at Camp Muir after a summit attempt, will be answered by those who agree to participate in this study. The questionnaire, which asks about symptoms such as headache and appetite, takes approximately 5-8 minutes to complete. The investigator will ask you to perform a heel-to-toe walking test. In addition to completing the questionnaire, women will be asked several additional questions about the use of hormonal contraceptives and menstrual cycle timing.

Risks
I understand that the only potential risk is that of embarrassment: Women will be asked several questions about the use of hormonal contraceptives, and menstrual cycle timing.

Benefits
I understand that the only benefit to participants in the study will be the satisfaction of contributing to the knowledge about acute mountain sickness.

Exclusions
I understand that reasons for non-participation in this study include: Age under 18 years or over 51 years, cigarette or pipe smoker, pregnancy, or current use of any medications other than hormonal contraceptives (including acetazolamide [Diamox®], prednisone or other steroids, and medicated inhalers).
Participant costs and payment
I understand I will not be compensated or offered payment for participation in the study, and that no charges will occur related to my participation.

Reimbursement or compensation for medical treatment for related illness or injury
I understand that participating in this study involves no risk of related illness or injury. Therefore, I will not be given reimbursement or compensation for related illness or injury.

Confidentiality
I understand that any individual data related to this study will be kept confidential. Any publication of the study results will include group data only. To assure anonymity, my name is not being requested. My responses may be reviewed by medical personnel associated with this study.

Participant Rights
I understand that if I have questions regarding my participant rights I may contact Margaret Bruya PhD, project chair, at the Intercollegiate Center for Nursing Education, Spokane, Washington (509) 324-7360. Should I have further questions regarding my rights I may contact the Institutional Review Board-Washington State University, which has reviewed and approved this study, at (509) 335-9661.

Voluntary Participation and Withdrawal
I understand that participation in this study is voluntary and refusal to participate will not affect me in any way. Furthermore, I may withdraw from this study at any time without prejudice or loss of benefits to which I am entitled.

Legal Rights and Participant Consent
I have read, or have had read to me, the preceding information describing the study. All of my questions have been answered to my satisfaction, and I am volunteering to participate in this study. I am not waiving any of my legal rights by participating in this study. I understand that I will receive a copy of this consent form. By completing the study questionnaire, I am giving my consent to participate in this study and agree to accept the conditions discussed previously. If desired, I may request a summary of the results of this study after June 1, 1996 by contacting:

Sharon Reynolds R.N.-Certified
15208 N. Ferrall
Mead, WA 99021
(509) 466-3004
Appendix B

Data Collection Form
Gender: 1___ Male
    2___ Female

Age: ______

Did you summit? 1___ Yes
    2___ No

If you did NOT summit, estimate highest point or altitude reached: _______________________

Highest point or altitude previously obtained (excluding today): _______________________

On the average, for the previous two (2) months I have aerobically exercised for a minimum of 40 minutes during each workout:

1___ 0 to 1 times a week
2___ 2 to 3 times a week
3___ 3 to 4 times a week
4___ 5 to 6 times a week
5___ 7 times a week or more (doing more than 1 workout/day)

Please mark the number in each category that best describes how you feel today:

HEADACHE
0___ no headache
1___ mild headache
2___ moderate headache
3___ severe headache

GASTROINTESTINAL SYMPTOMS
0___ normal appetite
1___ loss of appetite
2___ nausea
3___ severe nausea and/or vomiting

FATIGUE AND/OR WEAKNESS
0___ no lassitude
1___ mild lassitude
2___ moderate lassitude
3___ severe lassitude, incapacitating

DIZZINESS/LIGHTHEADEDNESS
0___ no incoordination
1___ mild incoordination
2___ moderate incoordination
3___ severe incoordination
DIFFICULTY SLEEPING
0____ slept as well as usual
1____ did not sleep as well as usual
2____ wake many times, poor night’s sleep
3____ could not sleep at all

OVERALL, IF YOU HAD ANY SYMPTOMS, HOW DID THEY AFFECT YOUR ACTIVITY?
0____ no reduction in activity
1____ mild reduction in activity
2____ moderate reduction in activity
3____ severe reduction in activity (eg. bed rest)

WOMEN ONLY
I am using a hormonal form of contraception (the "Pill", Norplant, or Depo-Provera):
1____ Yes
2____ No

If YES, have you been using it for the previous three (3) months (or longer)?
1____ Yes
2____ No

Check which type of hormonal contraception currently using:
1____ Depo-Provera (injection every 3 months)
2____ Norplant (tiny rods placed in skin of arm)
3____ Oral contraceptives (the "Pill")

brand name: __________________________

Do you have menstrual periods?
1____ Yes
2____ No

If YES, circle the FIRST day that your LAST menstrual period started:

<table>
<thead>
<tr>
<th>April</th>
<th>May</th>
<th>June</th>
</tr>
</thead>
<tbody>
<tr>
<td>S M T W T F S</td>
<td>S M T W T F S</td>
<td>S M T W T F S</td>
</tr>
<tr>
<td>1 2 3 4 5 6 7 8</td>
<td>1 2 3 4 5 6</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>9 10 11 12 13 14 15</td>
<td>7 8 9 10 11 12 13 14</td>
<td>11 12 13 14 15 16 17 18</td>
</tr>
<tr>
<td>16 17 18 19 20 21 22</td>
<td>14 15 16 17 18 19 20</td>
<td>18 19 20 21 22 23 24 25</td>
</tr>
<tr>
<td>30</td>
<td>29</td>
<td>31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>July</th>
<th>August</th>
<th>September</th>
</tr>
</thead>
<tbody>
<tr>
<td>S M T W T F S</td>
<td>S M T W T F S</td>
<td>S M T W T F S</td>
</tr>
<tr>
<td>1 2 3 4 5 6 7 8</td>
<td>1 2 3 4 5 6</td>
<td>1 2</td>
</tr>
<tr>
<td>9 10 11 12 13 14 15</td>
<td>6 7 8 9 10 11 12 13</td>
<td>3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>16 17 18 19 20 21 22</td>
<td>14 15 16 17 18 19 20 21</td>
<td>10 11 12 13 14 15 16 17</td>
</tr>
<tr>
<td>22 24 25 26 27 28 29 30</td>
<td>20 21 22 23 24 25 26 27 28 29 30</td>
<td>17 18 19 20 21 22 23</td>
</tr>
</tbody>
</table>
How many days apart are your menstrual periods?
1____ My periods are usually fairly regular & occur about every _______ (fill in number) days or so.
2____ I do not have menstrual periods.
3____ My periods are very irregular & have no pattern.

Thank you for your assistance with this research project!

RESEARCHER ONLY

CHANGE IN MENTAL STATUS
0 no change in mental status
1 lethargy/lassitude
2 disoriented/confused
3 stupor/semiconsciousness
4 coma

ATAXIA (HEEL TOE WALKING)
0 no ataxia
1 maneuvers to maintain balance
2 steps off line
3 falls down
4 can't stand

PERIPHERAL EDEMA
0 no peripheral edema
1 peripheral edema at one location
2 peripheral edema at one or two locations
Appendix C

Permission to use the Lake Louise Consensus Questionnaire
Dear Sharon,

There's no reason to ask Dr. Wright for permission; he had nothing to do with the Lake Louise Questionnaire - he only used it. The questionnaire belongs to no one, but if you need a permission, you have mine! As one of the organizers of the Committee I'm as qualified as anyone to give you permission. Good luck!

charlie

On Fri, 14 Apr 1995, Sharon Reynolds wrote:

> Dear Charlie,
> 
> It was great seeing you again at Hypoxia. I had an incredible time & am still talking about it. The research presented there was very helpful in getting my thesis on AMS off to a roaring start. I made a presentation to my research class about the conference; everyone was duly impressed! I'm looking forward to Hypoxia 1997.
> 
> Although I understand that written permission is not necessary to utilize the Lake Louise questionnaire, my graduate program requires it. I do not have a complete address for Dr. A.D. Wright; do you happen to have it? Also, do you know his full name? I have only his initials.
> 
> Thanks for your assistance!
Appendix D

Washington State University Human Subjects Summary Form

and Institutional Review Board Approval
Washington State University Human Subject Review Summary Form

University procedures require Institutional Review Board (IRB) review and approval of research involving human subjects. If a project is exempt, a completed copy of the first two pages of the Human Subject Review Summary Form must be submitted to the OORP. Any research can be initiated until approval has been obtained from the IRB. If the project is not exempt, 18 copies of this entire form must be filed with the OORP (Phone 335-9681; Zip 31401). The IRB approval must be kept with research data for three years after completion of the research.

Principal Investigator: Sharon Reynolds
Academic Title: graduate student
Department/Division: Nursing
Zip Code: 99204
Telephone: (509) 324-7273

Project Title: The incidence of acute mountain sickness as affected by the use of hormonal contraceptives

Research Qualifying for Exemption from Federal Regulations for the Protection of Human Subjects
(Quoted from the Code of Federal Regulations, Title 45, Part 46.101)

I. Circle the type of exemption applicable to the project:

0. No exemption.
1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or on the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (i) information obtained is recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior that is not exempt under paragraph (2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) without exception that the confidentiality of the personally identifiable information will be maintained through the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of the department or agency heads, and which are designed to study, evaluate or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level of and for a use found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

II. Abstract:

A. Briefly describe the purpose, procedures and research design (be sure to include what the subjects will do) (Use the back side if necessary).

Purpose: To describe the incidence of acute mountain sickness (AMS) as affected by the use of hormonal contraceptives.

Design: Descriptive.

Setting: Camp Muir, elevation 3,072 meters (10,080 feet), on Mt. Rainier, Washington. Data collection will be done during the summer climbing season, May through September 1995.

Subjects: Approximately 120 participants (60 male; 60 female) who are recreational climbers between the ages of 18 and 65, and are attempting the summit of Mt. Rainier will be studied, using convenience sampling.

Procedures: Data collection will be performed by the principal investigator. As climbers return to Camp Muir from a summit bid on Mt.
Rainier, those who are willing to participate and who also meet the study criteria will be identified. Informed consent will be obtained. Completion of the study questionnaire will imply consent; names of participants will not be asked to preserve anonymity. Participants will then complete the Lake Louise Consensus Questionnaire and a demographic questionnaire, as well as perform a simple heel-to-toe walking test, to quantify the occurrence of AMS. In addition, women will be asked several questions regarding the use of hormonal contraceptives, and the timing of menstrual cycles. Completion of the questionnaire and walking test takes approximately 5–8 minutes.

A. Check the method to be used:

1. Survey (submit a copy) _X_ Check how administered: Self _X_ Telephone _X_ Personal interview _X_ Other _
2. Observational _X_ Public Record _X_ Task Evaluation _X_ Pathological or Diagnostic Specimens _
3. Experimental _
4. Other _Describe ________

C. Is data anonymous _X_ or confidential _X_? (See page 4) Describe how anonymity or confidentiality will be maintained (e.g., coded to a master list and separated from data, locked cabinet, office, restricted computer, etc)? Who will have access to the data?

Anonymity will be maintained by not requesting subject names or identities. My clinical project chair and I will be the only ones to have access to the original questionnaires, which will be kept in a locked file. Any publication of the study results will present group data only.

D. Nature of data collected:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects under 18 years of age?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Subjects confined in a correctional or detention facility?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Is pregnancy a prerequisite for serving as a subject?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Are refusals in utero subjects in this research?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Subjects are presumed to be not legally competent?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Are personal records (medical, academic, etc.) used without written consent?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Are data from subjects (responses, information, specimens) directly or indirectly identifiable and place subject at risk (criminal or civil liability) or damaging to subjects' financial standing, employability or reputation?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Will specimens obtained from an autopsy be used in the research?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Will subjects be asked sensitive questions about sexual experiences?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Will questions be asked about alcohol or drug use?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Will alcohol or drugs be administered?</td>
<td><em>X</em></td>
</tr>
<tr>
<td>Will blood/body fluids be drawn?</td>
<td><em>X</em></td>
</tr>
</tbody>
</table>

If yes to any of the above, please explain rationale: _n/a_

E. Will any ethnic group or gender be excluded from the study pool? Yes _X_ No _X_

If yes, please explain: ____________________________

Principal Investigator: The information provided above is accurate and the project will be conducted in accordance with applicable Federal, State, and University regulations.

Signature: _______ Date: _____

Sharon Elizabeth Reynolds

25 April 1995
Faculty Sponsor: (If the principal investigator is a student) The information provided above is accurate and the project will be conducted in accordance with applicable Federal State, and University regulations.

Signature: ________________________________ Date: 4-25-95

Chair, Director or Dean: The information provided above is accurate and the project will be conducted in accordance with applicable Federal State, and University regulations.

Signature: ________________________________ Date: 4-25-95

Institutional Review Board: The information provided above is accurate and the project will be conducted in accordance with applicable Federal State, and University regulations.

Signature: ________________________________ Date: 4/27/95
Appendix E

Letter to Mt. Rainier National Park requesting Research Permit
5 June 1995

Superintendent William J. Briggle
Mt. Rainier National Park
Tahoma Woods, Star Route
Ashford, WA 98304

Dear Superintendent Briggle:

I am a graduate student at the Intercollegiate Center for Nursing Education through Whitworth College in Spokane. This summer I plan to do a research project at Camp Muir, "The Incidence of Acute Mountain Sickness as Affected by Hormonal Contraceptives". The study has been reviewed and approved by the Institutional Research Board of Washington State University.

Climbers will be surveyed about the development of symptoms indicating acute mountain sickness. In addition, women will answer questions about the use of hormonal contraceptives and the timing of menstrual cycles. Of course, participation is completely voluntary and individuals may withdraw from the study at any time simply by not completing the questionnaire. I am hoping to obtain responses from at least 120 climbers (60 male and 60 female). The time spent at Camp Muir will depend on how quickly I can recruit willing participants. At this point, I anticipate being there June 16-19.

Although I understand from other researchers that formal permission to conduct a study on Mt. Rainier is not required, I wanted to notify you and your staff, and to answer any questions or concerns that you may have.

Additionally, thank you again for permitting Roger Drake to attend the Waste Management Workshop in Calgary last November. The abbreviated proceedings were recently published; Roger's contributions are prominent. (He should have received a copy.) The Alpine Club of Canada is hard at
work planning this year's conference on environmental ethics and practices in alpine recreation. It is slated for November 12-14, 1995. *Summit* magazine has joined the sponsors and will be providing publicity as well as publishing an article post-symposium. Conference organizers are hoping Roger can be spared to come to Calgary again.

If you have any questions or concerns about my plans for this summer, please do not hesitate to contact me.

Sincerely,

Sharon Reynolds

Sharon Reynolds R.N.-Certified
(and member of the American Alpine Club's Conservation Committee for International Issues)

Enclosures:
Study questionnaire
Informed consent
Appendix F

Research Permit from Mt. Rainier National Park
United States Department of the Interior
National Park Service

RESEARCH PERMIT

In Accordance with the Conditions and Restrictions Appearing on the Back Permission is Granted

Name of Researcher: Ms. Sharon Elizabeth Reynolds
Area: MOUNT RAINIER NATIONAL PARK
Date Issued: June 12, 1995

To Conduct the Following Research
To determine "The incidence of acute mountain sickness as affected by hormonal contraceptives" at Camp Muir in Mount Rainier National Park.

Locality of Research Limited to:
Camp Muir and Camp Schurman

Expiration Date: December 31, 1995

Class of Collecting:
A

Special Conditions or Restrictions

Appraiser:

Dr. Richard Lockwood
Title: Ecologist, Mount Rainier National Park

*Two classes of collecting may be done under this permit.

Class A - That required for public exhibits and for research undertaken by persons who can establish their connections with public resources or other scientific or educational institutions. Specimens collected may be insects (Hexapoda), spiders (Araneida), plants, rocks, or minerals as designated in the permit.

Class B - That undertaken by federal employees or those working under cooperative agreements or contracts with NPS, only for scientific or educational purposes. Specimens collected may be plants, rocks, minerals, or animal life as designated in the permit.

THIS PERMIT MUST BE CARRIED AT ALL TIMES WHILE CONDUCTING RESEARCH IN THE PARK. SEE REVERSE FOR CONDITIONS AND RESTRICTIONS.