Theoretical Review

HIGH ALTITUDES, ANXIETY, AND PANIC ATTACKS: IS THERE A RELATIONSHIP?

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People exposed to high altitudes often experience somatic symptoms triggered by hypoxia, such as breathlessness, palpitations, dizziness, headache, and insomnia. Most of the symptoms are identical to those reported in panic attacks or severe anxiety. Potential causal links between adaptation to altitude and anxiety are apparent in all three leading models of panic, namely, hyperventilation (hypoxia leads to hypocapnia), suffocation false alarms (hypoxia counteracted to some extent by hypocapnia), and cognitive misinterpretations (symptoms from hypoxia and hypocapnia interpreted as dangerous). Furthermore, exposure to high altitudes produces respiratory disturbances during sleep in normals similar to those in panic disorder at low altitudes. In spite of these connections and their clinical importance, evidence for precipitation of panic attacks or more gradual increases in anxiety during altitude exposure is meager. We suggest some improvements that could be made in the design of future studies, possible tests of some of the theoretical causal links, and possible treatment applications, such as systematic exposure of panic patients to high altitude. Depression and Anxiety 16:51–58, 2002. © 2002 Wiley-Liss, Inc.

INTRODUCTION

Business travel, mountain tourism, and the popularity of snow sports bring an increasing number of people to high altitudes. Although high places like the Rocky Mountains, Alps, or Andes are visited for pleasure, a significant number of these travelers can expect to experience symptomatic distress related to adaptation to lowered air pressure with its reduced O_2 content. For a number of reasons discussed in this review, we suspect that the initial phases of this adaptation are accompanied by an increase in anxiety, particularly in those who suffer from certain anxiety disorders or are prone to them. There are several theoretical links between the physiology and psychology of altitude adjustment and panic disorder, as well as a small amount of empirical evidence for reduced atmospheric pressure producing anxiety in fit young people, either as a part of the syndrome of acute mountain sickness or separate from it. Recent studies have documented that, even at low altitudes, certain kinds of anxiety patients show signs of respiratory dysregulation [e.g., Papp et al., 1997; Wilhelm et al., 2001b,d; reviewed in Wilhelm et al., 2001c].

PHYSIOLOGICAL ADJUSTMENTS TO HIGH ALTITUDE

Rapid ascent to altitudes above 3,000 m leads to a series of respiratory adjustments that are often accompanied by subjective symptoms and objective signs. Rise in altitude causes a logarithmic fall in atmospheric pressure and a corresponding decrease in the partial pressure of O_2. At 3,000 m (approximately 10,000 ft) above sea level, the alveolar PO_2 (partial pressure

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of O_2) is about 60 mm Hg, reducing arterial O_2 saturation to 90% from the 97% saturation at sea level. This activates chemoreceptors that increase ventilation, ultimately via medullary brain circuits. Minute volume increases, at first predominantly due to an increase in tidal volume and after several days, supported by an increase in respiratory rate [Bender et al., 1987]. Since this increased ventilation is not accompanied by an increase in the body's aerobic metabolism, alveolar pCO_2 declines, resulting in respiratory alkalosis, an acute challenge to acid-base balance (pH) of the blood. The hypocapnia and alkalosis limits the extent of hypoxic chemoreceptor stimulation and this prevents ventilation from rising further. Hypoxia enhances this braking effect by making chemoreceptors more sensitive to pCO_2 [Fitzgerald and Lahiri, 1986]. Cardiac output, the product of heart rate and stroke volume, increases to compensate for the decreased O_2 saturation [Grover et al., 1986].

Over a period of days at high altitude, hypocapnia increases, but renal compensation reduces the alkalosis. Over weeks and months, longer-term adaptations ensue, for example, increase in red blood cell production, elevated buffering capacity of the blood, increase in the diffusion capacity of the lungs, and increase in tissue capillarity [Guyton and Hall, 1996]. These changes assure sufficient transport of O_2 to tissues while at the same time limiting the amount of hypocapnia and the respiratory and cardiac workload.

The most common subjective symptoms that accompany ascent to a higher altitude are dyspnea (shortness of breath), easy fatigability, headaches, dizziness, reduced appetite, heart racing, and insomnia [Honigman et al., 1995; Missoum et al., 1992]. The dyspnea and easy fatigability are most noticeable during physical effort. In some people symptoms of high altitude are severe enough to be called "acute mountain sickness" (AMS). Headaches may be accompanied with nausea and vomiting. After 2 or 3 days, even if the sufferer remains at the altitude where symptoms began, AMS usually eases as physiological adaptation occurs [Missoum et al., 1992]. On the other hand, if pulmonary or, less commonly, cerebral edema develops, symptoms can worsen, requiring emergency on-site pressurization or evacuation to a lower altitude [Porcelli and Gugelchuk, 1995]. Acute cognitive deficits are present in these more severe forms of mountain sickness.

Susceptibility to AMS apparently is a relatively stable individual trait, but its physiological basis is uncertain. It cannot be predicted from reactions to acute hypoxic challenges in the laboratory, but it is related to adaptation to longer lasting exposure to moderate altitudes. For example, resting arterial hypoxemia during an ascent was correlated (r=.48) with later development of AMS at higher altitudes, implicating a decreased ventilatory response to hypoxia or abnormalities of gas exchange [Roach et al., 1998].

THEORETICAL LINKS BETWEEN ALTITUDE AND ANXIETY OR PANIC

The three leading explanatory models of panic attacks provide strong links between adjustment to high altitude and panic anxiety, although for all of these theories, high altitude is only one of a set of stimuli capable of provoking panic attacks. These links are so compelling that evidence for an absence of panic in acute high altitude adjustment among panic patients could be used as arguments against their validity. These models make specific predictions about the relationship between respiration and anxiety, each emphasizing different aspects [Smoller et al., 1996].

The hyperventilation model was stimulated by the observation that hyperventilation (excessive ventilation from a combination of increase in respiratory rate and depth, resulting in hypocapnia) was sometimes observed in acutely anxious patients that appeared in the emergency room. If hyperventilation is intense and sustained enough, symptoms such as dizziness, blurred vision, tingling, muscle cramps, trembling, cold hands or feet, shivering, derealization, palpitations, chest pain, and a warm feeling in the head may develop. Paradoxically, considering the absence of hypoxia or hypercapnia, a sensation of dyspnea usually accompanies this condition, most likely because of feedback from lung stretch receptors and respiratory muscle effort.

Kerr et al. [1937] introduced the term "hyperventilation syndrome" (HVS) for anxiety-related prolonged overbreathing without a distinct organic etiology. When panic disorder (PD) was defined, the similarity between symptoms attributed to acute HVS and PD was immediately apparent [e.g., Clark et al., 1985]. Ley, in a series of perceptive papers, has discussed the implications of this similarity [e.g., Ley, 1985]. Critical questions that remain are whether hyperventilation is the cause or effect of anxiety attacks and how often spontaneous attacks are actually accompanied by hyperventilation [Garssen et al., 1996; Hibbert and Pilsbury, 1988, 1989]. In spite of these questions, the causal relevance of hyperventilation to PD is widely accepted by therapists, who use voluntary hyperventilation as a modality of intereoceptive exposure [Barlow et al., 1989] and promote paper bag rebreathing as an emergency antidote to panic and breathing training techniques as a longer-term solution [Smoller et al., 1996].

The link between high altitude adjustment and hyperventilation is that increased ventilation and hypocapnia are prominent in the first few days of altitude exposure. Hypocapnia itself may produce anxiety as is implied by most proponents of the hyperventilation syndrome, although as pH normalizes over the first days the experiential and physiological effects of hypocapnia may diminish. To some, the

sensations of hypocapnia may be alarming and produce anxiety secondarily (see the cognitive-behavioral model below). In addition, emotional learning, whereby episodes of intense anxiety and hyperventilation were associated at lower elevations, could result in a conditioned anxiety at higher elevations [Bouton et al., 2001].

The basic premise of hyperventilation theories is that anyone who hyperventilates is likely to become anxious, and that a propensity to anxiety is a propensity to hyperventilation. People with hyperventilation syndrome or PD would be more susceptible to anxiety at a high altitude, only if it causes them to hyperventilate more than comparison groups.

The suffocation false alarm model was originated by Klein [1993], who proposed that panic attacks could be triggered by a hypersensitive brainstem autonomic control mechanism that may fire spontaneously or after minor suffocation related stimulation, thereby initiating both panic and a sensation of dyspnea. Either rises in CO_2 or proportionately greater falls in O_2 can result in feeling of suffocation, and increased ventilation. Empirically, PD patients have shown a greater subjective anxiety response to CO_2 increases than comparison groups in a number of studies. However, not all found increased ventilatory responses [discussed in Papp, 1995]. The one study that tested PD patients' sensitivity to hypoxia demonstrated that they reacted to a 12% O_2 challenge (air normally contains 20%) with more anxiety and ventilatory responses than controls [Beck et al., 1999]. In the suffocation false alarm model, hyperventilation has a secondary role of reducing anxiety: panic patients prophylactically hyperventilate to lower their CO_2 levels, which reduces the likelihood of their hypersensitive suffocation alarm being triggered.

The link between high altitude adjustment and the suffocation alarm is that the hypoxia that results from the lower O_2 levels encountered at higher altitudes should trigger such an alarm, the intensity of which should depend on the altitude. In this case, the feeling of suffocation is not a false alarm since the subject's O_2 supply really is insufficient. On the other hand, the hyperventilation of acute altitude exposure will tend to counteract respiratory drive and dyspnea. Thus, the suffocation alarm will receive mixed signals from the combination of hypocapnia and hypoxia, the latter ordinarily being the weaker signal. Exactly how all of these effects balance out in provoking dyspnea and anxiety is not clear. As an added complication, hypoxia changes the sensitivity of the chemoreceptor mechanisms to CO_2.

In any case, Klein's theory would predict that people with PD or a diathesis for it will have an increased frequency of panic attacks at high altitudes if high altitude promotes a feeling of not getting enough air. In addition, people without any tendency to PD may also become more anxious at higher altitudes, since the suffocation alarm mechanism is present in every normal human. PD patients differ from normals only quantitatively, in that they have lower thresholds for the alarm being activated.

The cognitive misinterpretation model of Clark [1986] considers attitudes and thoughts about somatic and psychic manifestations of anxiety to have a primary role in the degree of anxiety such symptoms produce. Panic attacks occur when the sufferer believes that symptoms like dyspnea, a racing heart, or mounting anxiety itself are a forewarning that a somatic or psychic catastrophe is imminent. Thoughts of immediate disaster lead to new or more intense anxiety-induced bodily sensations, which feed the false interpretations, and so on around in a vicious circle culminating in a panic attack. This model is supported by the evident hypochondriacal preoccupations of many PD patients and their endorsement of fear of bodily sensations upon systematic questioning. Therapies that successfully effect "cognitive restructuring" abolish panic attacks [Clark et al., 1999].

Since arrival at a high altitude results in a number of symptoms, people with the beliefs that predispose them to misinterpret these symptoms as dangerous can be expected to become anxious. People who have experienced panic attacks are especially liable to do this because the symptoms of panic and high altitude are similar, and panickers are known to fear anxiety symptoms ["anxiety sensitivity," Reiss et al., 1986]. To some extent this may be the result of interoceptive conditioning to previous attacks [Bouton et al., 2001]. Insofar as altitude symptoms overlap with anxiety symptoms, fear of them may intensify them in a vicious circle: fear leading to more symptoms, and more symptoms leading to more fear. Some of those symptoms are easily perceptible, such as dyspnea, increased ventilation, and increased stroke volume of the heart, although whether conscious awareness is necessary for a vicious circle to operate is not clear. Whether hypoxia increases or decreases emotional reactivity is unknown. Not only anxiety symptoms, but symptoms of AMS not directly related to anxiety such as headaches and nausea might also give rise to hypochondriacal thoughts. A headache might be feared as a prodrome of a stroke or fatal brain swelling, and nausea and vomiting might evoke images of dehydration, debility, and death.

Opposing the misinterpretation of symptoms, however, would be the availability of a benign attribution for them, namely, the change in altitude. Experimental tests of the power of such attributions in PD have given mixed results. Rapee et al. [1986] found that people with panic attacks reacted with less anxiety to single inhalations of a 50% CO_2/50% O_2 mixture when, in advance, possible sensations were described attributed to the gas. Salkovskis and Clark [1990] provided nonclinical subjects with a negative or positive interpretation of the symptoms of voluntary hyperventilation, and these considerably influenced their affective ratings of the hyperventilation experience. On the

other hand, Papp et al. [1995] did not find that an instructional set could alter the anxiogenic effects of room air hyperventilation, or 5% or 7% CO_2 inhalation in PD patients. Of course, attributing threatening somatic sensations to altitude is not completely reassuring: the body can still be considered as being at risk when altitude causes symptoms associated with medical crises, particularly if the person has heard stories that altitude can have adverse health consequences.

The cognitive misinterpretation model would predict that panic attacks would also occur in other situations where unusual or unexpected bodily sensations might occur. For example, diving can produce unusual sensations, including feelings of suffocation, which could be particularly potent in precipitating panic according to Klein's theory. Indeed, panic attacks have been reported as a complication of diving [Morgan, 1995; Tochimoto et al., 1998]. Another example is the use of recreational drugs or drugs of abuse, which can provoke panic attacks, especially in inexperienced users [Moran, 1986; Roy-Byrne and Uhde, 1988].

EMPIRICAL LINKS BETWEEN ALTITUDE AND ANXIETY OR PANIC

Somatic symptoms of panic as defined in DSM-IV [American Psychiatric Association, 1994] overlap to a large extent with the symptoms of acute altitude exposure. Panic attacks are characterized by rapid pulse (tachycardia), shortness of breath (dyspnea), dizziness, chest pains, sweating, faintness, hot flashes, tremor, and nausea. On the other hand, the psychological symptoms of panic (increased anxiety, experiences of depersonalization or derealization, and fears of dying, going crazy, or losing control) are not usually mentioned in descriptions of AMS. Furthermore, panic attacks usually terminate in less than an hour, while the effects of high altitude may persist for days unless the person returns to a lower altitude. Thus, AMS is not identical with panic anxiety, but its similarities strengthen the possibility that it could act to elicit anxiety and panic as a conditioned stimulus is those who had experienced similar symptoms when anxious before, or through the mechanisms postulated by the theories outlined above.

A few studies have administered psychological questionnaires to young volunteers exposed to altitude under more or less controlled conditions and have found small but significant increases in psychopathology scores. For example, Nelson [1982] gave the Symptom Check List-90 [Derogatis, 1977] to 16 men and 4 women, ages 17–30 years, at sea level, 3,810 m, and 5,000 m during a 35-day climbing expedition. Subjects were tested a few hours after their arrival at the two higher altitudes. Scores for somatization,

paranoid ideation, obsessive-compulsiveness, depression, hostility, and anxiety increased. Bolmont et al. [2000] investigated mood and performance changes in eight physically fit male climbers, ages 24 to 37, during gradual decompression over 31 days in a hypobaric chamber from sea level to 8,848 m equivalent altitude (the height of Mount Everest). Anxiety as assessed by the state scores of the Spielberger State-Trait Anxiety Inventory [Spielberger et al., 1970] remained stable in these men until 5,500 m, but increased significantly at 6,500 m and above, following the course of development of AMS. Increases correlated significantly with added scores for headache, difficulty sleeping, and ataxia, but not with scores for dyspnea alone [Nicolas et al., 1999]. Shukitt-Hale et al. [1991] noted an increase in tension as assessed with the Profile of Mood Scale with a rise from 500 to 4,700 m simulated altitude in 20 soldiers. Tension scores were correlated with symptoms of AMS. In none of these studies were time effects controlled for, nor was it possible to distinguish whether an increase in anxiety was a reaction to AMS symptoms, an integral part of AMS, or an independent response to altitude. An additional possibly anxiogenic factor in the hypobaric chamber experiments was confinement for a month in the chamber.

Missoum et al. [1992] found that anxiety prior to ascent could predict AMS symptoms. They showed a relationship between higher trait anxiety, measured with the Spielberger State-Trait Anxiety Inventory 2 or 3 months before a Himalayan expedition, and reports that suggested AMS in diaries maintained during the subsequent climb. In addition, subjects' expectations before the expedition about the level of anxiety they would experience at high altitude predicted AMS on the actual climb. More anxious people may have been more apprehensive about the somatic symptoms of altitude and reported them more readily in their diaries, and they may have even exaggerated them.

The studies described above were limited in many ways. For example, their subjects were principally men, although anxiety disorders are usually more prevalent in women. Presumably these subjects liked being in the mountains at higher altitudes, having had pleasant experiences in such settings, or they are unlikely to have volunteered. Furthermore, the questionnaires and scales used for measuring anxiety were not designed to be sensitive to the symptoms of clinical anxiety and panic that theories of panic disorder try to explain.

Respiration during sleep at low altitudes in patients with PD is characterized by greater instability of tidal volumes and more frequent brief pauses (micro-apneas) than in comparison subjects, especially during REM sleep [Stein et al., 1995]. PD patients also have a propensity for being woken from sleep with panic attacks [Uhde, 2000]. Similar sleep disturbances occur in normal unacclimatized lowlanders sleeping at high altitudes, depending on their ventilatory sensitivity to hypoxia. Observations of sleep at 5,400 m demonstrated the following: 1) lowlanders, who generally had

high ventilatory sensitivity to hypoxia, showed periodic breathing with apneas, while 2) high altitude natives, who had attenuated ventilatory sensitivity to hypoxia, did not [Lahiri et al., 1983]. The low altitude inhabitants with the highest ventilatory sensitivity showed the highest frequency of apneas, and such apneas are associated with arousals and fragmented sleep [Masuyama et al., 1989]. Thus, since normals develop the respiratory patterns of PD patients at high altitudes, normals at high altitudes might be prone to the same kind of anxiety that PD patients have, assuming that the respiratory disturbances are related to similar causal mechanisms. By the same reasoning, the incidence of attacks in PD patients might rise. A candidate for a common causal mechanism is sensitivity to hypoxia, which may trigger suffocation feelings, leading among other things to increased arousal. However, a difference between the sleep of panickers and sleep at high altitudes is that people with panic disorder have a tendency to wake up in panic, while at least anecdotally, people waking from Cheyne-Stokes or other disturbed breathing at high altitudes feel a sense of relief.

Long-term respiratory adaptation to high altitudes was studied for example in permanent inhabitants working as miners in Chile at 5,950 m. Arterial pCO_2 values were lower than the standard sea level values, indicating a modest hypoxic hyperventilation. However, arterial pH levels were normal, so renal compensation of respiratory alkalosis was essentially complete [Santolaya et al., 1989]. Often studies of PD patients have found lower resting arterial or end-tidal pCO_2 levels in panic patients compared to control subjects [e.g., Papp et al., 1997; Wilhelm et al., 2001d], which was interpreted as a sign of chronic hyperventilation. PD patients supposedly show blood pH levels in a normal range [see Kenardy et al., 1990]. In that case, renal compensation restoring normal pH is a long-term adaptation aiming at elimination or reduction of symptoms attributable to hyperventilation in both high altitude inhabitants and PD patients.

Case histories of panic disorder patients enrolled in a breathing training treatment study in our laboratory [Meuret et al., 2001] lend credibility to the idea that acute exposure to high altitude can contribute to having panic attacks. Both of the patients below reported that their worst ever panic attack had taken place at higher than accustomed elevations.

Mr. A had a history of mild panic attacks beginning at age 35, which became more severe a few years later. At age 45, he and his family were planning to spend the weekend at a national park. They drove from their home near sea level for 5 hr to an altitude of 1,500 m where they rented a cabin. On the second day at this altitude, they decided to take a scenic hike. After driving up to 3,000 m, they hiked down a 3.5 km trail to its end at 1,900 m, where at an exposed viewpoint they could look down into the valley. Mr. A suddenly felt

quite nervous but had no physical symptoms. An hour later they headed back up the trail when Mr. A suddenly felt dizzy and short of breath, and felt his heart pounding hard. "It felt as if I was having adrenaline rushes going through my body and sending up my heart rate dramatically." He took his pulse and it was around 170 beats per min even though he had only walked for 5 min. He decided to sit down to catch his breath and wait for his heart rate to normalize, but when it remained high even after 15 min, a feeling of fear and despair overwhelmed him. Since there was no medical help in the vicinity, he began to think he might die of a heart attack. He managed to walk up the trail by taking breaks where he would lie down 15 to 30 min waiting for his pulse to drop below 120 beats per min. When he arrived back at the cabin he took a 0.5 mg tablet of his wife's prescription for lorazepam. Since his heart racing still did not improve, he went to a local medical clinic, where no medical basis for his complaints were found.

Previous to this incident, Mr. A had experienced such extreme heart racing only when he exercised. He had not developed anxiety or major symptoms at high altitudes before, but after this experience felt extremely reluctant to return to the mountains. Subsequently his panic attacks became worse, and he began to avoid any activity that would increase his heart rate, even at sea level.

Ms. B had been diagnosed as having panic disorder with agoraphobia at age 27, one year prior to her first severe panic attack at high altitude. She had planned to spend the weekend with friends in the mountains, and drove 5 hr from where she lived at an altitude near sea level to a cabin at approximately 2,000 m. After sleeping there the first night, Ms. B woke up feeling slightly anxious and decided to take it easy by reading a book for most of the day. That evening she felt extremely tired and went to bed early. The next morning she woke up feeling confused, detached from reality, light-headed, and anxious. She forced herself out of bed and ate breakfast. Afterwards, her feelings of unreality and disconnection worsened. She told us, "I noticed myself disengaging from the rest of the group. I felt dizzy, like I was in a different world from my friends." After lying down, she began to have chills, her body felt cold and clammy, and her heart was racing. Different from previous panic attacks, she noticed that her feet and legs had turned blue and felt numb. She tried to take deep breaths, but that worsened feelings of breathlessness, suffocation, and chest pressure and pain. At that point she decided to take 5 mg of clonazepam. This afforded little relief, so she decided to return home, fearing that she would "go insane" or have a heart attack. "I was very dizzy, disoriented, and had cold, blue feet until we were out of the mountains." By the time she arrived home, she felt better but exhausted and sleepy.

Ms. B reported that even before this mountain experience she had felt a little bit nervous, confused,

and dizzy in higher altitudes. For 6 months after this incident, she avoided high altitudes.

FUTURE DIRECTIONS

In spite of compelling theoretical connections between anxiety (at least of the panic type) and adaptation to altitude and the histories of some of our panic disorder patients, our search of the relevant literature found only a few studies where anxiety on ascent was actually reliably measured under more or less controlled conditions. The evidence from these studies suggests that at least in young volunteers, anxiety increases modestly with acute altitude exposure. In all likelihood the design of these studies minimized the size of the effect. The subjects were hardly a cross-section of the population, tending to be more physically fit than average, ready for physical and mental challenge, and with a history of successful adaptation to high altitudes. Since the ethos of adventure sports discourages admission of "weak" emotions such as anxiety or depression, subjects in many studies were probably reluctant to complain about psychological problems and more readily endorsed physical symptoms of AMS. Thus, generalization of results to the average person or to someone with an anxiety disorder is limited. In some studies the effects of altitude are confounded with the effects of severe physical exertion, dehydration, and temperature extremes. Mastering risky situations and breaking personal records are goals that increase effort beyond a comfortable level.

To investigate the anxiety-high altitude link further, several improvements should be made in the design of future studies. The sample of subjects tested should be broadened, symptoms of AMS and anxiety should be distinguished, and the specific mechanisms suggested by the three panic theories should be evaluated. To test if high altitude exposure raises anxiety in people in general, experimental subjects could be recruited from tourists traveling to high altitude resorts, taking trams to mountain peaks, or flying to high altitude cities. Participants in mountaineering expeditions are probably less suitable because of confounding effects of the physical effort and exposure to the environmental conditions that such expeditions entail, and a sampling bias towards those who have not reacted to altitude with anxiety in the past. Alternatively, laboratory experiments where high altitude conditions are simulated can provide a controlled and a time efficient test situation, though the hypobaric chambers in which these simulations occur might incite claustrophobic fears in patients with anxiety disorders. It is possible that severe anxiety reactions to high altitude occur only in those with PD or a diathesis to it. To test this, specific recruitment of that group would be necessary since the incidence of PD in unselected populations is low. People with a diagnosis of PD planning high altitude trips might be contacted through national organizations such as the Anxiety Disorders Association of America, whose members include both individuals with anxiety disorders and professionals.

The simplest assessment method is to administer questionnaires before, during, and after a controlled altitude exposure. Questionnaires could be those used to predict and assess anxiety reactions to CO_2 provocations in laboratory studies of panic. These should include a subjective units of distress scale of anxiety, Spielberger's State-Trait Anxiety Inventory (State), and questionnaires for establishing panic attacks like the Acute Panic Inventory [Dillon et al., 1987]. Questionnaires could have a structured diary format where mood and symptoms would be reported several times a day for a number of days before and during altitude exposure. Two questionnaires have been developed to assess the symptoms of AMS. The General High Altitude Questionnaire [Stamper et al., 1971] contains several empirical symptom clusters: Arousal Level (active, energetic, etc.), Somatic Discomfort (nausea, shortness of breath, dizziness, etc.), and Mood (happy, satisfied, etc.). Another is the Environmental Symptom Questionnaire with 55 items, including those about breathing, nausea, chest pain, and worry [Wright et al., 1985].

Finally, the theoretical links outlined in this paper should be examined empirically. The role of hyperventilation can be assessed by measuring end-tidal pCO_2 levels in the participant's exhaled air before, during, and after exposure to altitude. A hand-held device that measures and stores this variable is available [Capnocount™, Weinmann, Inc., Hamburg, Germany; see Wilhelm et al., 2001a]. Ventilation and ventilatory instability can be measured with the LifeShirt System [Wilhelm et al., 2002]. Urine electrolytes and pH and venous blood electrolytes would give additional information about how hypocapnia is being buffered. Hypotheses about reactions to altitude exposure derived from the suffocation false alarm theory's postulation of increased chemoreceptor sensitivity in the panic-prone should be tested in procedures in which pCO_2 in the inspired air is increased, and pO_2 decreased, in a controlled manner [see, for example, Papp, 1995]. Subjects should be tested before, during, and after altitude exposure of various lengths. The additive effects of exercise at high altitude might be studied separately. Ventilatory reactivity to exercise has been found to be normal in PD patients [Stein et al., 1992], but exercise at altitude, which decreases arterial blood O_2 saturation, may intensify the effects of altitude exposure selectively in this group.

The importance of catastrophic cognitions could be assessed to some degree with the Anxiety Sensitivity Index [Reiss et al., 1986]. Anxiety sensitivity is defined as fear of bodily symptoms of anxiety and expectations that these symptoms will result in aversive or possibly deleterious consequences. Elevated scores on the Anxiety Sensitivity Index are a likely cognitive risk factor for the development of anxiety upon altitude

exposure. A special version of this questionnaire should be developed that includes symptoms of AMS unusual in acute anxiety reactions, such as headache, lack of energy, and nausea. However, the essence of the catastrophic cognitions theory is that panic is associated with certain kinds of thoughts, which may be fleeting, difficult to articulate, and biased by the demands of how they are elicited. As a causal theory of panic, the catastrophic cognitions theory may not be falsifiable (Roth and Wilhelm, submitted), but that does not mean thoughts are totally beyond empirical examination. One approach would be to have subjects keep a diary of thoughts that relate to fear and sickness while on trips to high altitudes.

A crucial variable in any study of altitude effects is what altitude was attained. It is an open question how high the altitude must be to be relevant. Altitudes less than 3,000 m, although perhaps unable to produce the full syndrome of acute mountain sickness, may cause physiological and subjective changes that lead to anxiety reactions in susceptible people. Cabins of commercial aircraft flying at high altitudes are pressurized to about 2,000 m (up to 2,440 m is allowed by the US Federal Aviation Administration). Could exposure to the lower pO_2 at these altitudes contribute to anxiety attacks and the development of flight phobia [cf. Wilhelm and Roth, 1997]? In their review of medical events during commercial flights, Gendreau and DeJohn [2002] wrote that "Vasovagal episodes (fainting, near-fainting, dizziness, and hyperventilation) are the most common events." The more inclusive rubric "anxiety reactions" probably would have been more accurate.

In conclusion, we believe that the time is ripe for new research in the psychological effects of acute exposure to hypobaric environments. Theoretical links between at least one anxiety disorder, PD, and the symptoms and signs of acute exposure to high altitudes are strong, and a few empirical links between altitude and anxiety in general have been established. The study of how high altitudes affect anxiety will provide data not only of theoretical relevance but also of clinical importance. For example, currently clinicians are unable to make empirically supported recommendations to patients with anxiety disorders planning to travel to higher altitudes. Is prophylactic medication for AMS or anxiety indicated for such patients before and during the trip? Would exposure to altitude be of therapeutic value for PD patients by provoking the sensations that they fear? Interoceptive exposure is already an accepted component of cognitive-behavioral treatment packages for PD [Barlow et al., 1989], but the sensations produced by conventional techniques are fleeting compared to 2 or 3 days of acute altitude adjustment. Only new data from well designed studies can tell us what we need to know clinically and theoretically.

REFERENCES

American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders, 4th edition. Washington, DC: American Psychiatric Association.

Barlow DH, Craske MG, Cerny JA, Klosko JS. 1989. Behavioral treatment of panic disorder. Behavior Ther 20:261–282.

Beck JG, Ohtake PJ, Shipherd JC. 1999. Exaggerated anxiety is not unique to CO_2 in panic disorder: a comparison of hypercapnic and hypoxic challenges. J Abnorm Psychol 108:473–482.

Bender PR, Weil JV, Reeves JT, Moore LG. 1987. Breathing pattern in hypoxic exposures of varying duration. J Appl Physiol 62: 640–645.

Bolmont B, Thullier F, Abraini JH. 2000. Relationships between mood states and performances in reaction time, psychomotor ability, and mental efficiency during a 31-day gradual decompression in a hypobaric chamber from sea level to 8848 m equivalent altitude. Physiol Behav 71:469–476.

Bouton ME, Mineka S, Barlow DH. 2001. A modern learning theory perspective on the etiology of panic disorder. Psychol Rev 108:4–32.

Clark DM. 1986. A cognitive approach to panic. Behav Res Ther 24:461–470.

Clark DM, Salkovskis PM, Chalkley AJ. 1985. Respiratory control as a treatment for panic attacks. J Behav Ther Exp Psychiatry 16:23–30.

Clark DM, Salkovskis PM, Hackmann A, Wells A, Ludgate J, Gelder M. 1999. Brief cognitive therapy for panic disorder: a randomized controlled trial. J Consult Clin Psychol 67:583–589.

Derogatis LR. 1977. SCL-90 Administration, scoring, and procedures manual-I for the revised version. Baltimore: Johns Hopkins University School of Medicine.

Dillon DJ, Gorman JM, Liebowitz MR, Fyer AJ, Klein DF. 1987. Measurement of lactate-induced panic and anxiety. Psychiatry Res 20:97–105.

Fitzgerald RS, Lahiri S. 1986. Reflex responses to chemoreceptor stimulation. Handbook of physiology. II. The respiratory system. Bethesda: American Physiological Society. p 313–351.

Garssen B, Buikhuisen M, van Dyck R. 1996. Hyperventilation and panic attacks. Am J Psychiatry 153:513–518.

Gendreau MA, DeJohn C. 2002. Responding to medical events during commercial airline flights. N Engl J Med 346:1067–1073.

Grover RF, Weil JV, Reeves JT. 1986. Cardiovascular adaptation to exercise at high altitude. Exerc Sport Sci Rev 14:269–302.

Guyton AC, Hall JE. 1996. Textbook of medical physiology, 9th ed. Philedelphia: WB Saunders.

Hibbert G, Pilsbury D. 1989. Hyperventilation: is it a cause of panic attacks. Br J Psychiatry 155:805–809.

Hibbert GA, Pilsbury D. 1988. Hyperventilation in panic attacks: ambulant monitoring of transcutaneous carbon dioxide. Br J Psychiatry 153:76–80.

Honigman B, Read M, Lezotte D, Roach R. 1995. Sea-level physical activity and acute mountain sickness at moderate altitude. West J Med 163:117–121.

Kenardy J, Oei TP, Evans L. 1990. Hyperventilation and panic attacks. Aust N Z J Psychiatry 24:261–267.

Kerr WJ, Dalton JW, Gliebe PA. 1937. Some physical phenomena associated with anxiety states and their relationship to hyperventilation. Ann Intern Med 11:961–992.

Klein DF. 1993. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis [see comments]. Arch Gen Psychiatry 50:306–317.

Lahiri S, Maret K, Sherpa M. 1983. Dependence of high altitude sleep apnea on ventilatory sensitivity to hypoxia. Respir Physiol 52:281–301.

Ley R. 1985. Agoraphobia, the panic attack and the hyperventilation syndrome. Behav Res Ther 23:79–81.

Masuyama S, Kohchiyama S, Shinozaki T, et al. 1989. Periodic breathing at high altitude and ventilatory responses to O_2 and CO_2. Jpn J Physiol 39:523–535.

Meuret AE, Wilhelm FH, Roth WT. 2001. Respiratory biofeedback assisted therapy for panic disorder. Behav Modif 25:584–605.

Missoum G, Rosnet E, Richalet J. 1992. Control of anxiety and acute mountain sickness in Himalayan mountaineers. Int J Sports Med 13:S37–S39.

Moran C. 1986. Depersonalization and agoraphobia associated with marijuana use. Br J Med Psychol 59:187–196.

Morgan WP. 1995. Anxiety and panic in recreational scuba divers. Sports Med 20:398–421.

Nelson M. 1982. Psychological testing at high altitudes. Aviat Space Environ Med 53:122–126.

Nicolas M, Thullier-Lestienne F, Bouquet C, et al. 1999. An anxiety, personality and altitude symptomatology study during a 31-day period of hypoxia in a hypobaric chamber (experiment 'Everest-Comex 1997'). J Environ Psychol 19:407–414.

Papp LA. 1995. Respiratory neurobiology of panic. In: Asnis GM, Van Praag HM, editors. Panic disorder: clinical, biological and treatment aspects. New York: John Wiley and Sons. p 255–275.

Papp LA, Martinez JM, Klein DF, et al. 1997. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. Am J Psychiatry 154:1557–1565.

Papp LA, Welkowitz LA, Martinez JM, Klein DF, Browne S, Gorman JM. 1995. Instructional set does not alter outcome of respiratory challenges in panic disorder. Biol Psychiatry 38: 826–830.

Porcelli MJ, Gugelchuk GM. 1995. A trek to the top: a review of acute mountain sickness. J Am Osteopath Assoc 95:718–720.

Rapee R, Mattick R, Murrell E. 1986. Cognitive mediation in the affective component of spontaneous panic attacks. J Behav Ther Exp Psychiatry 17:245–253.

Reiss S, Peterson RA, Gursky DM, McNally RJ. 1986. Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. Behaviour Res Ther 24:1–8.

Roach RC, Greene ER, Schoene RB, Hackett PH. 1998. Arterial oxygen saturation for prediction of acute mountain sickness. Aviat Space Environ Med 69:1182–1185.

Roy-Byrne PP, Uhde TW. 1988. Exogenous factors in panic disorder: clinical and research implications. J Clin Psychiatry 49:56–61.

Salkovskis PM, Clark DM. 1990. Affective responses to hyperventilation: a test of the cognitive model of panic. Behav Res Ther 28:51–61.

Santolaya RB, Lahiri S, Alfaro RT, Schoene RB. 1989. Respiratory adaptation in the highest inhabitants and highest Sherpa mountaineers. Respir Physiol 77:253–262.

Shukitt-Hale B, Banderet LE, Lieberman HR. 1991. Relationships between symptoms, moods, performance, and acute mountain sickness at 4,700 meters. Aviat Space Environ Med 62:865–869.

Smoller JW, Pollack MH, Otto MW, Rosenbaum JF, Kradin RL. 1996. Panic anxiety, dyspnea, and respiratory disease: theoretical and clinical considerations. Am J Respir Crit Care Med 154:6–17.

Spielberger CD, Gorsuch RL, Luchene RE. 1970. State-trait anxiety inventory. Palo Alto: Consulting Psychology Press.

Stamper D, Sterner R, Kinsman R. 1971. Symptomatology subscales for the measurement of acute mountain sickness. Percept Mot Skills 33:735–742.

Stein J, Papp L, Klein D, et al. 1992. Exercise tolerance in panic disorder patients. Biol Psychiatry 32:281–287.

Stein MB, Millar TW, Larsen DK, Kryger MH. 1995. Irregular breathing during sleep in patients with panic disorder. Am J Psychiatry 152:1168–1173.

Tochimoto S, Kitamura T, Kurata K, Nakamura I, Koshino Y. 1998. 'Chiyamai', a panic-like disorder in woman divers from Hegura Island. Psychiatry Clin Neurosci 52:425–427.

Uhde TW. 2000. Anxiety disorders. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine, 3rd ed. Philadelphia: WB Saunders Company. p 1123–1139.

Wilhelm FH, Alpers GW, Meuret AE, Roth WT. 2001a. Respiratory pathophysiology of clinical anxiety outside the laboratory: Assessment of end-tidal pCO_2, respiratory pattern variability, and transfer function RSA. In: Fahrenberg J, editor. Progress in ambulatory assessment. Göttingen: Hogrefe and Huber. p 313–343.

Wilhelm FH, Gerlach AL, Roth WT. 2001b. Slow recovery from voluntary hyperventilation in panic disorder. Psychosom Med 63:638–649.

Wilhelm FH, Gevirtz R, Roth WT. 2001c. Respiratory dysregulation in anxiety, functional cardiac, and pain disorders: assessment, phenomenology, and treatment. Behav Mod:513–545.

Wilhelm FH, Roth WT. 1997. Clinical characteristics of flight phobia. J Anxiety Disord 11:241–261.

Wilhelm FH, Roth WT, Sackner M. 2002. The LifeShirt: an advanced system for ambulatory measurement of respiratory and cardiac function. Behav Mod (in press).

Wilhelm FH, Trabert W, Roth WT. 2001d. Physiological instability in panic disorder and generalized anxiety disorder. Biol Psychiatry 49:596–605.

Wright A, Jones G, Fletcher R, Mackintosh J, Bradwell A. 1985. The Environmental Symptoms Questionnaire in acute mountain sickness. Aviat Space Environ Med 56:572–575.