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The parable of panic: suffocation, social attachment, and the critical role of an integrative, biopsychosocial formulation.

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Anthony recalls it coming out of nowhere. A cold, clammy wave spread from his head all the way down his body. His heart, as if it was hooked up to an internal amplifier, began beating louder and faster than ever before. Then the air hunger hit: the more he tried to breathe, the worse the feeling became. Surely, he was going to die.

But he didn't. Within ten minutes, everything slowly returned to normal.

At first, Anthony figured the whole thing was a fluke and tried to write it off. Then, a week later, it happened again. And then again two days after that. His family doctor and even a cardiologist assured him that he was fine – but this did little to quell his visceral fear that something was deeply wrong. He became increasingly anxious and tense all the time: what if he had another episode – what would he do? Desperate to prevent another attack, he began avoiding situations that could leave him helpless or without escape. Being alone felt unsafe. Being in crowded areas felt unsafe. Even the thought of leaving his home left Anthony in a conflicted paralysis.

If Anthony presented for psychiatric treatment today, the case would seem almost trivial: he would be diagnosed with Panic Disorder with Agoraphobia. Following standard treatment guidelines, he would likely do well and have a good chance of returning to pre-morbid functioning.

But in 1960, things were different. Panic disorder had yet to be recognized as a distinct diagnosis (lumped instead under the broad category of "Anxiety Neuroses"). Chlorpromazine, one of the only psychiatric medications available, offered little benefit. Neither did the primary psychotherapeutic techniques of the time (largely psychoanalysis). Without effective treatment, patients like Anthony were often hospitalized for prolonged periods of time.

Yet as dark as this portrayal may seem, 1960 was also the dawning of a new era in the field. On the heels of chlorpromazine, a handful of new drugs had just been introduced and a generation of researchers were eager to explore their potential.

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Enter Donald Klein, a psychiatrist and early psychopharmacological researcher with a particular interest in patients like Anthony. Like many of his colleagues, Klein was intrigued by the recently released antidepressant, imipramine. Despite its efficacy in treating depression, there were no data to suggest it might work for anxiety. But figuring that he had nothing to lose, Klein began administering imipramine to his inpatients with agoraphobia. At first, it seemed to be a bust. Neither the patients nor the hospital staff noticed any difference. But eventually a change occurred, seemingly without the patients realizing it. They still reported high overall levels of anxiety and refused to leave the hospital grounds. But the actual episodes of panic were much less frequent and, sometimes, they ceased altogether (1).

The observation that imipramine was effective at reducing panic (while seeming to do less for anticipatory anxiety) suggested that panic might have a unique neurobiology. One of the first key findings in support of this idea was that patients with panic disorder demonstrated a heightened sensitivity to carbon dioxide (CO2). Inhalation of 5% CO2 induced panic attacks in this patient group but not controls. These findings prompted Klein to propose the False Suffocation Alarm hypothesis – essentially, that a panic attack reflects the primitive response to suffocation that is either aberrantly triggered or can be triggered by actual increases in CO2 concentration. (This latter idea explains why panic can be seen in patients with asthma, chronic obstructive pulmonary disease, or in the context of weaning off of ventilators (2), a process that appears to be mediated by activation of the dorsal periaqueductal gray (3).)

But Klein intuitively understood that there was more to the story than just biology. As tidy as the False Suffocation Alarm hypothesis was, it failed to integrate key psychological and social elements. Some 50% of patients showed evidence of separation anxiety in childhood occurring well before the onset of their panic attacks. Furthermore, the initial panic episode was often preceded by significant loss (4). To Klein, this suggested that psychosocial factors may still play a critical role.

In order to explain these observations, Klein turned away from the prevailing psychoanalytic theories of anxiety and towards a new area of research being done by John Bowlby and Harry Harlow. Their research focused on the relationship between infants and their mothers. More specifically, they postulated that there is a primary biological instinct for infants to attach to their caregivers (5). Parents provide food, warmth, and protection from predators – separation is a potential death sentence. As a biological response to this threat (and thereby to maximize chances for survival), separation prompts first an intense *protest* phase followed by an eventual *despair*.

A key aspect of Attachment Theory was that while separation reactions had their origins (and were most apparent) in young mammals, elements of this patterned behavior may carry over into adults. Social attachments continue to be a crucial source of security, and separation remains a potential threat. Translating from infants to adults, the *protest* phase, with its high arousal and sense of impending doom, may be akin to panic and *despair* may be analogous to depression (6). Based on this model, Klein offered the radical hypothesis that panic attacks might not simply be an aberrant biological signal but could also reflect a misfiring “separation alarm” (7).

Initially, these two models – one “psycho-ethological” and one biological -- seemed irreconcilable. Klein was thus faced with the same challenge that psychiatry faces today: how can we bridge the seemingly distinct biological, psychological, and social aspects of patient experiences?

For the story of panic, the crucial link would come from research on the mu-opioid receptor. When Klein first began researching panic, it was already well established that mu-opioid agonists increased the body’s tolerance to CO2 (a key aspect of how opiate overdoses can lead to death via suppressed respiratory drive). Klein’s group later showed that blocking opioid receptors in healthy controls could create the same sensitivity to CO2 as was seen in patients with panic disorder (7). But it wasn’t until the late 1970s that researchers first showed that the opioid system also played a key role in mediating separation distress. Specifically, in an animal model of separation, researchers showed that low doses of morphine quelled separation cries, while mu-opioid antagonists exacerbated separation distress (8). Klein’s group saw this as the missing link: what if the same underlying differences in the opioid system could underpin the panic attacks caused by both excessive CO2 and also from separation?

Klein’s work was prescient: in subsequent years, the role of the mu-opioid receptor in adult human attachment has been confirmed through a range of studies (9). For example, certain genetic polymorphisms of the mu-opioid receptor have been linked to social rejection sensitivity. Intriguingly, a recent PET study showed that individuals who were resilient to separation showed increased mu-opioid activity in the dorsal periaqueductal grey. These data suggest a potential mechanistic explanation for how endogenous opioids may directly block panic attacks.

So where does this leave us for treatment? Obviously, in our current age of the opioid epidemic, no one is going to prescribe opioids for panic disorder. But it turns out that it might not be necessary. Circling back to imipramine, chronic serotonin re-uptake inhibition has been found to sensitize both serotonin and mu-opioid receptors in the dorsal periaqueductal gray (10). The fact that this impact is only seen with extended treatment also provides a possible explanation for why the anti-panic effects in both humans and animals are not seen immediately.

In the modern era, cases like Anthony’s remain “easy” to treat – if a patient presents with anxiety, it may be tempting to simply prescribe a selective serotonin re-uptake inhibitor and move on. After all, if the medications we prescribe across anxiety and depressive disorders are all drawn from the same family, why bother attending to the complex puzzle pieces of patient experience?

The history of research into panic illustrates the value of a comprehensive formulation. Understanding the role of increased sensitivity to CO2 cautions clinicians to pay particular attention to patients whose medical illnesses may predispose them to panic; it also guides the selection of medications to ensure appropriate action. At the same time, recognizing the psychological aspects – such as the evolutionary roots of separation responses– may guide

key psychotherapeutic and psychosocial interventions. We can easily imagine patients who will respond to one but not the other of these treatments.

In a sense, the story of Klein's work may be seen as a parable for our field: a clear demonstration of the value of integrating biological and psychosocial aspects from our patients' stories, to guide both our research agenda and, ultimately, to develop effective treatments.

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