False Suffocation Alarms, Spontaneous Panics, and Related Conditions

An Integrative Hypothesis

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• A carbon dioxide hypersensitivity theory of panic has been posited. We hypothesize more broadly that a physiologic misinterpretation by a suffocation monitor misfires an evolved suffocation alarm system. This produces sudden respiratory distress followed swiftly by a brief hyperventilation, panic, and the urge to flee. Carbon dioxide hypersensitivity is seen as due to the deranged suffocation alarm monitor. If other indicators of potential suffocation provoke panic, this theoretical extension is supported. We broadly pursue this theory by examining Ondine's curse as the physiologic and pharmacologic converse of panic disorder, splitting panic in terms of symptomatology and challenge studies, reevaluating the role of hyperventilation, and reinterpreting the contagiousness of sighing and yawning, as well as mass hysteria. Further, the phenomena of panic during relaxation and sleep, late luteal phase dysphoric disorder, pregnancy, childbirth, pulmonary disease, separation anxiety, and treatment are used to test and illuminate the suffocation false alarm theory.

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Biologic causal theories may address ontogenetic "how" questions or phylogenetic "why" questions.[1] Such theories are supplementary rather than contradictory. Elsewhere, we have postulated that the *how* of spontaneous panic often is carbon dioxide hypersensitivity (D.F.K., L. Papp, MD, and J. M. Gorman, MD, unpublished data, 1992). Herein we address *why* carbon dioxide hypersensitivity elicits panic. We propose that many spontaneous panics occur when the brain's suffocation monitor erroneously signals a lack of useful air, thereby maladaptively triggering an evolved suffocation alarm system. The central nervous system significance of even partial suffocation is shown by the fact that the brain, only 2% of body weight, uses 24% of total oxygen consumption.[2] The central importance of carbon dioxide as a panic stimulus is due to the fact that a rising P_{CO_2} suggests suffocation may be imminent. During evolution almost the only experience of breathing excessive carbon dioxide would be when forced to rebreathe one's own exhalations, as during a cave-in. Other confrontations with high carbon dioxide concentrations are usually asphyxial[3,4] or due to pathologic hypoventilation. Therefore, carbon dioxide hypersensitivity would be an aspect of a hypersensitive suffocation detector.[5]

Fear of suffocation is an extremely intense, remarkably common fear reported by many normal subjects,[6] indicating a common adaptation. Claustrophobia and panic disorder overlap since many claustrophobes also panic in nonenclosed spaces. In the study of S. J. Rachman, PhD (written communication, April 18, 1991), almost half of the claustrophobic subjects also reported panics in nonenclosed places, although these were not classifed as "spontaneous" or "situational."

Reactions to psychosocial indicators of suffocation broaden our perspective beyond carbon dioxide to other releasing stimuli. During World War I, "gas hysteria" caused entire army units to break ranks and run without objective provocation.[7]

Modern, cocoonlike full protective gear caused three of 70 to panic immediately after donning the protective mask.[7] They manifested hyperventilation, shaking, confusion, and fear of dying. Eleven others had marked anxiety and hyperventilation within the first 10 minutes, which came under control only after removal of all protective gear.

These observations are consistent with a hypersensitive suffocation detector false-alarm model of panic that integrates all asphyxia-relevant cues, including external observations. Over evolutionary time, a no-exit situation or one where stuffy, stale air implies no exit, where there are crowded, immobilized people, or someone appears to be smothering, might all elicit panic if the suffocation alarm threshold is pathologically lowered or the cues are particularly salient.

We present the suffocation false-alarm theory of panic in many contexts. To aid the reader, we tabulate our argument in an outline of the argument regarding suffocation false alarm:

1. Suffocation fears are common in normal subjects. 2. Suffocation is extraordinarily aversive. 3. Physiologic mechanisms for detecting potential suffocation are monitoring increasing P_{CO_2} and brain lactate values. 4. Carbon dioxide sensitivity has an evolutionarily derived set point that can become dysfunctional. 5. Carbon dioxide hypersensitivity in panic disorder is one aspect of a more general suffocation hypersensitivity. 6. D- and L-lactate as a panicogen is not understandable by simple carbon dioxide theory but finds an explanation within suffocation alarm theory. 7. Clinical panic is not a typical emergency fear response, because of the prominence of dyspnea and the lack of hypothalamic-pituitary-adrenal (HPA) activation. 8. Ondine's curse proves the existence of a suffocation detector; it is the pharmacologic converse of panic disorder. 9. Challenge studies indicate heterogeneity of panic disorder. 10. Chronic hyperventilation, common in panic disorder, predicts lactate-induced panic, which links such panics to triggering of suffocation detector. 11. Sighs and yawns, common in "neurosis," are understandable on grounds of suffocation alarm theory. 12. Panics during both relaxation and sleep are understandable by suffocation alarm theory. 13. Late

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luteal phase dysphoric disorder (LLPDD) relationship to panic is understandable by suffocation alarm theory. 14. Reduction of panic during pregnancy, delivery, and lactation is consistent with suffocation alarm theory. 15. Mass hysteria is understandable on grounds of suffocation alarm theory and is related to separation anxiety. 16. Pulmonary conditions are consonant with suffocation alarm theory. 17. Clinical differences within panic disorder parallel distinctions between challenge studies.

SUFFOCATION ALARM THEORY AND THE SUBDIVISION OF PANIC

The specific emergency reaction to suffocation is acute breathlessness, panic, and the urge to flee. Indeed, dyspnea is a key feature of panic,[8] but not of the fearful reaction to danger.

A review[9] of six studies of fearful bodily sensations in endangered non-patients tabulated each study's seven most frequent symptoms with remarkable consistency. Sweating and pounding heart occurred in all studies and were the leading symptoms in three studies each. Trembling occurred in five studies, stomach sensations and dry mouth occurred in four studies, and hot face and urge to urinate occurred in three studies. Deep or heavy breathing was noted in only two studies. Even this is ambiguous since rapid, deep or heavy breathing is not necessarily dyspnea or breathlessness, the salient features of panic in panic disorder.

In 1950, Cohen and White[10] studied combat-frightened soldiers to contrast fear with anxiety attacks. Only 28% reported dyspnea during combat. The primary symptoms were palpitations and trembling. Therefore, normal fear and pathologic panic overlap but their leading features differ. It is incorrect to equate panic with fear, as the cognitive theory of panic does.[8]

Barlow,[8] Cowley and Roy-Byrne,[11] and Nutt[12] also consider panic a false alarm, but they believe it is due to any nonspecific stimulus that elicits a fearful psychophysiologic vicious circle. However, good engineering requires specific alarms, eg, burglar, smoke, and radiation alarms, with quick, built-in, adaptive actions. We have specific detectors for heat, cold, punctures, and the like. Since escape, appeal, and avoidance are common reactions to threat, the specific danger detectors and adaptations are obscured.

We hypothesize that lactate, bicarbonate, 5% carbon dioxide, and isoproterenol hydrochloride challenges elicit a suffocation false alarm, a state close to the distinctive spontaneous panic of panic disorder in diagnostic specificity, physiology, and pharmacologic reactivity. In contrast, yohimbine, caffeine, meta-chlorophenylpiperazine (MCPP) (a serotonin agonist), and *N*'methyl-B-carboline-3-carboxamide (FG 7142) (a benzodiazepine-inverse agonist) produce varying degrees of autonomic surge and HPA activation, similar in physiology and pharmacologic reactivity to those released by fear, stress, or pain,[13,14] common to both anxiety disorders and normal emergency reactions. That dyspnea is specifically a feature of panic disorder compared with similar anxiety states is shown by a comparison of panic disorder with generalized anxiety disorder.[15] Dyspnea occurred in most patients with panic disorder but in none with generalized anxiety disorder. In contrast, palpitations were reported by almost all patients with panic, but also by most with generalized anxiety disorder.

CARBON DIOXIDE HYPERSENSITIVITY THEORY SUBSUMED IN SUFFOCATION FALSE-ALARM THEORY

The carbon dioxide hypersensitivity theory does not provide a compelling direct link to panic. Vague metaphors of autonomic storms or ad hoc, unsupported hypotheses of antecedent catastrophizing traits have been invoked.

Why should panic usually be initiated by marked dyspnea? The belief that hyperventilation causes breathlessness is incorrect. Analysis of 5% carbon dioxide inhalation in patients with panic disorder indicated that although all patients experience hyperpnea, only those who went on to panic complain of breathlessness. Also, during voluntary room air overbreathing by normal control subjects, complaints of breathlessness are initially minor and then decrease despite marked respiratory alkalosis (D.F.K., unpublished data, 1991).[16] Breathlessness is a preliminary phase of panic, initiating rather than being caused by hyperventilation. That a triggered suffocation alarm would initially release acute distressing breathlessness, thus inciting urgent efforts to escape to open surroundings, provides a meaningful link between disturbed physiology and affective/behavioral reaction. This model also allows for the limited symptom attack, since an adaptive alarm could be released with forcefulness proportional to the cogency of the input.

EXPERIMENTAL PANICOGENS AND THE SUFFOCATION FALSE ALARM

We initially guessed that the panicogenic effects of lactate were due to its metabolism to bicarbonate, which on hydrolysis to water and carbon dioxide might induce brain hypercarbia,[17] since peripheral metabolic alkalosis accompanied by central respiratory acidosis had been noted. Our studies of bicarbonate infusion proved this incorrect since only patients who panicked showed respiratory stimulation, as indicated by a precursor fall in P_{CO_2}. Therefore increased peripheral bicarbonate could not be a sufficient cause of brain hypercarbia. Nevertheless, since lactate induces cerebral vasodilation, it acts like carbon dioxide, one of the few cerebral vasodilators.

Gorman et al[18] showed (to our surprise) that D-lactate, not normally a bodily constituent, is a panicogen and respiratory stimulant in patients with panic disorder. Pyruvate, the sole lactate metabolite, did not approach the level produced by racemic lactate infusion, indicating the absence of D-lactate metabolism. Therefore, lactate metabolism is not a necessary precondition for panic induction or respiratory stimulation. A simple carbon dioxide hypersensitivity theory is contradicted by this observation. Can the suffocation alarm theory do any better?

Dager et al[19-21] has shown in animal models that D- and L-lactate cross the blood-brain barrier. On asphyxiation there is a sharp increase in the brain production of lactate due to anaerobic glycolysis.[22] The cerebral production of lactate may be another signal to the suffocation alarm mechanism, and exogenous lactate may mimic this cue.

Pathologic elevations of central nervous system lactate levels may accompany brain lymphoma, meningitis, and encephalitis. In these cases, hyperventilation has been found to correlate roughly with cerebrospinal fluid lactate levels.[23-26]

However, exercise is not a panicogen despite peripheral hyperlactatemia, although pathologic fatigue occurs in

patients with panic disorder.[27] Why is hyperlactatemia insufficient to release the suffocation alarm during exercise? Perhaps the proposed integrative suffocation monitor considers the level of muscular exertion when evaluating lactate levels. If in keeping, an alarm is not released; however, if blood lactate level increases despite lack of exercise, hypoxia is signaled.[28,29] Sudden running may abort panic[30] because the exertion provides countervailing information to the suffocation monitor.

The suffocation monitor, which evolved during exposure to L-lactate only, may not distinguish optical isomers. Therefore, the same physiologic message of potential suffocation may derive from both D- and L-lactate, accounting for D-lactate's panicogenic effects. This hypothesis is open to direct physiologic test.

If the metabolizable L-lactate was the only active panicogenic substance within racemic lactate, a dose response relationship would be expected. However, preliminary evidence (A. J. Fyer, unpublished data, 1990) indicates that pure 0.375 mol/L and 0.5 mol/L L-lactate do not increase the rate or speed of panic production in patients with panic disorder in excess of that produced by 0.5 mol/L racemic lactate, which contains only 0.25 mol/L L-lactate.

Those who panic to 5% carbon dioxide inhalation and bicarbonate infusion are a subset of those who panic to racemic lactate. This follows since increasing brain lactate levels should more powerfully signal potential asphyxiation than increasing P_{CO_2}, thus precipitating panic in a wider range of those with hypersensitive suffocation detectors.

EMERGENCIES, FALSE ALARMS, FEAR, AND THE HPA SYSTEM

Why distinguish the spontaneous panic-suffocation alarm concept from the emergency emotions of Cannon[31] and the General Alarm Syndrome of Selye[32] that mobilize the HPA axis against stressors? The simplest answer is that clinical or lactate-, bicarbonate- or carbon dioxide–induced panics are not associated with HPA activation (D.F.K., and L. Papp, MD, J. M. Gorman, MD, unpublished data, 1992),[5,33-37] which does occur in physical emergencies[38] and some, but not all, specific phobic responses.[39] Spontaneous panic is not fear, although it is often confused with it.

That there is no HPA activation during the panic itself does not indicate that panic disorder and its complications have no relationship to HPA activation. Studies cited in Coryell and Noyes[40] describe escape from dexamethasone suppression test (DST) in nondepressed patients with panic disorder. Baseline urinary free cortisol levels[41] were significantly higher only for patients with panic disorder and agoraphobia or depression as compared with control subjects, but not for patients with uncomplicated panic disorder. After benzodiazepine treatment, urinary free cortisol levels fell in the patients with complicated disorders but not in the patients with pure panic disorders.

Further, Coryell et al[42] have shown that more patients with panic disorder were nonsuppressors on at least one of three DSTs than control subjects. The DST results did not predict subsequent course, but they were strongly related to relapse after discontinuation of medical therapy.

Comparing patients with panic disorder with and without agoraphobia, Westberg et al[46] found significantly higher cortisol levels and abnormal DST results in the agoraphobics. A marked reduction in anxiety attacks was not always accompanied by normalization of a pathologic DST result. Westberg et al suggest that the propensity for an abnormal DST result might be more connected to the tendency toward agoraphobia (ie, chronic fear of panic) than to panics per se.

That DST nonsuppressors[40] were not likely to benefit from placebo, plus the fact that patients with panic disorder who develop DST abnormality were likely to deteriorate whereas in those who normalize their DST improved, implies that extra-panic HPA activation indicates further pathology.[44]

Garvey et al[45] compared patients with panic with patients with high vs low 3-methoxy-4-hydroxyphenylglycol (MHPG) excretion. Unexpectedly, patients with low MHPG excretion had more spontaneous panics during the preceding month. Garvey et al suggest two subtypes of panic disorder. One has reduced MHPG excretion, normal baseline cortisol level, rapid panic during lactate infusion, and is likely to have both spontaneous and situational panic attacks. The second subtype has elevated MHPG excretion, increased Hamilton anxiety symptoms, elevated baseline cortisol level, delayed panic during lactate infusion, and relatively uncommon spontaneous panics.

We suggest their first subgroup experiences suffocation false alarms. However, some may shift subtypes since early in panic disorder spontaneous panics predominate, whereas anticipatory anxiety, situational panics, depression, and avoidance come to the fore later. This may account for the second fearlike subtype of Garvey et al.

Fear must be distinguished from spontaneous panic marked by abrupt, seemingly causeless, transient crescendos of somatic symptoms, often respiratory, as well as its termination and prevention by certain "antidepressants" even if depression is absent.[46] Fear does not respond to antidepressants; "patients taking effective antipanic medications may nonetheless experience normal intense fear in acutely frightening situations. This finding contradicts the hypothesis that these medications block a final common pathway of the panic response".[47]

The distinction between episodic spontaneous panic and chronic fearlike anxiety was first made plain by the specific ablating effects of imipramine hydrochloride on spontaneous panic, while chronic anxiety and agoraphobic avoidance persisted. Acute anxiety derives from fear as a recently evolved anticipation of danger. Chronic anxiety may be a primitive response to repeated traumatic sensitization.[48-51] Panic seems an even more primitive response to an endogenously detected danger, specifically suffocation.

ONDINE'S CURSE (CONGENITAL CENTRAL HYPOVENTILATION SYNDROME) DEMONSTRATES A SUFFOCATION DETECTOR

Is there a distinct suffocation detector? Hypoxia or hypercapnia might distressingly derange many bodily functions. Is a suffocation detector a reification?

A direct answer is provided by the experiment of nature called *Ondine's curse*. In this strange condition (congenital central hypoventilation syndrome), an infant breathes while awake, but once asleep, stops breathing, plunges into hypoxia, and may die. Only recently have ventilatory support procedures allowed such children to survive. Astonishingly, these children show no distress when severe-

ly hypoxic or hypercapnic, a striking indication of the loss of a specific suffocation detector.

Mellins et al[52] and Haddad et al[53] report three evocative facts. (1) The limited neuropathologic findings are medullary. (2) The disorder disproportionately co-occurs with another rare disorder, Hirschsprung's disease (megacolon), marked by absence of the serotonergic myenteric plexus ganglion cells. That both diseases may arise from a common defective serotonergic stem neuron is suggested by Mellins et al. (3) Of pharmacologic agents studied (doxapram hydrochloride, progesterone, aminophylline, chlorpromazine, physostigmine salicylate, and imipramine), only doxapram (a respiratory stimulant and panicogen),[54] which beneficially increased ventilation and imipramine (antipanic), which counterproductively decreased ventilation, were active. Congenital central hypoventilation syndrome seems panic disorder's converse with an insensitive rather than hypersensitive suffocation detector and an inverse pharmacologic reactivity.

CHALLENGE STUDIES AND SPLITTING PANIC

Are all panics the same? Laboratory panicogens should mimic clinical reality. For instance, clinically effective tricyclic treatment blocks panic induced by lactate,[5] isoproterenol,[55] and carbon dioxide (H.H.A. Lousberg et al, unpublished data)[56] (and probably bicarbonate since it is a metabolite of lactate), whereas intravenous diazepam only delays lactate panicogenesis (M. R. Liebowitz, MD, unpublished data, 1990).

However, the opposite is true for yohimbine,[57] whose panicogenic effects are blocked by diazepam but not by imipramine. Panic, induced by the benzodiazepine inverse agonist FG 7142,[58]is blocked by benzodiazepines. Imipramine treatment failed to block caffeine's panicogenic effects (T. W. Uhde, MD, oral communication, 1990). Clinical and experimental[59,60] observations indicate diazepam is effective against caffeine anxiogenesis. Useful distinctions are possible between "panics" now lumped together.[61]

Cortisol level increases during acute fear, uncontrollable stress,[62] yohimbine, caffeine,[63,64] MCPP,[65,66] and the inverse benzodiazepine agonist FG 7142, as Selye[32] would predict. However, remarkably, clinical panics[67] as well as those induced by lactate,[68,69] carbon dioxide,[70] and bicarbonate[71] show no HPA activation. Only one normal subject of many we have studied had a lactate-induced panic, applying rigorous criteria. No cortisol increment occurred, suggesting that the HPA system is not disconnected by repeated trauma in panic disorder.

Lactate, bicarbonate, 5% carbon dioxide, and isoproterenol are rarely panicogenic in normal subjects, nor is lactate a panicogen in any anxiety disorder not associated with spontaneous panic. Woods et al[72] report paniclike reactions in normal subjects to 7.5% carbon dioxide. Since this approaches actual asphyxiation, it may simply indicate a higher threshold in normal subjects than in patients. Only one study[73] reports lactate to be panicogenic in a substantial proportion of normal subjects, but there was also a very high panic rate in patients. Since the difference between lactate and placebo panicogenesis was as usual, this suggests a low threshold for panic diagnosis in this study. In contrast, yohimbine, caffeine, and FG 7142 are all anxiogenic to panicogenic in normal subjects. Yohimbine and caffeine are more panicogenic in patients with panic disorder than normal subjects,[57,74] but these agents may be more anxiogenic in all patients with anxiety disorders than in normal subjects.

Whether different panicogens produce different symptom patterns has been insufficiently studied. Patients with panic disorder given MCPP have significant increments in nausea, hot and cold flashes, lacrimation, faintness, weakness, tremors, restlessness, vertigo, paresthesias, unreality, and loss of control.[66] However, the cardinal symptoms of shortness of breath, chest discomfort, palpitation, and choking feeling did not occur.

Intravenous flumazenil, a benzodiazepine antagonist with no intrinsic activity, produced dizziness and lightheadedness in normal subjects but provoked a panic in eight of 10 patients with untreated panic disorder. Nutt et al[75] theorize that flumazenil's panicogenesis indicates that patients with panic disorder have a changed benzodiazepine receptor set point, so that flumazenil acts as an inverse agonist rather than a simple antagonist. Klein predicted to Nutt[75] that because inverse agonists cause cortisol release, flumazenil-induced panic should not have respiratory symptoms. This prediction was borne out in Nutt's study. Several patients mentioned that flumazenil panic differed from clinical attacks by absence of respiratory symptoms.

CHRONIC HYPERVENTILATION AS PREDICTOR OF LACTATE-INDUCED PANIC

Can lactate-induced panic be predicted? Anticipatory anxiety increased panic likelihood, although neither necessary nor sufficient. Surprisingly, low baseline venous phosphate level (a sign of chronic hyperventilation) was a powerful panic predictor. All patients below a certain phosphate level panicked.[76]

Prior to lactate infusion, shortly after intravascular lines are placed, an increase in ventilation often occurs that correlates with lactate-induced panic.[2] However, low bicarbonate level, a concomitant of chronic rather than acute hyperventilation, may facilitate stress-induced hyperventilation and it also predicts lactate panic.

Venous blood is buffered by drained tissues, damping P_{CO_2}, and pH fluctuations. Even though venous and arterial blood have a linear relationship with regard to average P_{CO_2} and pH, transient arterial fluctuations may not be reflected in venous levels.

Our clearest findings came from arterial blood studies. Panics occurred in patients with low bicarbonate levels. High P_{CO_2} levels and low pH levels virtually precluded developing panic.[77]

That relatively high arterial P_{CO_2} protects against panic does not fit a simple carbon dioxide hypersensitivity model. Yet, it fits nicely with the suffocation false alarm hypothesis, amplified by the clinical observation that patients with panic disorder have good and bad periods. Presumably during bad spells the suffocation alarm threshold is pathologically depressed. Chronic hyperventilation avoids dyspnea by adaptively lowering P_{CO_2}. Respiratory alkalosis induces renal pH compensation by bicarbonate excretion, thus returning blood acidity to near normal. Therefore, concomitant low blood bicarbonate level, low P_{CO_2}, and high blood pH suggest a current pathologically lowered suffocation threshold. That they also predict lactate panicogenesis ties these phenomena together.

den Boer et al[78] did not find a relationship between phosphate level and lactate-induced panic, perhaps due to

sample variations in chronic hyperventilation. However, on reanalysis, J. A. den Boer, MD, and H. G. M. Westenberg, PhD (written communication, December 18, 1990) did find that those who panicked in the first 5 minutes of lactate infusion had significantly lower baseline phosphate levels than the combined group of late panicking patients, nonpanickers, and control subjects, indicating some concordance of chronic hyperventilation and ease of panic induction.

An integrated suffocation alarm needs to deal with both carbon dioxide and oxygen. Even very mild hypoxia synergistically enhances respiratory stimulation by carbon dioxide as well as sympathetic activity. Those overstimulated by hypoxia are also overstimulated by hypercarbia. Further, those with a low baseline venous P_{CO_2} show a greater ventilatory response to both hypoxia and inspired carbon dioxide.[79-81] Both the synergistic effect and the correlated ventilatory sensitivity to both hypoxia and hypercapnia require a suffocation rather than a simple carbon dioxide detector. For instance, daytime hypercapnia (indicating a hyposensitive suffocation detector) predicts nocturnal hypoxemia in awake normoxic patients.[82] A complex defensive system against suffocation is shown by the synergistic effects of hypercarbia and hypoxia.

CHRONIC HYPERVENTILATION DURING PANIC DISORDER

Chronic hyperventilation causes both low P_{CO_2} and bicarbonate levels. These normalize during panic remission,[76] suggesting that chronic hyperventilation does not cause panic, but rather it adaptively compensates for a lowered suffocation alarm threshold by keeping P_{CO_2} below the triggering range.

Chronic hyperventilation might entail a vicious circle if hypocapnia produced a deafferentation hypersensitivity, thus further decreasing the alarm threshold. However, chronic hyperventilation effects on carbon dioxide sensitivity are markedly variable, so this remains an interesting possibility.[83]

SIGHS AND YAWNS AS COMPENSATORY ADAPTATIONS

Chronic hyperventilation as an adaptive hypocapnia-inducing mechanism is consonant with frequent sighing, a venerable feature of neurosis.[84-86] A feeling of respiratory oppression precedes sighing. The deep inspiration that initiates a sigh, triple the normal tidal volume, abruptly lowers P_{CO_2} and relieves respiratory distress. Therefore, chronic hyperventilation and sighing may adaptively keep P_{CO_2} below a depressed suffocation alarm threshold. (It is arresting that frequent extreme yawning inspirations often accompany increased sighing, indicating a common function.[84,87]) A sigh or yawn may serve as a bioanalytical test for high ambient carbon dioxide. If, on deep inhalation, the P_{CO_2} failed to fall sufficiently, an asphyxial cue would be detected.

That suffocation serves as a particularly traumatic unconditional stimulus was made plain by Sanderson et al[88] and Campbell et al.[89] These investigators gave alcoholic volunteers an injection of succinylcholine, producing a "harrowing" period of 90 to 130 seconds in which they were unable to move or breathe while remaining conscious. A tone, to which they had previously been habituated, was played during the apnea.

After the paralysis, many took occasional deep breaths that led to an immediate suppression of respiration for 12 to 15 seconds. Curiously this re-creation of the traumatic stimulus was not aversive. This becomes comprehensible if the sighs served as ambient carbon dioxide bioassays. Since the sigh-induced apneas diagnosed a safe low carbon dioxide environment they were safety signals, although they should be anxiogenic by conditioning theory. The potency and specificity of the suffocation stimulus is indicated by the marked resistance to extinction of these subjects' sighing.[88,89]

The mysterious contagious effects of yawns and sighs are well known. Observed acute inspirations may be interpreted as tests of increased ambient carbon dioxide or efforts to overcome breathlessness. Thus, observing another's yawn incites ones' own yawning test without any relevant cognition, thus resembling an ethologic fixed action pattern.

PANIC DURING RELAXATION AND SLEEP

Panics occur during relaxation[8] and deepening non–rapid eye movement sleep[90-92] despite lack of danger cues or cognitions. However, both states cause sharply increasing P_{CO_2}, especially in those with chronic hyperventilation.[93]

If sensitivity to increasing P_{CO_2} incites panics during relaxation and sleep, then those who panic during deepening sleep should also be likely to panic during relaxation. Mellman and Uhde[90,91] have shown this.

Ley[94] suggests that patients who panic during sleep are chronic hyperventilators with diminished buffer. Therefore, minor nocturnal ventilatory reductions cause hypercapnic respiratory acidosis, which incites hyperventilation, swinging into hypocapnia that triggers panic.

However, even given that nocturnal panickers chronically hyperventilate, carbon dioxide increase due to nocturnal ventilatory reduction might lead only to a compensatory tidal volume increase, producing eucapnia rather than hypocapnia. Ley's model does not account for overshoot. Further, even given overshoot, it does not follow that acute hypocapnia produces panic since controlled studies indicate hypocapnic hyperventilation is insufficient.[75,95-97]

In our model, hyperpnea, hypocapnia, and alkalosis are consequences of panic rather than causal antecedents. If nocturnal carbon dioxide challenges were panicogenic prior to respiratory alkalosis onset, this would resolve this disagreement.

CARBON DIOXIDE, THE MENSTRUAL CYCLE, AND LLPDD

Premenstrual exacerbation of panic disorder is commonly observed,[98] except for two[99,100] small, prospective studies. However, one[100] did find that the intensity of full panics increased significantly. This might indicate a low threshold for considering an anxiety increase as a panic, so that only their "high intensity" panics would be relevant to the LLPDD panic-exacerbation hypothesis. Clinical observations are powerful enough that only larger, prolonged, prospective negative studies could be considered definitive.

After ovulation, increasing progesterone stimulates chronic hyperventilation. Approximately 3 days before menses, progesterone level falls, incurring a substantial rise in P_{CO_2},[101,102] just when increasing dysphoria and pan-

ic occurs. It is commonly, incorrectly, stated that the luteal phase is persistently hypocapnic.

Halbreich et al[103] studied women with and without chronic premenstrual dysphoria. The most symptomatic women had the highest progesterone production and the fastest rate of progesterone decrement just prior to dysphoria onset. Further, the most severe symptoms occurred while decreasing from peak progesterone levels. Therefore, the most dysphoric probably had the sharpest P_{CO_2} increase.

The correlation of premenstrual dysphoria with postpartum symptomatology suggests sudden progesterone withdrawal as a common mechanism,[103] causing an acute carbon dioxide increment provocation to the carbon dioxide sensitive. Backstrom[104] and Hammarback et al[105] report that women who had cycles with higher luteal concentrations of estradiol and progesterone had more severe premenstrual symptoms than women who had cycles with lower concentration. Also, cyclic mood changes disappeared during anovulatory cycles.[106] Similarly, treatments that block ovulation benefit premenstrual syndromes.[107,108]

How does this relate to panic? Harrison et al[109] reported panic precipitation by 35% carbon dioxide during all menstrual phases in about half of women with marked chronic premenstrual tension but no effect on normal control subjects. Sandberg et al[110] reported that women with chronic LLPDD, tested only during their luteal phase, also had a high rate of lactate-induced panic. If the pathophysiologic features of LLPDD resemble panic disorder, a chronically low suffocation threshold may be clinically problematic only during the premenstrual carbon dioxide increase.

Since panic to lactate and 5% carbon dioxide is highly specific,[111-113] LLPDD pathophysiology may relate to panic vulnerability. LLPDD is marked by panics more often than usually noted (S. K. Severino, MD, and M. L. Moline, PhD, written communication, January 15, 1992). LLPDD dysphoria, tension, irritability, and anxiety may be linked to a subthreshold stimulation of the suffocation alarm system, leading to limited symptom attacks. Unfortunately, current LLPDD symptom inventories do not include breathlessness or limited symptom attacks. That spontaneous panics predominantly occur in women, and rarely start before puberty[114] or after menopause, seems more than coincidence. Further, women, in their resting state, have a greater minute ventilation per milliliter of endogenous carbon dioxide production consistent with a relative sensitivity to asphyxial cues. They also have greater hypoxic response in the luteal than follicular menstrual phases.[115] That women have an increased vulnerability to panic disorder is well known.[8]

A trial of 300 mg/d of orally administered micronized progesterone (rather than the usual suppository), given luteally, benefited women with premenstrual syndrome in a well-designed placebo-controlled crossover study.[116] This is controversial.[117] Negative studies are often due to large placebo effects, probably due to syndromal instability. Our theory does not propose that progesterone deficiency accounts for progesterone benefit, but rather to the blunting of sharp progesterone decrements. In a double-blind randomized placebo-controlled trial of fluoxetine hydrochloride in LLPDD, nine of 10 subjects receiving fluoxetine responded to treatment, whereas only two of the 10 receiving placebo did,[118] suggesting a panic parallel.

Interestingly, estrogen is also a respiratory stimulant and most women experience well-being during the preovulatory estradiol surge. Brief troublesome premenstrual syndrome–like symptoms coincide with the decline in circulating estradiol level that occurs transiently after ovulation.[119,120]

DECREASE OF PANIC DURING PREGNANCY, DELIVERY, AND LACTATION

R. Swinson, MD (written communication, June 18, 1990), confirming common clinical opinion, states that pregnancy protects against panics. Further, postpartum panic exacerbation regularly occurs unless the patient breast feeds; then there is a postlactational exacerbation (A. Skrobala, MA, and D. F. K., unpublished data, 1992).

In the late first trimester, before substantial fetal growth, hyperventilation develops, to remain throughout pregnancy, due to the respiratory stimulant effect of placental progesterone, and to a lesser degree, estrogen.[121-125] This facilitates fetal excretion of carbon dioxide waste.

Is there a contradiction here? Patients with panic disorder with the lowest P_{CO_2} and bicarbonate are most likely to panic during lactate challenge, but now we state that the low P_{CO_2} of pregnancy protects against panic.

However, a low P_{CO_2} and bicarbonate level in a patient with panic disorder indicates adaptive chronic hyperventilation due to a low suffocation alarm threshold. Therefore, lactate may fire the pathologically sensitive alarm. In contrast, patients with panic disorder with normal pH, P_{CO_2}, and bicarbonate levels must have a phase of suffocation alarm normality. Such patients would not be susceptible to lactate or carbon dioxide panicogenesis.

In contrast, during pregnancy, lowered P_{CO_2} and bicarbonate levels are due to progesterone's respiratory stimulation, not suffocation threshold abnormality. The widened gap between P_{CO_2} and the suffocation alarm threshold makes a false alarm less likely.

Childbirth's marked hyperventilation drives P_{CO_2} to a minimum.[124] The venerable Lamaze birth training programs teach maintaining deep hyperventilation during delivery, suggesting an adaptive role.[126] The remarkable lack of panic during delivery in patients with panic disorder flatly contradicts the belief that hyperventilation, hypocapnia, and perceived danger are panic triggers (A. Skrobala, MA, and D. F. K., unpublished data, 1992).

Shortly after parturition there is a marked P_{CO_2} increase coinciding with the onset of transient postpartum blues, and, less definitively, panic.[127-131] There is a marked symptomatic resemblance between postpartum blues and LLPDD (J. Endicott, PhD, written communication, February 13, 1992).

Why does lactation protect against panic since progesterone returns to normal post partum? Panksepp[132] and Insel[133] point out that an exclusively mammalian neuropeptide, oxytocin, which increases during breast feeding, is active against separation anxiety in animal models. This may influence panic as well.

MASS HYSTERIA

The contagious symptomatology of "mass hysteria" is often precipitated by reports of peculiar odors and the sight of distressed hyperventilating people. Of 990 women exposed to increased humidity and faulty air conditioning, 250 had development of choking with hyperventilation, excessive sweating, and dizziness.[134] Psychiatric evaluation diagnosed these as panic attacks. No loss of consciousness occurred. Although most expressed an ex-

cessive fear of an impending health threat, they were not chronically somatically focused. There was no history of unexplained illnesses, frequent physician visits, or social dysfunction. Of 16 closely studied subjects, 10 had one to two previous panic episodes but had never consulted physicians or taken sick leave. All returned to work the next day or even during the attack day.

Sparks et al[135] studied 200 employees with dizziness, nausea, headaches, fatigue, shortness of breath, palpitations, and cognitive impairment following exposure to phenol-formaldehyde resin, despite no evidence of organic damage. Numerous subsequent episodes of dizziness, palpitations, dyspnea, and faintness on exposure to pungent odors, as well as clinical syndromes indistinguishable from typical panic disorder developed. Unfortunately, there was no clinical psychiatric appraisal of history of panic. In a workplace epidemic,[136] seven of 11 subjects showed respiratory alkalosis consistent with hyperventilation.

An unusual all-male, military recruit epidemic occurred in a setting that included markedly elevated temperatures, brush fires, and a high pollution index.[137] More than 1800 recruits were evacuated. Awareness of odors or smoke and emergency medical evaluation were strongly associated. Those who witnessed cardiopulmonary resuscitation or saw others become ill had a threefold increased risk of being a case. However, as with other studies,[134] the overall attack rate was only 18%, indicating a minority predisposition was necessary for this reaction. The suffocation false-alarm theory affords a new approach to this complex, stereotyped group phenomenon.

SEPARATION ANXIETY, MASS HYSTERIA, AND PANIC

Is there a relationship between suffocation alarm theory and the high incidence of early separation anxiety[138,139] and recent loss as panic disorder antecedents? Might separation anxiety lower the suffocation alarm threshold?

Mass hysteria[140] occurred in the context of loss of a respected principal, impending graduation and departure from school, and a planned camping trip in which many would sleep away from home for the first time. There were substantially higher rates of parental divorce and familial death in the hospitalized symptomatic children (who had severe, early symptom onset) compared with nonhospitalized symptomatic and asymptomatic children, who did not differ from each other. The authors conclude that early losses predispose children to severe "hysterical" symptoms. This suggests two mechanisms, severe suffocation false alarms enhanced by a vulnerability to separation anxiety and milder stress reactions. A similar report emphasized the importance of early loss and the observation of sick friends in mass hysteria.[141]

Sighs and anxiety disorders are common during acute grief and threatened loss. Jacobs et al[142] found a distinct increase in panic disorder and generalized anxiety disorder in bereaved spouses. History of panic disorder was the only significant predictor.

In an epidemiologic study, Tweed et al[143] found significant associations between maternal death and agoraphobia with panic attacks, as well as parental separation or divorce and agoraphobia with panic attacks and panic disorder. However, these disorders developed in only a small proportion with those life events, and most patients with panic disorder did not have these antecedents. These relationships were not found in any other anxiety disorder, suggesting specific relationships in predisposed people between separation or loss and the panic diathesis.

That panic disorder may be expressed as limited symptom attacks may account for reports (based on questionnaires) that separation anxiety equivalently antecedes other anxious states.[144] However, in the only controlled, long-term, direct, blind, clinical interview follow-up of school-phobic, separation-anxious children, the only significant finding was an increased rate of panic disorder (R. G. Klein, PhD, unpublished data, 1991).

The evolutionary significance of a link between separation anxiety and the suffocation alarm is obscure. That endogenous opioids and exogenous opiates decrease both respiratory sensitivity[145] and separation anxiety suggests a physiologic commonality.[146-148]

Withdrawal of opiate therapy is characterized by recurrent yawning. This may indicate a withdrawal-induced increase in suffocation sensitivity, so that yawning adaptively decreases P_{CO_2} while testing for potential asphyxiation. Naloxone hydrochloride (which blocks opiate receptors) increases ventilatory response to hypercapnic hypoxia, implying that endorphins diminish suffocation sensitivity.[149] A placebo-controlled trial[150] in normal subjects showed that codeine allowed high levels of carbon dioxide to be tolerated during breath holding. It also reduced breathlessness and ventilation during exercise.

However, Eriksson et al[151] reported that cerebrospinal fluid concentrations of β-endorphinlike immunoreactivity were higher in patients with panic disorder than matched control subjects. This seems to contradict our hypothesis. However, recently E. Eriksson, MD (written communication, May 7, 1991) stated the following:

> The antibody we used in the radioimmunoassay recognizes not only β-endorphin but also some shorter fragments of this molecule (the biological activity of which are unknown). When we analyze our samples using HPLC, we got some indications that the levels of the large β-endorphin molecule in fact were *decreased* in PD patients whereas the levels for these shorter fragments were markedly elevated. Thus, whether PD patients displayed *increased* or *decreased* endorphinergic function is yet somewhat obscure. Clearly, however, in our group of PD patients, the endorphinergic activity was *different* as compared to that of controls.

Also, level differences may not be directly proportional to function differences. The finding of Eriksson et al requires replication, using such advanced techniques. Other studies[152-155] must be considered in this context.

PANICS IN PULMONARY CONDITIONS RELATED TO SUFFOCATION

Respiratory illnesses may cause panic unless the suffocation alarm threshold is defensively raised.[156] In patients with chronic obstructive pulmonary disease, some have development of a decreased sensitivity to increased carbon dioxide and decreased oxygen, becoming torpid and obtunded (blue bloaters). Others maintained a low suffocation threshold. Their distress spurs hyperventilation, achieving eucapnia and normoxia (pink puffers). Panic disorder is frequent among patients with pulmonary disease. Further, panic disorder is the most prevalent psychiatric disorder in pulmonary disease.[157-159] In addition, "panic-fear" scores were negative predictors of hospital discharge in asthmatic patients.[162-164]

Yellowlees and Kalucy[159] cite an uncontrolled literature indicating tricyclics are useful in asthma. A controlled therapeutic trial of imipramine in asthmatics with panic

disorder and a diagnostically clarifying lactate challenge is suggested.

Burns and Howell[165] compared patients with respiratory disease with inappropriate breathlessness with comparably breathless patients with appropriate pulmonary impairment. Disproportionate breathlessness was characterized by acute hyperventilation attacks, breathlessness at rest, difficulty getting air in, and fear of sudden death in an attack. This suggests pulmonary disease complicated by panic disorder. Nocturnal panics in patients with obstructive sleep apnea responded to continuous positive airway pressure.[166]

Chronic hypoxic dyspnea is symptomatically alleviated[167,168] by ablating the carotid body, a peripheral hypoxia detector. Might antipanic agents be effective antidyspneics in patients with chronic obstructive pulmonary disease whose suffocation alarm system did not downregulate, but remained carbon dioxide sensitive? This would require careful medical monitoring.

That panic regularly accompanies smothering diseases does not prove that a disorder of the suffocation alarm causes spontaneous panic. However, if panic did not occur in such contexts, the theory would be invalidated.

TREATMENTS RELEVANT TO UNDERSTANDING PANIC SYNDROMES AND ATTACKS: RESPIRATORY TRAINING

Chronic hyperventilators benefit equally from biofeedback or instruction.[169] Treatments caused increases in P_{CO_2} that correlated with a moderate fall in complaints. This casts light on the reported benefits of teaching slow shallow breathing to patients with pure panic disorder.[170] Slow, shallow breathing causes slight P_{CO_2} increments, attenuating deafferentation hypersensitivity, perhaps at the cost of initial panic exacerbation. If the primary pathologic threshold lowering has spontaneously remitted, relief of secondary carbon dioxide hypersensitivity should make remission manifest. Franklin,[171] in a small, imaginative pilot trial, found respiratory training particularly effective against panic attacks as compared with cognitive and relaxation components that preferentially diminished avoidance.

CARBON DIOXIDE EXPOSURE

Repeated carbon dioxide exposure progressively decreased the propensity to panic although complete cessation did not occur.[172] Between sessions, carbon dioxide sensitivity recurred. This was interpreted as psychological habituation, but why should repeated trauma be calming? One could have predicted incremental sensitization.

Short-term carbon dioxide exposure, like shallow breathing, may be a physiologic treatment. Another possibility is the common phenomenon of time-limited tachyphylaxis. Yet another is a decrease in startle, which may be mismeasured as panic.

In five hyperventilating patients with low P_{CO_2},[93] carbon dioxide inhalations increased P_{CO_2}. Despite this increase, the P_{CO_2} returned to the hypocapnic set point within 5 minutes of the resumption of air breathing. Therefore, short-term carbon dioxide inhalation did not reverse the chronic hypocapnia of these patients.

Haslam[173] gave patients with panic who had received lactate infusions a 6-week course of carbon dioxide inhalation therapy. Surprisingly, in view of later studies, there was an immediate relief of anxiety. Of the patients with lactate-induced panic, almost all had a good carbon dioxide treatment result, whereas almost none of the nonlactate responders benefited.

Response was not well defined. Nevertheless, if a lactate panic response indicates current carbon dioxide hypersensitivity, then carbon dioxide treatment might raise the threshold, specifically benefiting lactate panickers. In the lactate nonpanickers, carbon dioxide would have nothing to treat. These findings require replication, with controls for spontaneous remission.

TRICYCLIC ANTIDEPRESSANT AND ALPRAZOLAM TREATMENT

Imipraminelike antipanic agents may normalize the deranged suffocation alarm threshold. Severe "hyperventilation syndromes" refractory to intensive respiratory management techniques benefited markedly from clomipramine hydrochloride.[174]

The suffocation false-alarm theory received unexpected support from A. C. Briggs (written communication, July 18, 1990) who compared alprazolam, imipramine, and placebo. A cluster analysis of panic symptoms indicated two groups. When panics were distinctively marked by respiratory distress, imipramine was superior to alprazolam. Without respiratory distress, alprazolam was superior to imipramine.

Serotonin system activation decreases carbon dioxide–stimulated respiration[175] in a fashion similar to inferences about endorphin effects on respiration.[149] This may be a clue to the antipanic benefits of some antidepressant medications as well as the ineffectiveness of the non–serotonin-active antidepressants, buproprion hydrochloride and maprotiline hydrochloride. It may also explain the respiratory depressant effect of imipramine in Ondine's curse.

DIFFERENTIATION AMONG CLINICAL PANICS

Therapeutic distinctions with regard to respiratory panic complaints parallel the two groups of panicogens; those specifically blocked by imipramine and those blocked by benzodiazepines but not imipramine. More traumatic spontaneous panics may stem primarily from a fluctuating suffocation alarm disturbance, lack acute HPA activation, regularly incite marked phobic avoidance, and are particularly benefited by serotonin reuptake blocking antidepressants. Patients who panic during carbon dioxide inhalations also have more frequent naturally occurring panics,[72] implying enduring, marked, pathologic suffocation sensitivity. Such panics are limited to patients with panic disorder and are distinct from fear.

Other surges of anxiety reflect or perhaps discharge through a hypersensitive HPA/autonomic system causing sweating, trembling, and heart pounding. High-potency benzodiazepines are particularly effective. Such fearlike attacks cut across nosologic boundaries. Both acute disturbances can coexist and interact sequentially and synergistically and are not mutually exclusive.[45] For many patients with panic, the initial severe respiratory panics eventually cause secondary fearful HPA-related surges.

Norton et al[176] found that 34.4% of normal young adults had one or more panics in the past year (by self-ratings). The most severe, frequent panic symptoms were heart pounding, trembling, and sweating rather than difficulty in breathing. Therefore, in infrequent nonclinical panickers, the most common paniclike symptomatology is fearlike.

In an ordinal multidimensional scaling analysis of 12

panic symptoms from epidemiologic data,[177] two dimensions were isolated. One consisted of breathing difficulty, heart pounding, tightness or pain in the chest, smothering sensation, and fear of dying. The other lesser dimension was marked by a sense of unreality, fingers and feet tingling, trembling and shaking, and fear of dying or of acting crazy.

In a second interview wave, 383 patients with newly developed nonphobic (ie, spontaneous) panics were compared with 766 control subjects. The development of spontaneous panics was strongly associated with a history of cardiac symptoms, shortness of breath, depression or a major grief episode, drug abuse or dependence, alcohol abuse or dependence, and seizures. Respiratory distress as both an antecedent and a distinctive feature of panic is thereby documented. The antecedent relationships of depression, grief, and substance abuse to panic are evocative. That these relationships were detected by the Diagnostic Interview Schedule (an oral questionnaire) suggest that, in reality, the relationships are even stronger.

PANIC AND PHOBIC DEVELOPMENT

Which patients with panic disorder develop phobic avoidance and which do not? Severity, number of attacks, and high anticipatory anxiety[178] have been associated with phobic development.

Gorman et al[71] compared bicarbonate and lactate infusions in panic induction. Only patients with panic disorder and agoraphobia, as opposed to those with pure panic disorder, were sensitive to bicarbonate infusion. Perhaps bicarbonate requires a markedly decreased suffocation threshold to be an effective panicogen. Frequent traumatic suffocation panics incite agoraphobia.

Noyes et al[179] report that patients with agoraphobia have a more severe panic disorder. Compared with pure panic disorder, they had an earlier age of onset, a longer duration of illness, more severe symptoms, greater illness-related disability, and were more likely to have axis I or II comorbidity.

The many contradictions concerning the relationship of panic to avoidance may be due to methodologic difficulties in defining degrees of avoidance. Turner et al[180] found even those clinically diagnosed as having simple panic rated themselves with substantial agoraphobia. Many patients diagnosed as having agoraphobia with panic rated themselves lower on an agoraphobia scale than supposedly pure panic disorders.

Enduring, moderately sensitive suffocation thresholds should cause fluctuating breathlessness and limited symptom attacks. This should incite anticipatory anxiety, increasing phobic avoidance. Therefore, degree of avoidance should and does predict the subsequent frequency and severity of panics and chronic anxiety.[181]

Contrasting anxiety disorders in 407 patients with anxiety, the one significant discriminant function had two major loadings: "Fears" and "Respiratory."[182] It loaded most highly on panic disorder with agoraphobia followed by panic disorder and, at some distance, social phobia and generalized anxiety. This indicates an intimate relationship among respiratory distress, panic, and phobic development. Anticipatory anxiety is usually considered in a conditioning or cognitive psychological framework. Although a sensitivity to nonspecific endogenous stimuli by patients with panic disorder has often been postulated, anticipatory anxiety may be maintained and amplified by specific respiratory abnormality.

Katerndahl[183] contrasted spontaneous panic with panics in simple phobics. He concluded loss of control was more characteristic of simple phobic panic, while dyspnea and dizziness were more prevalent in spontaneous panic. Three panic stages are reported. Early symptoms are dyspnea, palpitations, chest pain, and hot or cold flashes followed by shaking, choking, feelings of unreality, sweats, faintness and dizziness, and finally fear and paresthesia.

Using a modified path analysis, Katerndahl and associates[184,185] studied the transition from panic disorder to agoraphobia. They concluded that patients having panic attacks with chest pain, trembling, dyspnea, and fear may be at greater risk for agoraphobia.

CONCLUSION

The suffocation false-alarm theory of panic disorder integrates much apparently unrelated clinical, physiologic, pathologic, and pharmacologic data within a concrete evolutionary model. Other abnormalities, including a hypersensitive HPA axis,[186] may play a role in fear, chronic anxiety, and anxious surges, which need to be differentiated from the spontaneous panics distinctive to panic disorder. The physiologic distinctions between the two groups of laboratory panicogens, those with and without HPA activation, respectively parallel fearlike clinical anxiety and spontaneous panic.

The history of medicine amply demonstrates the value of the splitting diagnostic approach[187] as well as the dangers of hardening of the categories. An active experimental, therapeutic, and physiologic challenge approach to psychopathology may move us from symptoms to a grasp of deranged circuitry. Although genetic derangement may be necessary for many spontaneous panics, this does not mean that life events may not modify the suffocation alarm threshold. We speculate that separation anxiety, loss, and grief may lower this threshold in some, causing chronic anxious symptomatology as well as heightening panic vulnerability. These speculations need confirmation.

Inferring failure of a particular evolved adaptive system from stereotyped psychophysiologic, behavioral, and affective abnormalities has great heuristic potential. The suffocation alarm hypothesis stimulates investigations concerning the antecedents, correlates, exacerbators, and rectifiers of both suffocation and spontaneous panic under normal and pathologic circumstances.

Prospective psychobiologic studies of separation, divorce, grief, bereavement, abortion, birth, and adoption, in the context of challenge studies, family history, and therapeutic experimentation offer pointed investigatory opportunities.[188] Falsification and amplification of this hypothesis are possible.

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