Panic Disorder

An Evolutionary View

By RANDOLPH M. NESSE, MD

A complete explanation of any behavior pattern requires both a proximate and a separate evolutionary explanation.[1] A proximate explanation elucidates the psychophysiological mechanism that accounts for the behavior pattern. An evolutionary explanation elucidates the adaptive functions and selection history that account for the mechanism's existence and form. Proximate knowledge about the mechanisms that mediate panic is advancing so rapidly that it is hard to keep up. As the articles in this issue attest, we now know a great deal about the genetic, developmental, and psychosocial factors that contribute to panic susceptibility; the physiological correlates of panic; the role of cognitive and conditioning factors; and the efficacy of new pharmacological and psychological treatments. In contrast, evolutionary knowledge about the selective forces that shaped the capacity for panic remains relatively undeveloped. The recognition that both proximate and evolutionary explanations are necessary has led to rapid advances in ethology,[2] but is just now spreading to psychiatry and psychology.[3-5] We need to ask why people have the capacity for panic. Is it, like epilepsy, an uncoordinated expression of a physiological abnormality? Or is it an evolved defensive function, like the capacity for cough?

The capacity for panic requires both a proximate explanation and an evolutionary explanation.

EVOLUTIONARY PSYCHOBIOLOGY AND ANXIETY

Evolution cannot explain anxiety disorders directly, but it can explain the capacity for anxiety. Such explanations for normal functioning are the basis for explanations of pathology in the rest of medicine. For instance, immunologists use their knowledge of the selective forces that have shaped the immune system (diseases caused by parasites and microorganisms) as the basis for trying to unravel the proximate mechanisms responsible for autoimmune disease. Psychiatrists need to know the selective forces that have shaped normal anxiety to achieve a comparable understanding of the mechanisms responsible for panic disorder.

Anxiety is rarely welcome, but often useful. It is, like pain, cough, and nausea, an adaptive capacity that is aroused only when something is amiss. Because we know that such defensive capacities are useful,

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we try not to disrupt them unnecessarily. Thus, we hesitate before prescribing antitussives for cough caused by pneumonia or antiemetics for nausea caused by toxins in the stomach. Nonetheless, we try to relieve the symptoms caused by these defensive systems. When we can intervene by modifying the factors that arouse a defensive system, there is no dilemma; therapy simply assists a natural process. Often, however, we can intervene only by disrupting the defensive system, and we therefore must decide if the symptom is: 1) normal and useful, 2) normal but not useful in this situation, or 3) caused by a disorder of the defensive system itself. When the symptom is pain, cough, or nausea, it is relatively easy to see the adaptive function and to seek the cause in some threat that has aroused the defense. Only when all other explanations have failed do we consider the possibility that the symptom arises from a defect in brain mechanisms. When the symptom is anxiety, it is hard to specify exactly how it increases Darwinian fitness and, thus, easy to overlook threats that have aroused the defensive system. We, therefore, assume that the system must be defective. Our limited knowledge about the normal functions of anxiety becomes more apparent, and less acceptable, as we gain increasing power to disable parts of the anxiety system.

Anxiety contributes to fitness via its specific aspects. Anxiety:

- increases physical capacities by altering physiological states.
- motivates avoidance of situations that have been associated with danger.
- inhibits behaviors that will lead to danger, especially social danger.
- sharpens attention to cues of possible danger.
- induces planning based on past narrow escapes and future anticipated dangers.

These changes are not part of one undifferentiated pattern of arousal. Anxiety is the name we give to a group of related responses that are selectively deployed in response to different threats. Organisms that can distinguish different kinds of threats and respond to them with specific subtypes of defensive arousal have a selective advantage.[6] A wolf that encounters a hostile member of its own species will always become aroused, but whether it fights, flees, or submits will depend on the specific situation. The subtypes of human anxiety are specialized states of arousal that prepare us for coping with specific threats, much like specific software programs prepare a computer to deal effectively with specific tasks. Small dangerous animals induce simple phobias, social threats induce social anxiety, etc. Similarly, the specific behaviors associated with anxiety—flight, aggressive defense, immobility, and submission—are deployed selectively when they will be adaptive. The various kinds of anxiety are specialized states of arousal that have been shaped to give a selective advantage in the face of certain specific threats.

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If anxiety is so useful, why isn't it constantly present? It is, in fact, present to some degree most of the time. Complete, calm contentment is so sought after precisely because it is so elusive. There are, however, three additional reasons that natural selection would shape mechanisms that closely regulate states of defensive arousal. First, such states squander precious calories. Second, they decrease effectiveness in routine situations. Finally, there may be physiological states that offer benefits but that also damage tissues. Such states are worth their costs only when a regulatory system restricts their expression to extreme situations in which the benefits exceed the costs, ie, the stress system. Of great interest is the recent suggestion that the adrenal cortex may have evolved not to serve the stress response, but to protect the body from the effects of the stress response.[7]

THE FUNCTIONS OF PANIC

How has natural selection shaped the capacity for panic? There are three main possibilities. The first is that panic has not been shaped by natural selection at all. Panic could be a manifestation of an abnormality in some physiological system unrelated to anxiety. This seems unlikely. Normal people all seem to have the capacity for panic, and it is consistently elicited by exposure to extreme danger, as noted by the DSM-III in its instructions to exclude panic attacks that occur "in a life-threatening situation."[8] People are more susceptible to panic after experiencing dangerous life events that involve threat, but not after life events that involve loss.[9] The pattern of panic also includes extreme manifestations of ordinary anxiety, accompanied by specialized behaviors and physiological changes that facilitate quick escape. It seems improbable, to say the least, that panic is completely unrelated to normal anxiety and natural selection.

Two other possibilities are that: 1) panic is an abnormality that results only when anxiety regulation mechanisms fail, or 2) panic is a coordinated pattern of defensive response shaped by natural selection in response to specific dangers. A choice between these possibilities requires an assessment of the evidence that panic, as distinct from more general anxiety, has been shaped by natural selection. What specific selective forces would take more of a toll on an individual who

lacked the capacity for panic? There are clues in the situations that elicit panic; in the details of its physiological arousal; and in the perceptual, mental, and behavioral changes that accompany panic.

Walter Cannon, coined the enduring phrase "fight or flight" to describe a pattern of arousal essentially the same as panic.[10] He recognized the functional significance of each component and viewed the coordinated pattern of response as shaped specifically to facilitate flight or aggressive defense. Sweat is excreted to cool the body, blood clots more easily to prevent excessive loss from lacerations, blood is shunted to the large muscles to increase their strength and endurance, respiration increases in rate and depth to increase blood oxygenation and expel carbon dioxide, heart rate increases to circulate the blood faster, and metabolic changes occur that increase the availability of glucose. These patterns, the accompanying behavioral predispositions to flee and seek the proximity of relatives, and the characteristic mental activation and focus on threats and escape options, are exquisitely matched to the needs of an individual faced with immediate danger of attack.[5] They are components of a specialized state that increases the likelihood that a threatened individual will escape from mortal danger. Individuals without this capacity are at a substantial disadvantage. The pattern of panic suggests that it has been shaped by natural selection to enhance the ability to escape or fight when in immediate danger of attack.

PANIC DISORDER

The capacity for panic may be adaptive, but panic disorder is not. How is panic disorder related to normal panic? Panic disorder could be an: 1) adult manifestation of a defensive pattern that is adaptive only in childhood, 2) abnormality of a control mechanism that releases the panic response at inappropriate times, 3) abnormally low threshold in a panic mechanism that is otherwise normal, or 4) abnormal attribution of dire significance to anxiety symptoms so that they induce more anxiety that spirals, by positive feedback, into full-blown panic.

The pattern of agoraphobic fears offers further clues to the evolutionary functions of panic.

Klein emphasizes the similarities between panic anxiety and childhood separation anxiety. He hypothesizes that "the protest-despair mechanisms have co-evolved over our species' history to deal with the regular evolutionary contingency of the lost toddler. Conceivably the appearance of apparently spontaneous panic attacks or apparently spontaneous depressive episodes are the results of a pathologically lowered threshold for release of these distressing affective regulatory states."[11] This perspective rightly emphasizes the evolutionary functions of separation anxiety for toddlers, but neglects the possible functions of panic in adults. Panic in adulthood may use some of the same mechanisms that mediate childhood separation anxiety, even though it serves different functions. This explains possible correlations between behavioral inhibition in childhood and susceptibility to panic in adulthood,[12] without discrediting the possibility that panic can be useful for adults. Furthermore, the behaviors and kinds of arousal needed to protect against attack are similar in children and adults. There should, however, be certain differences. Adults experiencing panic should not cry in the same way that children do when separated; separated children should not tend to run wildly away from wherever they are, as adults do during panic. These predictions seem correct. Panic and separation anxiety are related, but not identical defensive patterns.

To the extent that panic is differentiated from general anxiety, it must have its own control mechanism. In some patients this mechanism seems to release panic without cause or warning, even during sleep. Although many patients describe the onset of panic at a time of life stress, in the moments before the first unexpected attack they may be perfectly calm. This pattern of onset implies either a defect in the switch that releases panic or the operation of unconscious forces unconnected with conscious emotion. Other patients report unease when alone in public that grows over days to weeks until it finally becomes a panic attack. Such patients may have a low panic threshold in a regulatory system that is otherwise normal. Most patients become sensitive to internal as well as external cues that have been repeatedly paired with panic. False feedback of increasing heart rate feedback induces anxiety and panic in many patients.[13] Behavioral exposure to panic cues and reattribution of symptoms to hyperventilation are treatments that substantially decrease panic and agoraphobia for a majority of patients.[14] These learning theory models provide valuable explanations for the maintenance of panic and the spread of avoidance, but they do not explain the initial origins of panic. An evolutionary view suggests that abnormalities of panic regulation and of cognitive response to panic symptoms are not mutually exclusive alternatives. It suggests further that we may eventually find subtypes of panic disorder that result from several different pathophysiological sequences.

THE PANIC-AGORAPHOBIA CONNECTION

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the agoraphobic are not random and do not develop according to simple laws of conditioning. Agoraphobics fear situations they cannot leave immediately. Lines in stores, the dentist's chair, small enclosed spaces, crowds, and riding in cars driven by others are especially common examples. Agoraphobics also fear wide-open places, such as beaches, arenas, and wide highways. It seems odd that they fear both closed and open places. But these situations—trapped alone in a small place or exposed on an open plain—are exactly those in which primates are most vulnerable to attack. Other factors that increase agoraphobic fear include being far from home, the absence of a trusted companion, and the presence of strangers. These cues are reliable indicators of situations in which Pleistocene humans were especially likely to encounter attack. Accumulating evidence suggests that threats from other humans may have been at least as great as threats from predators,[5] and that outside groups would pose a special threat.[15] A person wandering alone far from home who encounters strangers would indeed be in danger. In such situations, it would be advantageous for the panic mechanism to be adjusted to a hair-trigger. One wonders as well if women with young children might especially gain advantage from a low panic threshold and from ready development of agoraphobic fears.

Panic attacks do not occur completely at random. Most first attacks occur outside the home. Subsequent panic attacks tend to occur where they have occurred before. If a person has an attack while lifting a can of orange juice from the freezer at the grocery store, there will be a substantial likelihood of another attack occurring when the person returns to the same place, but little likelihood of attacks in response to cans of orange juice. A single panic attack is sufficient to condition such fear responses. If nonspecific learning mechanisms were responsible for these patterns, repeated trials would be necessary to establish the classically conditioned fear response and the orange juice could become a phobic cue. This one-trial learning and prepotency of locations as phobic cues are consistent with the hypothesis that agoraphobia motivates avoidances of, and arousal in, situations associated with danger of attack.

Panic disorder is strongly heritable, perhaps more so than any other common mental disorder.

Why does the experience of one panic attack make others more likely? Natural selection often shapes mechanisms that regulate systems to fit current conditions. For instance, repeated muscular exertion induces muscular hypertrophy and exposure to high altitude increases blood hemoglobin concentration. If a mechanism regulates the panic threshold depending on the degree of threat in the current environment, what cues would correlate with danger reliably enough that they could be used as input? If the best indicator of the dangerousness of the environment is the frequency of experience of intense danger, the repeated experience of intense unpredictable anxiety should decrease the panic threshold. Repeated exposure to real danger would do this, but so would the experience of unpredictable panic. Panic disorder patients develop fear of fear, but the experience of panic may itself lower the panic threshold. When panic attacks cease completely for a period of months, as occurs with medication treatment, the threshold should increase. The neurological phenomenon of kindling has been suggested to explain the same phenomenon[5] and could be part of the proximate mechanism that gives rise to this phenomenon.

GENETIC AND PHYSIOLOGICAL FACTORS

An evolutionary perspective on panic has implications for interpreting recent genetic and physiologic findings in panic. Panic disorder is strongly heritable, perhaps more so than any other common mental disorder,[16] and panic patients differ from normals on a variety of physiological variables.[17] Do these findings imply that panic disorder is a genetic disease with a specific brain defect? The answer depends on whether we view panic as inherently abnormal or as an adaptive response the expression of which is poorly regulated in panic disorder.

The genetic factors that increase susceptibility to panic disorder may represent specific defects, but, if the capacity for panic is normal, they may instead be akin to inherited differences in susceptibility to pain or nausea. No one would assume that an inherited low threshold for nausea or pain implied the presence of a genetic defect, but it is easy to make such assumptions about panic if its normal functions are not recognized. The panic threshold probably varies genetically, just as height does. Panic patients may just be at one end of the normal distribution. At the opposite end are those who lack the normal capacity for panic, a disorder that has not yet been studied. Accumulating evidence suggests that a proportion of individuals in a variety of species have an inherited tendency to be hyperreactive. Studies of monkeys,[18] shy human infants,[19] and the children of agoraphobics[20] all support this. In certain situations, such individuals may have an advantage. When we understand the origins and possible adaptive significance of this variation, we will understand panic disorder much better.

What about physiological differences between panic disorder

patients and normals?[19] They might be genetic markers for panic susceptibility, but it seems more likely that they are state markers associated with lowered panic threshold or that they are secondary effects of repeated panic. They may be normal effects of anxiety, unrelated to its proximate cause. Studies of neuroendocrine changes associated with anxiety[21,22] may well turn out to be analogous to studies of the gastrointestinal motility changes associated with nausea. An evolutionary view of panic suggests that a specific brain abnormality is likely to be found responsible for panic in only a few patients. In the next decade, studies of panic patients in remission and studies of nonsymptomatic kin of panic patients will begin to resolve these issues.

TREATMENT IMPLICATIONS

Patients who start having panic attacks often quickly conclude that they have severe organic illness. Extended medical examinations and tests tend to reinforce this fear, even though they are often ordered to provide reassurance. The symptoms of panic are thus feared more and more, until even small symptoms induce anxiety that spirals into panic.[23] The first step in treatment is to interrupt this cycle by providing a coherent explanation of panic disorder. This is not always easy to do. Some patients hear that panic disorder is caused by life stress or conflicts, others that it results from conditioning, others that it results from faulty habits of thought or breathing, and others that it is a genetic disease akin to diabetes. Patients quickly become confused by these apparently conflicting explanations, even though each may be correct on a given proximate level of organization.

Evolutionary psychobiology cannot yet offer a confident explanation of panic, but it can organize our knowledge in a coherent way. I explain to my patients that the ability to have a panic attack is useful when real life-threatening danger is present ("when a tiger is chasing you"). I then explain the symptoms of panic with reference to their adaptive functions. When the symptoms make sense and are viewed as potentially useful, the patient is more receptive to reassurance about the absence of organic disease and to exercises that demonstrate the role of hyperventilation in spiraling small fears into larger ones. When patients ask why they have attacks when there is no danger, I explain that some people are born with a tendency for this pattern to be triggered especially easily and that stressful life situations make panic attacks even more likely. The fear spreads especially easily to situations similar to the one in which the first attack occurred because it was once important for people to avoid places where they had actually been attacked ("the rock the tiger hid behind"). This gives the patient a rationale for psychotherapeutic work on current conflicts and for using medications to stop the panic attacks. It simultaneously provides a justification for exposure therapy to extinguish the fear response to specific situations. For some patients, an evolutionary based explanation of panic is sufficient to induce remission. For other patients, it provides a foundation from which they can understand and cooperate with eclectic treatment plans, and a framework from which their clinicians can organize and use diverse new research findings.

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