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The Utility of the Panic Disorder Concept

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Summary. In this paper we discuss the theory that agoraphobic avoidances are central and spontaneous panics an epiphenomenon to the development of agoraphobia. Moreover we discuss the theory that posits a fixed cognitive-catastrophizing set as causal for panic. We conclude these theories do not fit the facts. We argue that it is important to distinguish between spontaneous panic and chronic or anticipatory anxiety and avoidance. Such a distinction allows for an understanding of the roles of anti-spontaneous panic medications such as tricyclics and MAOI's, as well as exposure therapy, in the treatment of panic disorder with agoraphobia. The former serves the purpose of blocking panic attacks while the latter undermines phobic avoidance, but only after the panic attacks have ceased through proper medication. We conclude that recognizing the key role of spontaneous panic and its variants in anxiety nosology is a necessary guide for etiological, psychophysiological and therapeutic research in this rapidly developing area.

Key words: Agoraphobia – Panic – Phobic disorders – Tricyclic antidepressants – Monoamine oxidase inhibitors

Introduction

Drug treatment is particularly useful for nosological progress and validation because it provides a strategy capable of isolating features closely linked with the underlying pathophysiology of a disorder. Patients often present with numerous confusing features and it may be difficult to know which features are tightly linked to fundamental disturbances, and which are secondary inconstant reverberations (Klein 1973). Effective drug treatment provides us with the opportunity to perceive reversible core psychopathological features that are key to syndromal complexities. This strategy has been labeled "pharmacological dissection".

The most easily discernible drug effect consists of marked amelioration of a salient aspect of psychopathology; e.g. antipsychotics on delusions and hallucinations, lithium on psychomotor acceleration, and antidepressants on spontaneous panic. Since these agents do little to normal subjects they must be normalizing the derangement.

In early treatment, patients are seen in an undifferentiated way and global improvement evaluations made. With further experience, the notion of improvement becomes refined when certain benefits are identified as regular drug effects. The nosology revision stage occurs when these key changes are recognized as due to amelioration of a pathological aspect of a previously undefined preexisting syndrome.

It was noted that severe episodic spontaneous panics were blocked by imipramine, (as shown by the disappearance of outbursts of helpless appeals) and that this blockade, after some time, initiated decreases in chronic anxiety and phobic avoidance. The remission of panics was obscured somewhat by the patients' anticipatory anxiety that they might recur (Klein and Fink 1962).

Imipramine, by its focused blocking action, singled out spontaneous panic as central to syndrome definition, since these patients often also present a secondary array of phobic, obsessional, hypochondriacal, affective, dependent, passive-aggressive, addictive, histrionic and manipulative features. Depending on the salient symptomatology, or selective diagnostic perception, they may be labeled obsessionals, hysterics, atypical depressives, passive-aggressive personality disorders, pseudoneurotic schizophrenics, acute schizo-

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phrenics, alcoholics, barbiturate addicts, severe mixed psychoneurosis, phobic neurosis, agoraphobics, depersonalization neurosis, borderline state, anxiety states, conversion reactions, etc. This diagnostic chaos is the natural result of the difficulty in establishing a causal sequence for this multiform symptomatology from simple observation.

In contrast, experimental imipramine treatment highlights the spontaneous panic as the proximal key causal link that often initiates secondary anticipatory anxiety, tertiary adaptive dependent-phobic behavioral sequence and maintains them both by an irregular aversive schedule. Such a reversible key symptom is extraordinarily helpful in recognizing homogeneous diagnostic subgroups with predictable drug benefit.

We have singled out the spontaneous panic as a key psychopathological component that helps us develop a set of valid syndromal distinctions and propositions about syndromal development. From our studies, the following are our views:

1) An episode of illness is often initiated by a sudden, surprising, unexpected, spontaneous, swift crescendo of terror associated with a wide range of autonomic, in particular cardiorespiratory symptoms: the spontaneous panic.

2) These Panic Disorders should be distinguished from Generalized Anxiety Disorders where spontaneous panics do not occur.

3) These spontaneous panics encompass substantial variability in severity, frequency of recurrence and development of secondary and tertiary symptoms.

4) A variant of spontaneous panic is the situationally predisposed panic. Here certain situations are prone to elicit panic but this is not inevitable and may occur only occasionally.

5) Spontaneous and situationally predisposed panics must be distinguished from the situation-bound panic that almost inevitably occurs in simple phobics on exposure to their phobic object.

6) Spontaneous panics wax and wane, occur in volleys or episodes, may remit and still later unexpectedly return.

7) Patients with spontaneous panic may:

a) Only have spontaneous panics;

b) May also develop a state of chronic anxiety and anticipation of the recurrence of panics.

c) May also progress, with variable speed, to a set of avoidances. These have the common theme of avoiding situations where if a panic occurs it would be difficult to get help or retreat to home. This set of avoidances, referred to by the misnomer agoraphobia, do not have the common theme of avoidance of public places.

10) Almost all agoraphobia, as it presents clinically, is initiated by spontaneous panics.

11) Patients with spontaneous panics often believe they have a severe physical illness and are in danger of dying, going crazy, or losing control.

12) The spontaneous panic is not simply a severe form of ordinary anxiety or Generalized Anxiety Disorder (GAD) but is distinguishable by:

a) Pattern of development

b) Psychopharmacological responsivity

c) Familial aggregation

13) The crescendos of anxiety that occur in stimulus-bound fashion in simple and social phobics differ symptomatically from spontaneous panics.

14) The childhood of agoraphobics is more frequently marked by abnormal degrees of separation anxiety than simple phobics.

15) The spontaneous panic is blocked by tricyclics, monoamine inhibitory (MAOIs), alprazolam and probably clonazepam. These anti-spontaneous panic benefits are not due to anti-depressant, anti-phobic or generally patholytic effects.

16) The tricylics and MAOIs do not directly benefit chronic or anticipatory anxiety or phobic avoidance. However, by blocking spontaneous panics they foster exposure and decrease avoidance and anticipatory anxiety.

17) Diazepam and chlordiazepoxide do not blockade panic but benefit chronic and anticipatory anxiety.

18) Exposure therapy does not block spontaneous panics but decreases avoidance by helping the patient to cope with their panics and anxiety.

19) The disruptive effect of the spontaneous panic may be accentuated by misconceptions such as that one is in severe danger of dying, but these catastrophizing cognitions are insufficient to explain the origin and recurrence of panic, even in the form of the psychophysiological vicious circle hypothesis.

Varieties of Panic: Problems of Definition

For clear discussion, there must be clear definitions. Definitions are simply stipulations about the use of words, so a definition's acceptance depends on its utility. Unfortunately, much difficulty stems from lack of consensus about panic terminology.

We wish to clarify the subtypes of panics. The DSM-III-R (following our usage) defines three types of panic: spontaneous, situationally predisposed and situationally bound.

Spontaneous panics are discrete crescendos of intense fear, associated with marked physical distress, that are unexpected, "out of the blue" or uncued. They are an essential feature of panic disorder.

Situationally predisposed panics often occur in certain settings but are cued only in a probabilistic sense. For instance, patients panic while driving or going to a supermarket, but on other such occasions only remain apprehensive, without panicking. Therefore, situationally predisposed panics resemble spontaneous panics (in not being stimulus bound). They regularly occur during panic disorder, and may come to dominate the symptomatology.

Stimulus bound panics are almost inevitable upwellings of fear on confrontation with a phobic object or situation, as is typical of simple phobias.

These definitions were prompted by the observation that imipramine blockaded spontaneous and situationally predisposed panics, but was ineffective against stimulus bound panics. These distinctions have not met universal acclaim or understanding.

Panic Anxiety Versus Chronic Anxiety

The literature is rife with confusion between panic, anticipatory and generalized anxiety. It is often mistakenly thought that panic is simply the quantitative extreme of generalized anxiety. For example: "...anxiety may be construed as panic mainly when it rises above a certain level, so subjects seeking treatment may have had more severe anxiety than those who did not. As panic and anxiety shade into one another, their distinction becomes rather arbitrary." (Marks, 1987, p 287)

This is a central issue; quantitative continuum vs. qualitative discontinuity. We agree that counting symptoms is not the central distinction between panic and anxiety; rather we emphasize the sudden crescendo and spontaneity of the attack. Of course, this is correlated with the number of symptoms and the degree of terror. Hoehn-Saric and McLeod (1985) point out the existence of a large number of patients with severe and chronic anxiety symptoms who do not have panic attacks: "If panic attacks were simply GAD in its more severe form, then we should not expect to see patients with severe and chronic anxiety symptoms who have never experienced panic attacks; but in fact we do."

Further, spontaneous panics respond to imipramine whereas generalized and anticipatory anxiety do not (discussed below). In contrast to its marked anti-panic effect, imipramine reduces only slightly (and probably secondarily) the anticipatory fear of future panics (Klein 1964, 1967). Also, neither anticipatory nor phobic anxiety in simple phobia respond to imipramine or phenelzine (Zitrin et al. 1978; Sheehan et al. 1980).

That panic is only severe anxiety cannot be reconciled with imipramine's effects. Why should the most severe form of an illness respond to a medication, while the minor form does not? If pneumonia was only a severe cold would it not be astounding if pneumonia remitted from penicillin, but mild colds did not? This does not speak for a severity continuum but rather to a qualitative distinction.

In a double-blind clinical trial of phenelzine and diazepam against placebo and diazepam, Mountjoy et al. (1977) found that phenelzine improved agoraphobic patients more than diazepam, but that anxious nonphobic patients did significantly worse on phenelzine than diazepam. This is further evidence for splitting agoraphobia from general anxiety, for the emptiness of the patholytic notion (discussed below), and for the improbability that panic is simply the quantitative extreme of anxiety.

The distinction of spontaneous panic from anticipatory anxiety has practical consequences since chronic anxiety often persists although panics disappear. Patients (and therapists) have to be trained to recognize this. Therefore, this is not an arbitrary distinction but is needed for effective treatment.

Psychopharmacology

The fact that phenelzine and imipramine block spontaneous panic attacks is one of the most supported in the psychopharmacological literature and the subject of several recent review articles; therefore we will not reiterate this evidence (Modigh 1987). Rather, we will address the criticisms that have been made of the efficacy of antidepressants in panic disorder.

For example, the claim is sometimes made that exposure is necessary for imipramine benefit on spontaneous panic. This has dubious support from one study (Telch et al. 1985; reviewed in Klein and Klein, 1988) and is contradicted by all other relevant studies. Mavissakalian et al. (1983) compared imipramine without exposure to imipramine plus self exposure in agoraphobics. Large differences favored imipramine plus exposure on avoidance measures. However, both groups improved substantially and similarly on panic measures, which does not affirm the necessity of exposure. Buigues and Vallejo (1987) show phenelzine stopped panics without exposure treatment in 100% of 35 agoraphobics.

Further, simple panic disorder without avoidance is successfully treated by imipramine (Garakani et al. 1984; Munjack et al. 1985; Mavissakalian et al. 1983).

That patients with simple spontaneous panics benefit from tricyclics is also suggested by data from open clinical trials with imipramine (Muskin and Fyer 1981) and clomipramine (Gloger 1981).

Antidepressants and Anti-Phobic Effect

Imipramine and phenelzine have no direct anti-phobic effect on avoidance, as shown by their lack of efficacy in simple phobics (Sheehan et al. 1980; Zitrin et al. 1978 and 1980). The decreased avoidance is a later secondary effect, since panic blockade fosters the maintenance of exposure efforts and consequent avoidance decrement.

Imipramine: Anti-Depressant, Patholytic or Anti-Panic Effects?

The anti-panic effects of imipramine are specific and not an epiphenomenon of anti-depressant or patholytic effects. The misunderstanding of this point is expressed in the claim that imipramine's anti-panic effect is actually an anti-depressant effect, because studies that show anti-panic effect also show anti-depressant effect.

Studies of the relationship of baseline depression to anti-panic outcome have either revealed no correlation (Sheehan et al. 1980; Tyrer 1973; Kelly 1970; McNair and Kahn 1981; Zitrin et al. 1983; Kahn et al. 1986; Telch et al. 1985) or a negative correlation (Zitrin et al. 1980).

Zitrin et al. (1978) showed anti-panic but no anti-depressant effects for imipramine; this is hardly surprising since patients with more than moderate levels of depression or diagnosable major depression were excluded from this study. Since there was neither antecedent depression nor specific anti-depressant effect, it is hard to see how anti-depressant benefit must be a precondition for agoraphobic benefit.

Zitrin et al. (1980) similarly excluded depressed patients. Here too, the anti-panic benefits of imipramine cannot be due to benefits on non-existent depression. Worse, "Those (patients) who were more depressed initially showed worse treatment results... the opposite of what one would expect if their improvement were due to the beneficial effect of imipramine on depression... that depressed mood was associated with a relatively poor outcome in both the imipramine and placebo group indicates that these symptoms were an aspect of demoralization, which was secondary to the phobic illness rather than endogenous in nature."

Sheehan's (1980) study showed imipramine's anti-panic efficacy. "Five vegetative signs of... endogenous depression... were studied to see if elevated... scores... were predictable guides to a positive drug response. They were not... good control of the spontaneous panic attacks, disability, anxiety, and somatic symptoms is achieved... in the absence of any depression or vegetative signs... The absence of vegetative signs of depression in the majority of patients and their own accounts suggest that their depression is reactive to the restrictions in their lives and the unrelenting and unexplained anxiety and somatic symptoms for which no relief is forthcoming. ...The spontaneous panic attacks come first and are only later followed by depressed mood."

Uhde (1985) reported "preliminary data from our laboratory suggest that concomitant symptoms of depression may blunt and delay the onset of imipramine's antipanic action".

Buproprion, trazodone, l-deprenyl, sleep deprivation and ECT are effective antidepressants but ineffective for panic (Sheehan et al. 1983; Charney et al. 1986; Mann et al. 1984; Roy-Byrne et al. 1986; Mendel and Klein 1969).

Mann et al. (1984) demonstrated that l-deprenyl (a specific MAO-B inhibitor and an effective anti-depressant in a placebo-controlled trial of atypical depressives; McGrath et al., personal communication), did not benefit panics. Further, panics were a significant predictor of depressive non-response. Mann et al. suggested that MAO-A inhibition is the critical property of MAOIs that makes them effective in the treatment of depressive disorders associated with concurrent panic attacks.

Sleep deprivation may exacerbate panics on the following day (Roy-Byrne et al. 1986). Anecdotal evidence suggests that imipramine treated patients with concurrent Major Depressive Disorder and Panic Disorder may have an anti-panic response dissociated from any anti-depressant response (Nurnberg and Coccaro 1982).

It would be strange if the same drug that blocks panic by a putative anti-depressant effect, also produced depression. Rickels and Schweizer (1986 manuscript not published) and Lydiard et al. (1987) observed patients whose panics remit after alprazolam treatment, but then develop a major depression (while still on the drug) without panic recurrence. Klein has made similar observations with clonazepam (unpublished data).

A recent review by Clum and Pendrey (1987) addressed the question whether the anti-panic effect of anti-depressants was due to their effect on depression. They conclude "...that there is no support for a link between depressive symptomatology and change in panic symptoms as a consequence of treatment with antidepressant medications".

Breier et al. (1985) reported that several studies supported the distinction between anxiety and depres-

sive states. The symptom of highest discriminant value was the panic attack (Roth et al. 1972; Gurney et al. 1972; Mountjoy 1977). To sum up, imipramine's anti-panic benefits cannot be related to either baseline depression or anti-depressant effects.

It is also claimed that the supposed specificity of anti-depressants for spontaneous panics is not correct, since they benefit many pathological states. Tyrer (1986), for example, claimed: "...a range of studies with large numbers of patients...demonstrate superiority of antidepressants compared with benzodiazepines in all forms of neurotic disturbance, and this does not depend on whether anxiety, phobic or depressive symptoms are primary (Johnstone 1980; Tyrer 1980; Lipman 1986; Kahn 1981 and 1986)".

The cited studies, except for Kahn et al. (1986), were of mixed anxious-depressed-phobic populations. This makes the imipramine benefit impossible to specify because its anti-depressant and anti-panic effects may well account for superiority to benzodiazepines which lack these effects. These studies did not consider this confounding possibility.

The most convincing evidence for a non-panic, but anxiolytic, effect of imipramine comes from Kahn et al.'s (1986) study. Imipramine, chlordiazepoxide and placebo were compared for anti-anxiety properties on 242 non-depressed, anxious patients. Unfortunately, prospective exclusion of panic patients was not done. The authors retrospectively excluded "35 panic-anxiety type cases". The grounds for exclusion are not plain, and the proportion of panic patients excluded is surprisingly small. Several centers have commented that the proportion of patients presenting for anxiety treatment who have GAD approximates only 10–15%. Also, some included patients may have had infrequent spontaneous panics, that did not warrant the diagnosis of panic disorder.

They conclude "The study unambiguously supports the efficacy of this tricyclic as a treatment for anxiety disorders. It requires replication". We agree and as the authors acknowledge, this study is not a definitive refutation of the specificity of imipramine's anti-panic effect. Tyrer is left with only tenuous support for his firm conclusion.

It has also been claimed (Marks 1987; Tyrer 1986) that anti-depressants have a generally patholytic effect and are not specific for panic. For example, Marks maintains that, "Many studies of anti-depressants in ...phobic disorders have found a significant broad-spectrum drug effect, reducing not only rituals and phobias but also depression, anxiety, panics, anger and other psychopathology. It might be misleading to concentrate on spontaneous panics as the focus of drug action in agoraphobia" (Marks 1983, p 344).

Marks asserts that drug effects are not restricted to phobias, rituals, and anxiety-depression, but seem more general. He supports this by referring to a group of univariate analyses which show many improvements with medication. There are real methodological problems with such an interpretation of multiple univariate contrasts. You do not know whether there is a general patholytic effect, a host of independent effects, or a central effect with a number of secondary beneficial reverberations. Finally, there may be a marked halo effect so that improvement in one area erroneously induces a perception of improvement in other areas (Klein 1983). These methodological issues are ignored by Marks, but have been pursued by Klein et al. using path analytic methods (Klein et al. 1987).

Substantively, if anti-depressants are nonspecific patholytics, why do they not benefit specific phobics who have no spontaneous panics (Zitrin et al. 1983; Sheehan et al. 1980)?

Even if anti-depressants have a broad spectrum action, it is illogical to conclude that panic disorder does not exist as an entity or that there is no specific anti-panic effect. Because imipramine works for spontaneous panic, depression, arrhythmias, and diarrhea, does not prove that enuresis is not a syndrome, or that imipramine's anti-enuretic effect is not specific.

Nosological Issues

The divergence of some of our views from European views is indicated by three important differences between the DSM-III-R and the current working draft of the ICD-10. First, ICD-10 excludes the diagnosis of panic disorder if phobia is coexists. Such a hierarchical exclusion subsumes panic disorder under agoraphobia and ignores the preponderant development of agoraphobic avoidance from initiating spontaneous panics. Second, panic disorder is similarly excluded by depressive disorder. DSM-III-R dropped this hierarchy in view of family studies indicating that joint panic and depression had a different significance from depression alone (Leckman et al. 1983). Third, an ICD-10 diagnosis of panic disorder requires the absence of anxious symptomatology between outbursts of panic. This seems an arbitrary restriction that will rule out the large proportion of people with panic disorder who develop some degree of anticipatory fear. Hopefully the field trials of this draft will demonstrate the infrequency of such non-anxious panic patients in clinical samples.

The initiating role of spontaneous panic in agoraphobia was first observed by Freud who wrote, "In the case of agoraphobia, etc., we often find the recollection of a state of *panic*; and what the patient actually fears is a repetition of such an attack under those special conditions in which he believes he cannot escape it" (1895, p 136). Today the evidence confirms Freud's

observation that agoraphobia is almost always preceded by spontaneous panic attacks, and that the panic attack differs qualitatively from other anxious states (Uhde et al. 1985; Argyle and Roth 1980; Garvey and Tuason 1984; Kleiner and Marshall 1987; Aronson and Logue 1987; Thyer and Himle 1985; Thyer et al. 1985; Breier et al. 1986; Sheehan et al. 1980).

Citing an epidemiological study by Weissman (1986), it is sometimes claimed that agoraphobia without antecedent panic attacks does exist. These nonclinical samples are irrelevant to erroneous claims that clinical samples of agoraphobics often do not have initiating spontaneous panics.

The heuristically interesting discrepancy between epidemiological and clinical samples may be due to interview methodology or agoraphobia definition. Weissman (1986) said "misdiagnosis was very possible because the key DSM-III concept of agoraphobia – fear of being in a place from which escape might be impossible or difficult in case of incapacitation – is not asked in precisely that way in either the DIS or SADS. The key concept in the DIS is "strong fear of something or some situation that is avoided even though there is no real danger", and in the SADS-L it is "usually the avoidance is recognizable as unreasonable. In some cases, however, subjects avoid situations because they anticipate overwhelming anxiety". Either statement could describe simple or social phobia.

The DIS screening question for panic: Have you ever had a spell or attack when all of a sudden you felt frightened, anxious or very uneasy in situations where most people would not be afraid?" focuses entirely on the patient's awareness of the psychological symptoms of fear generated by intense anxiety. Katon et al. (1987) (agreeing with Freud 1895) pointed out that panic disorder patients may selectively focus on one of the autonomic symptoms such as tachycardia, chest pain, dizziness, and minimize symptoms of nervousness. Thus of 55 patients with panic disorder, 81% originally presented with a pain complaint, most commonly headaches, chest pain or epigastric pain (Katon 1984). Therefore, the DIS question may be insensitive and should be amplified by questions specifying the panic somatic symptoms as Klein does and is required by the DSM-III-R (Klein 1987).

Angst and Dobler-Mikola (1985) in a community survey report 34 agoraphobics without panic attacks. The ascription of agoraphobia rested entirely on four self rating items. Of the 34, only 11 were without depression and only 15 manifested avoidance behavior, which is difficult to reconcile with the agoraphobic diagnosis. Angst (personal communication) considered these results "preliminary". Therefore this study has not established the existence of agoraphobia without panics.

Depression was a common concomitant of both DIS defined and the Angst and Dobler-Mikola defined agoraphobia. Such subjects may have travel constricted by feelings of helplessness, low self esteem and social withdrawal, rather than anticipation of sudden incapacitation by panic. They may also fear incapacitation by depression, alcoholism or the accidents of old age.

In order to obtain more information about the clinical characteristics of the DSM-III-R diagnoses of Agoraphobia without Panic Disorder (AWOPD), Spitzer, Williams and First (personal communication) conducted a field trial of the DSM-III-R criteria. Over a hundred investigators in The Upjohn Company sponsored investigations of panic disorder were requested to provide cases. Ten clinicians, from several countries, submitted 24 cases which they believed fulfilled the DSM-III-R criteria for AWOPD. However, on reviewing the narrative descriptions, eight cases were eliminated for various reasons, such as inadequate description. In three cases the fear was of an external event (e.g., of a natural disaster, of being mugged, and of being raped in a patient recently raped), rather than of a symptom causing either embarassment or incapacitation, leaving 16 patients who fulfilled criteria for AWOPD.

One patient noted two symptoms (fear of vomiting and having diarrhea in public). Fourteen identified only a single fearsome symptom. Twelve different symptoms were identified. The most common were fear of dizziness or fainting (three patients) and fear of vomiting or diarrhea in public (two patients).

AWOPD is a relatively rare diagnosis, even in specialized anxiety clinics. Note that these patients did not fear public places but rather a *forme fruste* of the spontaneous panic; Freud's larval panics. Klein has noted that agoraphobics, dominated by separation anxiety since childhood, often have primarily gastrointestinal-limited symptom attacks.

The claim that spontaneous panics precede agoraphobia is based on strong clinical evidence. The epidemiological data may have relevance to travel avoidance on other bases. Weissman is currently clinically reviewing such subjects. The results should be critical for the AWOPD hypothesis.

Relationship of Agoraphobia and Avoidance Behavior

We view agoraphobia as initiated by spontaneous panics, which elicit immediate appeal behavior, e.g. running to emergency rooms. With repeated spontaneous panics, anticipatory and chronic anxiety develop. The patient then avoids situations where were they to panic, they could not get help easily, e.g.,

travelling alone, crowded elevators, bridges, tunnels, swimming alone, etc. These avoidances are called phobic, although it is not the situation per se that engenders fear but the realization that in such situations help cannot be easily gained, if a panic were to occur. Therefore, these avoidances are markedly ameliorated by a trusted companion, which seems incongruent with a fear of public places.

Marks (1987) offers a model of agoraphobic development in which agoraphobia is defined as a core cluster of phobias of public places, considered evolutionarily prepotent stimuli, associated with "nonphobic" symptoms including epiphenomenal mood disorders such as the spontaneous panic attack. Mysteriously, these avoidances wax and wane.

We maintain that variations in frequency and severity of the spontaneous panic explains the fluctuating course of agoraphobia. It is not generally thought that the potency of simple phobic stimuli wax and wane. Dog phobics do not have good days and bad days.

If agoraphobics suffer from a phobic cluster, why do they not avoid public places when accompanied? This phenomenon fits our hypothesis that the patients are not afraid of public places, but of spontaneous panic. Being accompanied assures them help is immediately available, and may also allay separation anxiety. In a survey of 477 agoraphobics, Doctor (1982, unpublished manuscript) observed that particular situations were panic provoking for some but not others. For example, 43% reported driving on freeways as panic provoking, vs. 29% who rated this as no problem. Similar differences were evident with regard to airplanes (39% vs. 18%), closed-in places (25% vs. 17%), heights (23% vs. 18%), department stores (20% vs. 27%), and crowds (18% vs. 15%).

The constellation of phobic situations differs markedly between individuals, as does the degree of phobic avoidance. This is inconsistent with a regular, well-circumscribed cluster of agoraphobic fears related to public places. Doctor's study indicates the range and variability of agoraphobic avoidances, consonant with our hypothesis that the individual's particular adaptation to spontaneous panic, not the "phobic" stimulus, incites agoraphobic avoidance.

Burns and Thorpe (1977) state that from a random sample of 100 agoraphobic subjects, 91% reported that it made them feel better if "When out, having a way open for a quick return home", indicating their concern about helplessness and possible relevance of separation anxiety. Moreover, the primary fears of 37.9% were of fainting or collapsing and for 13.2% was of dying. Thus primary fears are not related to phobic situations, but to the somatic manifestations of panic. Franklin (1985, unpublished manuscript) ranks the 20 worst fears of 76 agoraphobics "if entirely alone in these situations". Both at time of onset and currently, the number one item was "feelings of panic".

Cognitive Theory and Panic

We still do not completely understand spontaneous panic, but we hypothesize that spontaneous panics are due to the pathological central discharge of an evolved alarm mechanism, possibly linked to separation anxiety or asphyxia (Klein 1987). Cognitive-oriented psychiatrists suggest an alternative hypothesis that panics occur only if the subject has a catastrophizing attitude towards innocuous physiological fluctuations. These minor fluctuations are reminiscent of anxiety (Clark 1986) and result in a vicious circle of anxiety causing physiological reactions which provokes anxiety, etc., swiftly peaking to panic. Such positive feed back loops resemble an avalanche. This theory is referred to as cognitive or catastrophizing.

The cognitive catastrophizing theory of panic consists of a bald assertion, unsupported by testing of obvious corollaries and sustained by ad hoc dismissals of contradictory evidence. When analysed, it can be stated as follows: (1) a learned, (2) enduring predisposition, (3) to misunderstand, (4) and catastrophize, (5) on the perception of minute physiological changes, (6) that are reminiscent of changes experienced during anxiety that one cannot make a reasonable attribution about, (7) results in the key erroneous cognition that one is in severe danger, (8) which induces further physiological disturbance, (9) which affirms the cognition, (10) thus producing a vicious circle, (11) that terminates in maximum physical arousal, (12) and overwhelming fear. The central role of the belief that one is in danger should be emphasized. For some reason, the repeated lack of confirmation of the belief that they are in real danger does not extinguish this belief. It is noteworthy that the entire "cognitive" theory is simply subsumable under a conditioning theory that does not required cognitions (Teasdale 1988).

This catastrophizing phychophysiological vicious circle hypothesis implies that there should be (a) no limited symptom attacks, since the experience of an oncoming panic should, via vicious circle catastrophizing, always eventuate in a full panic, (b) that all patients with panic disorder should panic upon exposure to any anxiogen, e.g. lactate infusion, CO_2, yohimbine, etc., (c) unless they make a reasonable attribution of cause, in which case, there should be no panic, (d) that patients with panic disorder should not have different strengths of panic, either clinically or on provocation, but should hit psychophysiological maximum every time, (e) that in so far as the vicious circle depends upon the perception of increased cardiac arousal,

beta blockers should be effective drugs, (f) that panics should not occur while completely relaxed, (g) that panics should not occur while asleep, (h) that the patients catastrophize before the onset of panics and would maintain this attitude after medication induced panic remission.

Further, this theory would deny the possibility of specific anti-spontaneous panic medications. On the basis of cognitive catastrophizing theory, propranolol should be an ideal antipanic agent because it blocks peripheral arousal such as tachycardia, tremor and sweating. However, Noyes et al.'s (1984) and Hafner and Milton's (1977) studies show that propranolol is not effective. Beta-blockers also do not block lactate-induced panic (Gorman et al. 1983), but do benefit acute performance anxiety (Brantigan et al. 1982; Neftel et al. 1982; Hartley et al. 1983). Catastrophizing theory might be more appropriate for acute performance anxiety than panic disorder.

In terms of catastrophe theory, medication could only block panics by blockading the minor anxious symptoms that precipitate catastrophic reactions. Therefore, tricyclics should increase, rather than decrease, panic attacks because they increase heart rate and cause tremor and dry mouth.

Buigues and Vallejo (1986) using the Eysenck Personality Inventory and the Neuroticism and Extraversion subscales as well as the Cattell-16 Personality Factor Questionnaire studied agoraphobic and panic disorder patients, who had responded well to phenelzine. They could hardly differentiate the personality features of the once neurotic patients from normal subjects. Therefore, the clinical features, that might lead one to hypothesize a catastrophizing attitude may be secondary to experiencing spontaneous panics rather than antecedent.

Systematic histories frequently show no evidence of catastrophizing, but rather of a stoical adaptation. Many patients exclaim, "How could this have happened to me? I was always the strong one".

Panic disorder patients often have extremely frightening and dangerous experiences, prior to developing panics, without panicking. In particular, we have interviewed hundreds of women with panic disorder who gave birth without panics occurring during delivery, although they often found this a frightening, painful and dangerous experience. To claim that they do not panic because they realistically attribute their distress to the delivery, misses the point, since they are also realistically apprehensive, in pain, and in increased danger. They have panicked before under far more benign circumstances, while receiving less enteroceptive stimulation, so why not now, if the issue is catastrophizing about danger?

Gorman et al. (1988) have shown that the tendency to panic during inhalation of 5% CO_2 does not correlate with the tendency to panic during room air hyperventilation (phi = 0.20). This suggests that these are different subgroups of patients, not one group with a generalized tendency to overreact to any anxiogenic stress.

Patients with panics do not have low pain thresholds or respond abnormally to pain experience, although pain experiences are frightening. Using both threshold pain measures and signal detection analog measures, Roy-Byrne (1985) failed to demonstrate any difference in pain sensitivity between patients with panic disorder and normal controls. Signal detection theory yields "a measure of the patient's propensity to call stimuli painful". This showed no difference between patients and normals which is inconsistent with a propensity to catastrophize.

Cognitive theory holds that catastrophizing attitudes precede panics. Therefore, panics should not remit unless catastrophizing attitudes have changed. However, then panics should not spontaneously return. This model is entirely inconsistent with the well known waxing and waning of panic disorder and the latter is sufficient to invalidate this theory.

Panic disorder patients often report good days and bad days. On awakening they may realize correctly 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 inter-panic anxiety as well as the propensity to panic is incompatible with an enduring catastrophizing attitude as the necessary etiological agent.

During early imipramine treatment, patients often report episodes when they feel a panic starting and helplessly observe their increasing distress, which stops, surprisingly, and does not peak. The catastrophizing theory has no place for these subpanics because it predicts that these people have a fixed cognitive set that reacts to moderate anxiogenic stimuli with the belief they are in severe danger.

It is illogical to believe that such people are *also* capable of spontaneously feeling mounting anxiety, but sometimes do not catastrophize. Why should they not? However, subpanics fit well with expectable biological variability in panic release and expression, and the beneficial effects of anti-panic agents.

Two non-pharmacologic provocations do not provoke panic in panic patients: the mental arithmetic test (Kelly et al. 1971) and the cold pressor test (Grunhaus et al. 1983). The former causes tachycardia, increased cortisol level and anxiety, while the latter is a potent, painful, alpha-adrenergic stimulant that produces significant vasoconstriction. This is inconsistent with cognitive theory. It does not follow that these patients do not panic because they know the source of their distress since that should then apply to lactate and CO_2 also. It is noteworthy that the panicogenic ef-

fect of CO_2 was discovered during a study that hypothesized CO_2 would not be panicogenic.

If panic is secondary to perceiving minute anxiogenic physiological changes, spontaneous panics should not occur during relaxation or sleep. Adler and Barlow (1987) reported panics precipitated by relaxation. Mellman and Uhde (unpublished manuscript) reported that of 40 non-hospitalized panic disorder patients, 65% experienced infrequent sleep related panics and 4% frequent sleep attacks. In their sleep study, 6 of 13 patients experienced nocturnal panic as a non-REM phenomenon associated with early delta sleep.

To preserve the cognitive-catastrophe theory, one would be forced to postulate an unconscious perception and cognition. The history of psychiatry indicates that explaining symptoms by postulated unconscious processes is a risky business, that comes too close to non-falsifiability.

Clark (personal communication) suggested that patients with panic disorder, wakened by a panic, were hypersensitive to the physiological shifts that occur during sleep. He thought this was analogous to the ability of a sleeper to awake simply on hearing his name called.

But you cannot have it both ways. If severe panics are induced by the unconscious perception of moderate physiological stimuli even while asleep, then why do different panicogens (e.g. lactate, CO_2, isoproterenol) produce different intensities of panic and affect different proportions of panic patient samples? For instance, lactate infusions cause panic in only about 60% of panic patients, and 5% CO_2 inhalation causes panic in a subset of these (Gorman et al. 1984).

Pitts and Allen (1979) showed that intravenous EDTA produced tetany but not panic in panic disorder patients. The Glucose Tolerance Test (Uhde et al. 1984) in panic patients produced symptoms of generalized anxiety (sweating, palpitations) but did not produce panic. Moreover, insulin sufficient to produce hypoglycemic autonomic symptoms (Schweizer et al. 1986), did not produce panic. Thus, it is unlikely that laboratory induction of panic is a positive feedback loop that can be initiated by any anxiogen.

What would cognitive theory predict if sleeping patients with panic disorder were infused with sodium lactate? The deduction follows that either they would continue to sleep or, if they "unconsciously perceive" the lactate effects, they should awake in a panic. In fact, neither happens. They awake, but do not panic (Koenigsberg et al. 1987).

Norton et al. (1985) showed that 34.4% of 186 presumably normal young adults report one or more attacks, characterized by heart pounding, sweating and trembling, in the past year. Cognitive theory implies that if a patient has a panic, whether provoked or spontaneous, this should lead to a series of panics by self-fulfilling prophecies, since the subject has had his catastrophic expectations fulfilled. This does not fit Norton's data concerning panic in normals.

Also, one would expect remitted panic disorder patients who discontinue medication and then get a lactate infusion one month later to be most apprehensive (which they are), and likely to panic, which they almost never do, even if they have previously panicked with such an infusion. However, panic does occur in 40% of clinically remitted panic disorder patients infused with lactate 6 months after stopping tricyclic medication (Fyer 1988). Strikingly, once having had this attack, they do not develop a series of panics. Would not cognitive theory imply that the demonstration of such a vulnerability should lead to marked apprehension, autonomic discharges, positive feedback, panics, etc.? These findings cannot be dealt with by cognitive theory.

Norton's (unpublished data, 1984) and Carey and Gottesman's (1981) studies showed that non-patient probands with "larval" (Freud 1895, p 81) panics transmitted increased risk for both full and partial panics to their relatives. The patient who only has limited symptom attacks, cannot have a catastrophizing attitude (in cognitive theory), so what is he transmitting? Therefore, catastrophizing is at best a secondary, inessential, report modifier, rather than a necessary component of spontaneous panic.

Catastrophe theory postulates a vicious circle resulting in maximum psychophysiological arousal. However, lactate-induced panics are not accompanied by upsurges of epinephrine, cortisol, or ACTH. Even changes in heartrate and blood pressure may be minimal (Liebowitz et al. 1985). Further, Woods et al. (1987) found that situationally-induced agoraphobic panics did not cause a rise in plasma MHPG or cortisol.

These findings are consistent with spontaneous panic being a central event with inconstant peripheral stress manifestations. They are inconsistent with the maximal peripheral activation called for by the psychophysiological vicious circle hypothesis.

Conclusion

The recent changes in the nosology of the anxiety disorders, centering on the spontaneous panic and its effects, have elicited many critical comments. We conclude they lack substance. Psychopharmacology, genetics and systematic clinical psychiatry achieve a remarkable concordance in supporting these nosological advances.

There are yet more data to consider, since we have not taken into account studies of panic provocation and blockade, except as they illuminate cognitive theory. We also have omitted demonstrations of specific physiological abnormalities in panic disorder (Charney et al. 1984; Nutt 1986), as well as genetic evidence (McInnes 1937; Brown 1942; Cohen 1951; Slater and Shields 1969; Noyes et al. 1978, 1986, 1987; Cloninger et al. 1981; Cloninger 1987; Crowe 1985; Crowe et al. 1983, 1987; Pauls et al. 1980; Harris et al. 1983; Torgersen 1983, 1985; Kendler et al. 1986).

We discussed the theory that agoraphobic avoidances are central and spontaneous panic an epiphenomenon, as well as the theory that posits a fixed cognitive-catastrophizing set as causal for panic. We conclude these theories do not fit the facts. Distinguishing spontaneous panic from chronic and anticipatory anxiety and avoidance allows for a simple integration of the respective roles of anti-spontaneous panic medication and stoicism-inducing exposure, in the treatment of panic disorder with agoraphobia.

Clearly recognizing the key role of spontaneous panic and its variants in anxiety nosology is a necessary guide for etiological, psychophysiological and therapeutic research in this rapidly developing area.

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