I was pleased to be offered the opportunity to contribute a chapter devoted to historical aspects of anxiety. However, my qualifications are clearly not those of a historian, who is properly concerned with documentation derived from primary data. Primary data consist of documents, records, notes, reports, data, clinical records, hospital charts, church dossiers, tax receipts, artifacts, etc, produced during the historical period in question. Skilled comparative evaluations yield relatively firm inferences, which nevertheless are often controversial and open to “revisionism.”

In psychiatry, much early theorizing derives from anecdotal case reports that often, as Freud noted, read like novelistic fiction. Unfortunately, that resemblance is more than superficial. Proper historical studies of primary data have shown that many reports were not only literally fiction in terms of clinical description, but also, more poignantly, in terms of clinical successes that apparently validated innovative therapeutic techniques and novel, insightful theories. Of particular note are the hospital records of Anna O., Freud’s actual clinical notes on the “Rat Man,” and the Freud–Fliess correspondence. These primary sources stand in stark contradiction to published reports. Further skepticism is warranted by the problematic evidence for “allegiance effects,” where an investigator’s investments closely parallel their findings. Therefore, critical skepticism is necessary.

My understanding of historical developments derives from two sources—personal experiences and studies—amplified by reading papers and summary accounts at some remove from primary data. This requires an informal essay rather than a detailed footnoted and referenced thesis. Therefore, these historical notes on anxiety are quite personal, emphasizing influences that affected my understanding of that important, ambiguous term. Hopefully, some inferences are justified.
Anxiety

The term “anxiety” is part of common language, referring to common experience, but also refers to pathological states that bear a confusing resemblance to fear and depression (which are also ill-defined lay terms). A chronological history of the development of ideas about anxiety may give a false impression of continuous cumulative development. As I understand it, different approaches achieved attention in almost direct proportion to the claims of therapeutic efficacy, especially when enhanced by a persuasive explanatory theoretical framework that fits cultural expectations. Rather than cumulative clarification, there is a series of zigzags in perspective.

Descriptions of fear and anxiety were common in classical literature, so that the passions received mythological expressions. The moons of Mars refer appropriately to his sons, the offspring of war, Phobos (fear) and Deimos (flight).

Evolution

The modern era dawned with Darwin, whose exposition of biological evolution through natural selection has recently come to the fore in psychiatric thinking. Darwin’s conclusion that emotions were adaptive evolutionary products had been obscured by Freud’s Lamarckism, his emphasis on drive and defenses, and his treatment of emotions as epiphenomena.

Since evolutionary theory is more directly informative about function, rather than dysfunction, recent evolutionary theorizing often asserts that many behaviors that are viewed as pathological, eg, mania, psychopathy, agoraphobia, etc, are actually evolved behaviors appropriate to our neolithic ancestors, but discordant with modern times. This viewpoint discounts the starkly minority status of these illnesses, their periodicity, the evidence of brain damage, their response to medication, etc. Such glib formulations obscure the real value of an evolutionary framework for hypothesizing the existence of covert functions that may become impaired, thus producing the syndromes associated with disease.

Cannon

Chronologically, Kraepelin, Pavlov, and Freud should now be in focus, but the direct intellectual descendant of Darwin was in fact Walter Cannon who in 1919 highlighted the emergency adaptive functions of anger and fear in terms of facilitating fight and flight. In strikingly modern terms, he referred to the thalamus as a discrete brain module that provided the integrative connection to the cortex and the sympathoadrenal system, and was therefore the primary instigator of emotional, visceral, and autonomic responses. A narrow focus on adrenergic mechanisms, as the exclusive generator of emergency responses, reemerged recently in attempts to link pathological anxiety to an impaired brain adrenergic system.

Pavlov

Pavlov, who considered himself a physiologist, made the pioneering conditioning observations. Attempts to develop animal models of “neurosis” were initiated when he found that presenting his restrictively harnessed dogs with progressively more difficult discriminations between excitatory and inhibitory conditional stimuli led to frantic agitation (or sometimes sleep). Pavlov also noted the importance of trauma, when a fortuitous kennel flood caused his carefully trained dogs to develop disruptive “neurotic” behaviors. Many drew the conclusion from Pavlov’s work that neuroses were learned, since purely experiential procedures caused them. (Pavlov’s emphasis on constitutional variation was ignored.)

Learning theory

Behavioral studies led to learning theory, which maintains that anxiety is the conditionable part of fear, serving as a secondary drive. This model, as formulated by Mowrer, seems both simple and powerful. An unconditioned stimulus (US), such as shock, causes unconditioned responses (URs), eg, fear, which leads to escape behavior. Decreases in fear, produced by successful escape, reinforce escape behavior.
Stimuli that regularly precede the US become conditioned stimuli (CSs), which serve as signals of the oncoming US/UR, and release a conditioned response (CR) anxiety, which then becomes a secondary drive inciting avoidant behavior. Successful US avoidance reduces anxiety and thereby reinforces avoidant behavior. Phobic behavior, then, is a learned avoidance maintained by decreases in anxiety. This formulation is still common among learning theorists and behavior therapists. Certain features of phobias are difficult to reconcile with such a model. What is the US (the shock)? Most phobias do not start with a traumatic incident. Second, why is the range of phobic objects and situations limited? Seligman pointed out that phobias of electric plugs or automobiles should be remarkably common, because many experience shocks from plugs and have to dodge cars, but in fact, such phobias do not exist. The range of phobic objects is limited, often to phylogenetically significant sources of danger. Classic learning theory, however, has no place for especially efficacious evolved CSs. Currently, there is debate on whether such stimuli (e.g., heights) directly engender fear or facilitate conditioning. Further, from a simple conditioning viewpoint, patients should learn to avoid stimuli that occur regularly before anxiety onset, but this is not usual. Patients often avoid situations in which they would feel helpless if panic or the phobic stimulus occurred, even if they never experienced panic there, e.g., tunnels or bridges. Situations, such as high grass, where snakes or insects might surprisingly appear, are shunned by these specific phobics, even if this experience has never occurred. Unmodified learning theory is insufficient as a theory of anxiety, since it does not explain how phobias start, i.e., the nature of the US, does not account for the limited variety of phobic stimuli, and gives the wrong predictors for the spread of avoidances. It is consonant only with the therapeutic efficacy of certain deconditioning procedures, but useless in explaining the equivalent effectiveness of alternative procedures that appear to work against deconditioning.

The equation of such animal behaviors with human neurosis raised many hackles regarding anthropomorphism and oversimplification. However, animal models are used in a thriving industry to (occasionally) discover humanly useful antianxiety agents. Many different procedures have been developed that nominally induce anxious anticipation and behavioral defenses against differing dangers. Remarkably, the intercorrelation of the effects of differing procedures is usually almost zero. This questions the presumption that “anxiety” univocally refers to a single adaptive function.

If neurosis is learned, why is it not spontaneously unlearned or extinguished? CRs extinguish when CSs fail to predict USs. This became known as the “neurotic paradox” and received many explanations. Paradoxically, behavioral learning theory, which eschewed mentalistic causal variables, in its current “modern” explanatory mode embraces predispositions such as anxiety sensitivity or catastrophizing tendencies. The historical controversy, typified by Hull and Tolman, is swept away by the ecumenical term “cognitive-behavioral.” Further, contextual and enteroceptive CSs are freely invoked as modern “explanations” of anxiety disorders without demonstration of their existence, causal relevance, or predictive validation.

The other branch of conditioning theory, operant learning theory, appears relevant to specific phobic avoidance. If a signal regularly precedes an electric shock delivered through a particular patch of floor grid, then after thrashing about a dog could learn, that if, when signaled, they left that patch they would not be shocked. This avoidance response would not extinguish even if the electricity were turned off since the avoiding animal could not learn that the CS no longer signified real danger. However, was this a model for chronic anxiety? Manifest emotionality ceased after the avoidance response was learned. However, if the dog was confined to the patch after the CS, emotional escape efforts occurred. These eventually ceased given repeated experiences that the CS no longer predicted shock. This supposedly laid the theoretical groundwork for effective exposure therapy for simple phobia, although it was already conventional grandmotherly wisdom that if one fell, then immediately getting back on the docile horse prevented the development of anxiety and riding avoidance.

Kraepelin

In a more directly relevant clinical tradition, Kraepelin closely, longitudinally, observed patients. Although Kraepelin was primarily concerned with psychotic inpatients, he described spontaneous panic attacks accompanied by fears of dying in his lecture *Irrepressible ideas and irresistible fears* about a patient who developed severe agoraphobia and somatic preoccupation. He advocated exposure therapy, however, with pessimistic
expectations and cautioned against lengthy hospitalizations. Kraepelin also described both circumscribed and generalized social phobia noting that patients experienced “overpowering feelings of aversion [...] when they had to establish relations of any kind with other patients,” whereas other individuals, who appeared otherwise healthy, were “unable to urinate or write a letter in the presence of other people.”

In the 6th edition of his textbook, he classified aspects of most contemporary anxiety disorders describing generalized anxiety (pervasive apprehensiveness and worry), obsessions (intrusive fears of contamination), compulsions (hoarding), the link between anxiety provoking obsessions and anxiety-reducing compulsive behaviors, phobias (fears of insects), agoraphobia, specific social phobia, and generalized social phobia. These references to anxiety states have been generally ignored since his excellent syndromal descriptions and prognoses were denounced as fatalistic, and thoroughly obscured (at least in the United States) by the rise of psychoanalysis in the late 1940s. Superficial descriptive diagnosis was to be replaced by therapeutically relevant dynamic understanding of unconscious depths.

Freud’s initial theory of anxiety was that accumulating libido, undischarged because of an unsatisfactory sexual life, as with abstinence or coitus interruptus, sufficed to cause an “actual” neurosis. Therefore, simple changes in sexual practices could cure anxiety. Freud’s original descriptions emphasized anxiety attacks. Freud then theorized that, in psychoneurosis, libido and aggressive drives were chronically undischarged because of persistent repression. The implicit assumption was that chronic anxiety, due to chronic repression, was the expectable symptom. Attacks were the occasional quantitative extreme with no particular significance. Simply advising patients about appropriate sexual hygiene was ineffective because it did not deal with the repressing forces.

Freud finally postulated a schema functionally identical with learning theory. Rising instinctual impulses, if ungratified, flood the infant with traumatic excitation equivalent to a US. The infant learns that certain situations, eg, the mother’s absence, regularly precede a painful lack of gratification. Therefore, the mother’s absence becomes a CS that releases anxiety, thus explaining separation anxiety. Signal anxiety develops in situations regularly associated with forthcoming traumatic excitation, thus exactly paralleling conditioned anxiety. In learning theory, the conditioned drive of anxiety leads to escape behavior. This also has a parallel in Freudian theory, but the escape from internal excitation is into defense mechanisms. Rising libidinal and/or aggressive impulses press for discharge, ie, action, but are met with threats of parental punishment (eg, castration), which are especially effective due to the race’s past history. The threat of punishment leads to “objective anxiety,” which seems definitionally indistinguishable from fear.

The increasing drives, the regular antecedents of punishment threats, become enteroreceptive CSs that release signal anxiety. Escape results when signal anxiety mobilizes the overwhelming power of the pleasure principle that enforces drive repression, produces a fall in anxiety, thereby reinforcing repression. From repression causing anxiety, Freud moved to anxiety causing repression. This theory received wide acceptance on the basis of supposed clinical benefits, although data supporting the existence of either benefits or repressive mechanisms was slim. However, relieving sexual repression seemed a good idea to many, which facilitated Freud’s blanket acceptance by them, but incited demonization by contrary ideologies.

Imipramine: panics and agoraphobia

While working in a long-term psychoanalytic hospital, my initial interest in panic attacks came in 1959 with the serendipitous observation that imipramine blocked spontaneous panics (manifested by desperate appeals for help) in patients in whom long-term intensive psychoanalytic psychotherapy had failed. Chlorpromazine (considered then our most potent anxiolytic) actually exacerbated their symptoms. Controlled studies supported this observation. These patients would now be diagnosed as having panic disorder (PD) with agoraphobia. Our model for the development of agoraphobia with panic attacks suggested that the initiating clinical event is the sudden appearance of spontaneous panics, abrupt crescendos of intense distress, and fearful apprehensions. Spontaneous means that there is no environmental danger sufficient to cause sudden extreme fear. Further, at illness onset, there are no specific phobic stimuli.
The spontaneous panic immediately leads to an outburst of appeals and attempts to get help, eg, telephone calls, precipitous emergency room visits, etc. After the initial attack, the patient may temporarily feel well, but after recurrent panics, enduring apprehension, chronic tension, and autonomic distress develop. The chronic distress fluctuates, but lacks the dramatic panic crescendo. Interpanic chronic anxiety probably has several components. Concern about panic recurrences causes chronic anticipatory anxiety, which is explicable by the uncertainty, insecurity, and helplessness engendered by unpredictable attacks. However, patients also report good days and bad days. On awakening, they may correctly realize that this will be a bad day in which panics are likely to occur. Conversely, they may feel fairly well and unlikely to panic, although not immune. This waxing and waning of interpanic anxiety cannot be entirely explained on the basis of learned, anticipatory fears. During imipramine treatment, there is a regular progression of antipanic effects. After several weeks, patients no longer have spontaneous full-blown panics. However, they often feel as if a panic is starting and helplessly observe their increasing distress, which suddenly, surprisingly, stops and does not peak into terror. (This experience is inconsistent with the theory that panic is simply a catastrophic overreaction to autonomic fluctuations.) Many recollect having such limited symptom attacks such as these between panics when not on medication. In Freud’s early lucid description of the agoraphobic process, he refers to “larval” anxiety attacks, which probably contribute to interpanic chronic anxiety. A third component of interpanic chronic anxiety may be sensitization, which occurs following repeated unexpected traumas, ie, panics. The sensitized organism overreacts to both conditioned and neutral stimuli, resulting in maintained tension. (In Aphysia, sensitization is due to presynaptic facilitation of neurotransmitter release by sensory neurons and structural changes that facilitate this functional increment.)

Some equate the interpanic anxiety with the anxiety of generalized anxiety disorder (GAD). Further, since imipramine benefits GAD, this is held by some to obviate the distinction between anxiety and panic in PD. This notion is incorrect on several counts. In PD, imipramine benefits acute somatic distress, particularly dyspnea, whereas low-potency benzodiazepines ameliorate anticipatory anxiety. In GAD, the reverse is true. Imipramine and selective serotonin reuptake inhibitors (SSRIs) benefit worrisomeness, whereas benzodiazepines relieve somatic distress, ie, muscular tension rather than autonomic distress.

Further, within PD, imipramine benefits panic associated with acute dyspnea (which is not a feature of acute danger–incited fear or GAD) more than alprazolam. Conversely, alprazolam is superior to imipramine in panics limited to palpitations, sweating, and tremor—the cardinal features of danger-incited fear. This issue is an example of confusing useful pharmacological dissection with superficially observed pharmacological amalgamation.

Once chronic interpanic anxiety develops, the patient often comes to believe that certain situations elicit panic, although, inexplicably, sometimes they do not. Patients also conclude that they are more prone to panic when alone or away from home. Therefore, they constrict traveling and demand companionship, believing that this decreases panic likelihood. They primarily avoid situations where they could not easily get help if panic strikes. Illness course is quite variable. Some develop panic attacks, but do not go on to marked chronic interpanic anxiety. This course would be unexpected if conditioning sufficed for chronic interpanic anxiety. Some slowly develop an increasing range of avoidances, whereas others precipitously plunge into a housebound state. The initial phase is dominated by apprehension of recurrent unpredictable panics. However, by the time the patient receives psychiatric attention, they focus on their constricted life, multiple avoidances, chronic anxiety, and high level of friction with family members drafted as guardians. Patients often believe that panics decrease in frequency, attributing this to phobic avoidances. This “post hoc” attribution is only partly true since exposure therapy does not cause any substantial increase in panics, although it may exacerbate anticipatory anxiety. It is not clear if spontaneous panics usually decrease in frequency over time, although this is frequently reported. Imipramine’s primary pharmacological effects are directly antipanic, requiring less than 6 weeks to take maximum effect, given adequate dosage. The spontaneous panic is blocked, first in its stark manifestation as a groundless crescendo of terror, and then in its larval form. We do not believe that there is any immediate pharmacological effect of imipramine upon either anticipatory anxiety or avoidant behavior. However, the antipanic effect allows patients to continue to expose themselves to avoided situations without set-back by
occasional panic. This provides the setting for increasing, indirect, nonpharmacological benefits on anticipatory anxiety and avoidance. On exposure, some become non-phobic despite continued panics, as if they become stoically convinced that panics are transient and more upsetting than dangerous.

Challenges

When it was discovered that lactate infusions, under controlled, double-blind circumstances, regularly precipitated panic in patients prone to panic, but not in normal subjects, an instant argument started. Was the lactate doing anything biochemically or physiologically specific or was it simply a stress reminding only the patients of past panics, therefore throwing only them into a panic? In rebuttal, Pitts demonstrated that infusion of EDTA, a powerful calcium-chelating substance, actually threw patients into tetany, but nonetheless did not produce panic. This lactate specificity has been amply documented because such noxious agents as physostigmine, insulin, 5-hydroxytryptamine, etc, also fail to precipitate panic attacks. Nonetheless, the conviction that the spontaneous panic attack was misplaced fear persisted, protecting the basis of several psychogenic theories.

The discovery that antidepressants that blocked the clinical panic attack also blocked lactate-induced (and later CO₂-induced) panic attacks made it seem likely that these laboratory-induced panics closely modeled the real clinical experience. This was supported by the inefficacy of lactate in producing panics in other anxiety disorders.³

Also, counterintuitively, lactate-induced panic, and later CO₂-induced panic, did not result in fear-like stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. Adrenocorticotropic hormone (ACTH), cortisol, and catecholamines, as well as 3-methoxy-4-hydroxyphenylglycol (MHPG), stayed flat or decreased during the attack. Further, cannulating ambulatory patients demonstrated that spontaneous clinical panic did not cause cortisol increases.

Another peculiar aspect of spontaneous clinical panic, especially those that led to marked anticipatory anxiety and eventually to agoraphobia, was the salience of dyspnea (air hunger) as an attack symptom. This was usually attributed to hyperventilation because patients often seem to hyperventilate during panic. In fact, many attributed panic attacks to acute hyperventilation and respiratory alkalosis. However, to our surprise, we found that directed voluntary hyperventilation did not regularly cause panic attacks in either patients or normal subjects, nor did it cause air hunger nor did it relate to respiratory alkalosis. Furthermore, studies indicate that palpitations, sweating, and trembling are features of fear during mortal danger, but dyspnea is not.

Suffocation false alarm theory

Increases in brain lactate and plasma CO₂ indicate impending suffocation. Combined with panic-induced hyperventilation and acute dyspnea, this suggested that the spontaneous panic attack may be a suffocation false alarm. That is, there is an evolved specific suffocation alarm system that, when pathologically disturbed, is triggered by minor physiological signals of impending suffocation, such as a rising blood CO₂ level or an increasing brain lactate level.

This is supported by much consonant evidence.³ Briggs et al⁴ used factor and cluster analysis to distinguish patients with dyspneic panic attacks, who responded better to imipramine than alprazolam. The patients with nondyspneic panic attacks responded better to alprazolam than imipramine.

A major incongruity with “panic equals fear” theorizing is the transience of the attack. Fear does not stop until the danger has gone. The spontaneous panic attack usually terminates after 4 minutes of marked distress. Perhaps this is due to acute hyperventilation adaptively dropping the blood CO₂ level while raising oxygenation, thus assuring the suffocation monitor that suffocation is not impending, which terminates the alarm. This is in keeping with the frequent finding of chronic hyperventilation and hypocapnia due to frequent sighing in panic patients.

That the HPA system is inhibited during panic may be because HPA release causes a precipitous rise in metabolic oxidation, which would be counterproductive under asphyxiating circumstances.

Further, Perna et al⁶ found that subjects with a history of unexpected panic attacks had a high rate of family history of PD, and that first-degree asymptomatic relatives of PD patients had a much higher rate of CO₂ sensitivity than normal subjects.⁶ Further, Perna et al⁶ showed that the PD probands with CO₂ hypersensitivity accounted for most of the familial loading. CO₂ hypersensitivity may be due to a particular genetic dysfunction among the multiple phenotypes called PD. It may cut across current syndromal boundaries.
The relevance of respiratory CO₂ sensitivity to the genetics of PD receives remarkable confirmation by Bellodi et al., who amplify the classic diagnostic concordance study of identical and fraternal twins by administering CO₂ challenges. With regard to PD, probandwise concordance rates were higher for monozygotic pairs (6 out of 9, 67%) than for dizygotic pairs (neither out of 2, 0%). For spontaneous panic attacks, the respective rates were 71% and 18%. For CO₂-induced panic attacks, the respective rates were 56% and 13%. These marked differences, if replicated in larger samples, indicate that the genetic relationship is not simply additive, but may be the emergent outcome of genetic interactions. Such complex genetics make attempts to link disease to single DNA regions even more problematic.

The search for cerebral markers is of great interest, but, lacking a detailed theory of how psychopathology relates to cerebral dysfunction, we must recognize that this is useful and exploratory, rather than definitive, work. Unfortunately, the history of biological psychiatry is replete with reports of baseline differences between patients and normal subjects that turn out to be artifacts, since these are not randomized, experimental studies, but naturalistic, multiply confounded studies. The differences between patients and normal comparison subjects that have stood up best have been due to challenge studies, eg, lactate infusion, sedation threshold, CO₂ inhalation. Many psychopathologies may be due to adaptive deficiencies in cybernetic control mechanisms, best revealed by perturbing the system rather than simply observing it at rest. Combining challenges with genetic studies may prove a useful strategy in dealing with the multiple phenocopy problem.

**Congenital central hypoventilation syndrome**

The discovery that children with congenital central hypoventilation syndrome (CCHS), who die from sleep apnea unless artificially ventilated, lack respiratory or affective response to CO₂ inhalation, makes it clear that the suffocation alarm system actually exists. I speculate that the benefits of serotonergic antidepressants are due to downregulation of this hypersensitive system. That children with CCHS, who have hardly any suffocation alarm system at all, should have their breathing inhibited by imipramine counterintuitively verifies that theory. Further, that these mortally endangered children, protected by anxious parents and fallible technology, should not be anxious, directly contradicts modeling and conditioning theories of anxiety. CCHS is rather like PD inside out.

Other findings support this theory, in particular, the frequency of PD in respiratory disease. Other findings suggest heterogeneity of the panic syndrome. In particular, the relationship to gastrointestinal disease, vestibular disorder, and premenstrual syndrome indicates that substantial extensions are in order.

The marked parallelism between Freudian and learning theory is due to their common emphasis on contiguity conditioning, which leads to anxiety as a signal of anticipated traumatic states. Neither theory distinguishes between panic attacks and chronic anticipatory anxiety, therefore, neither is consonant with the specific benefit of antidepressants on PDs.

**Separation anxiety**

Patients with agoraphobia often show clinging, dependent behavior and intolerance of being alone. The histories of severely impaired agoraphobic inpatients indicated that 50% recalled distinct separation anxiety disorder. Moreover, initial panic episodes were often preceded by significant personal losses, which perhaps indicated that some special early predilection for separation anxiety might be later manifested as agoraphobia. The initial Freudian theory of separation was not much help because it was simply another form of contiguity conditioning. Separation anxiety required recognition of the mother as a distinct object, the discrimination of her presence versus her absence, and the association of states of mounting tension with her absence. Freudian theory offered no basis for postulating a distinctive drug effect on separation anxiety any more than on any other anxiety.

Freud’s description of object choice could also be phrased in conditioning parlance. The US was oral gratification; the UR was pleasurable drive reduction. The CS was mother’s presence preceding the oral gratification (UR). Eventually, the mother (CS) released hopeful contentment (CR): the conditionable component of tension decrease. Therefore, the infant attached to the mother as a need gratifier.

It struck me that perhaps early separation anxiety was not like anticipatory anxiety, but due to an evolutionarily distinct process. Similarly, a learning theory of attachment via reinforcement seemed dubious. Bowlby also...
argued that the child’s tie to the mother did not depend on learning that she was a need gratifier but antedated such learning, thus resembling the ethological notion of imprinting. Furthermore, separation anxiety did not depend on learning that the mother’s absence was associated with distress, but was an evolved innate protest mechanism, instinctively released by separation during the appropriate helpless developmental phase. Distress after separation from nest or mother occurs in infant animals who could not yet have learned that separation means failure to gain relief from instinctual tension. The early lost piping of chicks separated from their nests and whining of puppies separated from the mother are clear examples. Separation anxiety occurs when infant monkeys raised in peer groups are separated from each other, although mothering does not exist in such groups. Harlow’s experimental work demonstrated that the developmentally isolated monkey attached to the contact comfort of a terry cloth model rather than to a wire feeder. Oral gratification was not the basis for object attachment. Naturalistic observation could never have produced this trenchant conclusion.

Separation anxiety, to the degree that it is learned, builds on an innate adaptive mechanism that causes an alarm, intense psychic distress, under conditions of naive separation. The evolutionary “purpose” is to cause the vulnerable infant to emit anguished signals that elicit maternal retrieval. Obviously, the helplessly dependent lost infant is fair game for predators. Even in the absence of predators, if the mother cannot find the infant, a dehydrated, weakened infant results. If hunger pain was necessary before emitting distress cries, many infants would die or be impaired. Evolutionarily, a built-in (unlearned) early warning alarm system for maternal recall makes good sense. It is better to cry before being actually hurt. Any biological control mechanism has a wide range of variations in strength and threshold. Perhaps some children have constitutional, familial, or pathogenic vulnerabilities. If antidepressants specifically raise this alarm threshold, panic is prevented, but no immediate effect on anticipatory anxiety should occur. It is striking that the only drugs that have this specific antipanic action are certain antidepressants (and morphine). High-potency benzodiazepines affect both processes. In a detailed longitudinal study of over 1000 children between ages 3 and 18, Poulton et al9 found self-reported separation anxiety largely, but not entirely, independent of experience. Before age 11, separation anxiety was only independently correlated with mothers’ “fear of going out alone,” which can be interpreted from either modeling or genetic viewpoints. However, the amount of variance accounted for was only 2.5%.

Initially, I speculated that all antidepressants would ameliorate both separation anxiety and spontaneous panic. This generalization was faulty, since we already knew that electroconvulsive therapy (ECT) did not ameliorate panic. Later work with bupropion and maprotiline demonstrated that some pharmacological antidepressants failed as antipanic agents. However, the benefit of imipramine did generalize to the other tricyclic antidepressants, as well as the SSRIs and monoamine oxidase inhibitors (MAOIs).

Theories of separation anxiety had important effects on treatment. Anna Freud considered school phobia a true psychoneurosis caused by repressed hostility toward the mother, rather than an upwelling of separation anxiety. The child magically believes unconscious hostility takes effect. To reassure him- or herself that this is untrue, the child insists on mother’s presence. Therefore, the proper treatment is play analysis to express and relieve unconscious hostility, without concern for return to school, since school refusal is only a symptom. Eisenberg observed that such children often never get back to school. He reconceptualized school phobia as resulting from maternal anxiety over the child’s individuation. This was communicated to the child making him secondarily anxious. Therefore, proper treatment was putting the mother into psychotherapy and insisting on the child’s immediate return to school. The psychotherapist made sure that the mother did not sabotage this return. This proved effective in approximately 75%. However, the other 25% proved refractory. We demonstrated, in a pilot study and then in a double-blind, placebo-controlled study, that children with such refractory school phobia responded to imipramine.

**Endogenous opioids**

The important works of Panksepp, Suomi, and Kalin show that separation anxiety is controlled by an endogenous opioid system. It can be specifically ameliorated by morphine (and imipramine) and exacerbated by naloxone, the opioid receptor blocker. It seemed too great a coincidence that endogenous opioids controlled both separation anxiety and respiratory...
driving by CO\textsubscript{2}. That an endogenous opioidergic dysfunc-
tion may underlie both the proneness to separation anxiety and to suf-
focation false alarms was proposed. This received recent preliminary experimental support from pilot work showing that normal subjects, usually unresponsive to intravenous lactate, develop acute dys-
pnea, distress, and hyperventilation when intravenous lactate is preceded by naloxone.

**Conclusion**

This incomplete, highly personal, historical note pro-
vokes the following generalization: our folk terms for
emotional distress are far too broad. Over evolutionary
time, organisms were faced by many recurrent natural
and social dangers. Natural selection fostered the develop-
ment of a complicated webwork of monitors, alarm
reactions, and specific physiological facilitators of many
distinct behavioral adaptations. We have not discussed
social anxiety disorder, which may have childhood
behavioral inhibition as an antecedent. Peculiarly, it
responds to MAOIs, but not to tricyclic antidepressants,
indicating a distinct physiological regulation and impair-
ment. The development of an alarm system, keyed to
social disapproval, would seem advantageous to a highly
social species. Judith Rapoport has suggested that cleaning
compulsions may be incited by a hypersensitive
release of grooming and self-cleaning monitors.

All-purpose learning mechanisms are primarily attuned
to nonemergency situations, where both repetitive drill
and cognitive insights enhance skills that have not been evolutionarily honed. Appetitive, flexible, goal-seeking,
nonemergency activities are the best context for such
learning. States of maladaptive, chronic distress are not
learned, but reflect malfunctioning alarms. Learning can
develop compensatory devices, eg, stoicism to mitigate
malfunctions, in a goal-seeking context.

Recent studies indicating the responsiveness of panic
attacks (in largely nonagoraphobic patients) to cogni-
tive-behavioral therapy (CBT) are of interest, but do not
validate conditioning theory. If anything, their results
contradict it, since antipanic effects occur far too rapidly
for either enteroreceptive deconditioning or decatastro-
phizing of chronic attitudes to occur, nor has this ther-
apeutic sequence been demonstrated. Adequate compa-
orative trials with non-CBT therapies have had
inconsistent differential benefits. Follow-up indicates a
waxing and waning of symptomatology, which does not
follow from CBT theory. Perhaps a therapeutic response
of separation anxiety to a strong persuasive ally provides
an alternative explanation for antipanic benefit. This has
not been investigated.

Only collaboratively conducted, expert, controlled exper-
imental approaches will enable the identification of covert
adaptive systems and their dysfunctions. Objective mea-
urements and analyses by collaborators with differing
views are required to obviate self-serving reports domi-
nated by allegiance effects.

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| Aspectos históricos de la ansiedad | Aspects historiques de l’anxiété |
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| “Ansiedad” es un término clave para observaciones y teorías conductuales, psicoanalíticas, neuroendocrinas y psicofarmacológicas. Resulta difícil hacer una revisión relacionado con los aspectos históricos, ya que la historia es básicamente un estudio de los datos originales. Desafortunadamente numerosas anécdotas clínicas no corresponden con registros los objetivos iniciales. Incluso reportes de estudios objetivos pueden sufrir los efectos de la lealtad. Por lo tanto este ensayo refleja primariamente el impacto personal del trabajo de otros comparado con el trasfondo de mi experiencia clínica y científica. Todo esta lleva a poner en duda de que la “ansiedad”, tal como existe en los trastornos sin- dromáticos, sea simplemente el extremo cuantitativo de la “ansiedad” normal que ocurre durante la anticipación del peligro. Se presenta una visión alternativa que enfatiza alteraciones de diferentes sistemas de alarma adaptativos y evolucionados. | L’“anxiété” est un terme-clé pour les théories et les observations comportementales, psychoanalytiques, neuroendocrines et psychopharmacologiques. Faire un commentaire sur son aspect historique est difficile, puisque l’histoire se fonde, à proprement parler, sur l’étude des données premières. Malheureusement, beaucoup d’anecdotes cliniques ne correspondent pas au rapport des faits survenus il y a longtemps. Même les comptes rendus d’études objectives peuvent souffrir d’effets d’allégeance. Le présent article est donc principalement le reflet de l’impact personnel du travail d’autres sur toile de fond de mes expériences cliniques et scientifiques. Cela me conduit à m’interroger sur l’hypothèse selon laquelle l’“anxiété”, telle qu’elle existe dans les troubles syndromiques, est simplement l’extrême manifestation quantitative de l’“anxiété” normale qui apparaît lors de l’anticipation face au danger. Une autre thèse est présentée, qui souligne les dysfonctionnements de systèmes d’alarme adaptatifs ayant évolué de façon spécifique. |