

EDITORIAL

Panic disorder: fact or fiction?¹

It has been known for many years that acute attacks of anxiety can occur in the course of anxiety and depressive disorders. For example, in 1879 Maudsley described anxiety attacks in severe depressive disorders (Maudsley, 1879, p. 365) and in 1893 Hecker pointed out their association with the less severe forms of depression and anxiety known as neurasthenia. Hecker also described anxiety attacks in which physical symptoms were more prominent than psychological ones. Cases of this kind were studied mainly by physicians, many of whom suspected a cardiac origin and used terms such as disorderly action of the heart or effort syndrome. Freud made similar observations in a frequently quoted paper on anxiety neurosis published in 1895.

In recent years, the interest of psychiatrists in anxiety attacks has revived. The term panic attack is now preferred, and a distinction (recognized by Hecker) is made between spontaneous and situational attacks. Patients with severe and frequent panic attacks, at least some of which are spontaneous, are now classified as panic disorder, and it is suggested that this disorder is distinct from most other anxiety disorders (the exception being agoraphobia). Furthermore, it is proposed that panic disorder has a specific neurochemical cause, and requires a particular kind of pharmacological treatment. Agoraphobia, it is suggested, is not a distinct diagnostic entity, but a variant of panic disorder in which anticipatory anxiety, situational anxiety, and avoidance behaviour have developed. These new ideas have been accepted widely in the United States, but they have been received more cautiously in the United Kingdom. How well are they supported by evidence?

Four claims will be examined here: that spontaneous panic attacks differ from situational panic attacks; that panic disorder is separate from other forms of anxiety disorder; that agoraphobia is a secondary development of panic disorder; and that panic disorder has a 'biological' aetiology. A fifth issue, the relationship of panic disorder to depressive disorder, cannot be considered in the space of this review. In most reviews, apparently complex issues are reduced to simpler ones. In this review, the conclusion will be that the situation is considerably more complicated than these four claims would suggest.

SPONTANEOUS AND SITUATIONAL PANIC

The new ideas about panic disorder rely heavily on a distinction between spontaneous and situational panic attacks. In principle the distinction is clear, but in practice it is often difficult to make. Since the main sensations experienced during the two kinds of attack are similar (Barlow *et al.* 1985; Margraf *et al.* 1987), the distinction depends on information about the circumstances in which an attack began. Patients do not always find the distinction easy to make and some 'spontaneous' attacks are found on closer enquiry to occur in circumstances similar to those in which situational attacks occur in agoraphobia (Margraf *et al.* 1987).

A second problem is that many attacks which are not related to situational cues have a clear relationship to internal triggers of anxiety. These triggers include the anticipation of future phobic situations, and the experience of visceral sensations perceived as dangerous (often palpitations construed as evidence of an impending heart attack – see Clark *et al.* 1988). It is difficult to distinguish, on the basis of patients' retrospective accounts, between these internally cued attacks of panic and true spontaneous ones.

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One way of establishing whether there is a real difference between spontaneous and situational panic attacks is to make physiological or biochemical observations. However, it is difficult to study spontaneous attacks in the laboratory because they do not occur frequently enough. Therefore, a way of provoking the attacks is generally used. Most research has used lactate infusions to provoke attacks with the (unproved) assumption that the attacks evoked in this way are identical with (or at least closely similar to) spontaneous attacks. In fact, a lactate infusion could equally well be provoking psychologically cued attacks, since it causes palpitations and other visceral sensations which are frightening to panic patients.

If lactate induced panic is accepted as a reasonable model for spontaneous panic, the crucial experiment is to compare, in the same patients, the biochemical, physiological and psychological responses during lactate induced and situational panic. This experiment does not appear to have been done but reports of findings of separate investigations of lactate induced (Liebowitz *et al.* 1985*a*; Levin *et al.* 1987) and situational (Woods *et al.* 1987) panics do not suggest that there are important differences between them.

It is reasonable to conclude that although all panic attacks do not have the same cause, the simple division into spontaneous and situational attacks is both difficult to make and unlikely to be valid. Also, the measurable aspects of the biochemistry and physiology of the attacks seem to be much the same whatever the cause of the attack.

PANIC DISORDER AS A DISTINCT ENTITY

Clinical experience suggests that there is a group of patients who experience repeated panic attacks but have neither marked generalized or phobic anxiety, nor a depressive disorder. Studies of families support this view with the finding that disorders meeting the criteria for panic disorder are found more frequently in the families of patients with panic disorder than in the families of healthy controls (Harris *et al.* 1983; Pauls *et al.* 1980), while rates of generalized anxiety disorder are not increased in the families of panic disorder patients (Crowe *et al.* 1983). To date, linkage studies have produced suggestive, but uncertain, evidence to support a genetic aetiology (Crowe *et al.* 1987).

One of the original reasons for separating panic disorder from other anxiety disorders was the reported response of the former but not the latter to imipramine (Klein & Fink, 1962; Klein, 1964). The response of panic disorder to imipramine has been confirmed (Zitrin *et al.* 1983; Judd *et al.* 1986), and suggestions that the effect is confined to panic patients who are depressed (Marks, 1987) are not well supported by recent evidence (Mavissakalian, 1987; Clum & Pendry, 1987). However, the claim that imipramine is ineffective in generalized anxiety disorders (allegedly showing their lack of relation to panic disorders) is open to doubt (Khan *et al.* 1986). The drug specificity argument has been weakened further by reports that some benzodiazepines are effective in panic disorder as well as in generalized anxiety disorder. It was suggested originally that this effect is specific to one compound, alprazolam (Chouinard *et al.* 1982; Ballenger *et al.* 1988). However, diazepam has also been found to be effective (Dunner *et al.* 1986) and this drug is, of course, used to treat generalized anxiety disorder. In any case, it is dangerous to argue from treatment response to aetiology because many drugs act on the expression of symptoms rather than on the cause of disease (for example phenothiazines affect delusions and hallucinations in organic states as well as in schizophrenia).

A more reliable way of establishing whether there is a separate syndrome of panic disorder is to study the course of cases diagnosed in this way. Surprisingly, there are no satisfactory long-term prospective follow-up studies of patients diagnosed as panic disorder and these need to be carried out. The evolution of the disorder has been studied, though from retrospective accounts. Periods of generalized anxiety before the onset of panics have been noted (Hoehn-Sarik, 1982), but the reported frequency of this association is uncertain, with reports varying from 100% (Cloninger *et al.* 1981) to 26% (Aronson & Logue, 1987). Depressive symptoms sufficient for the diagnosis of major depression occur in about 60–70% of cases (Breier *et al.* 1984, 1985; Cloninger *et al.* 1981; Leckman *et al.* 1983) but no direct comparisons are available to indicate whether this feature distinguishes panic disorder from generalized anxiety disorder. None of these data strongly supports the separation of panic disorder from generalized anxiety disorder.

Patients referred to psychiatrists are often unrepresentative and community studies are important as well. Epidemiological studies indicate that panic disorder can be identified separately from the other anxiety disorders in the community. However, at least as defined by DSM-III, it is not a common form of anxiety disorder. The prevalence of panic disorder in a large community survey was about 1 per 100 compared with about 3 to 6 per 100 for generalized anxiety disorder, and 3 to 6 per hundred for agoraphobia (Weissman & Merikangas, 1986; Weissman *et al.* 1986). Epidemiological studies suggest that the diagnostic boundaries of panic disorder drawn in DSM-III may be too restrictive: there are many people who have similar but less frequent attacks of panic (Von Korff *et al.* 1985).

On balance, the evidence supports the view that there is a group of patients with the characteristics now described as panic disorder. As defined by DSM-III it is not a common group of panic disorder. However, there are other people with less frequent or severe attacks of panic who are probably related closely to the narrowly defined group.

AGORAPHOBIA AS A DEVELOPMENT OF PANIC DISORDER

It is claimed that agoraphobia is a secondary elaboration of panic disorder in which situational anxiety and avoidance behaviour have developed, presumably through conditioning. Three main arguments support this claim: apart from the symptoms listed above the two syndromes are similar; agoraphobia usually begins with a spontaneous panic attack and the other symptoms follow; and agoraphobia responds to imipramine, a drug which is effective in panic disorder. Evidence of the first point is clear: comparisons of agoraphobia and panic disorder indicate that apart from situational and anticipatory anxiety and avoidance, the clinical pictures of the two conditions are closely similar (Noyes *et al.* 1987; Thyer *et al.* 1985).

The natural history of agoraphobia is difficult to determine accurately because all accounts are retrospective but the following points seem to be established. The majority of agoraphobic patients report that the condition began with an unexpected panic attack (Garvey & Tuason, 1984). However, epidemiological studies indicate that between 23 and 53% of agoraphobics do not have associated panic disorder (Weissman *et al.* 1986). Although few patients describe any immediate antecedent stressors, many say that there were background life problems at the time (Aronson & Logue, 1987; Roy-Byrne *et al.* 1986; Sheehan *et al.* 1981; Tearnan *et al.* 1984). The minority of patients who report a situational panic attack at the onset do not seem to differ in important ways from the majority who describe it as spontaneous (Garvey *et al.* 1987). After the first panic attack situational and anticipatory anxiety and avoidance develop, often quite quickly (Lelliott *et al.* 1989).

Although the above account is consistent with the idea that agoraphobia develops from panic disorder, other observations are less easy to explain in this way. The first observation is that established cases of panic disorder do not usually develop into agoraphobia (Buller *et al.* 1986). This might be explained if agoraphobia develops only when panic disorder is associated with another abnormality such as a dependent personality (Reich *et al.* 1987) or a tendency to avoid situations that provoke anxiety. The latter possibility is suggested by the association with agoraphobia of a history of school phobia (Deltito *et al.* 1986; Perugi *et al.* 1988). Alternatively agoraphobia might develop only when severe panic attacks occur in particular situations away from home. Larger follow-up studies of panic disorder are needed to examine these possibilities.

Studies of families also cast some doubt on the idea that there is a simple equivalence between agoraphobia and panic disorder. Agoraphobia is not increased among first degree relatives of patients with panic disorder (though, as noted above, the rate of panic disorder is increased among them). However, when the first degree relatives of agoraphobics were studied, the rate of panic disorder was found to be increased as well as the rate of agoraphobia (Noyes *et al.* 1986). The only twin study (Torgersen, 1983) has such small numbers that no firm conclusions can be drawn from it to clarify the issue. These findings could be explained if modelling were an important cause of the avoidance behaviour of agoraphobics. Adoption studies are needed to test this possibility.

There is good evidence that imipramine has therapeutic effects in agoraphobia as well as in panic

disorder patients (see Judd *et al.* 1986); also agoraphobics are helped by alprazolam, a drug which is effective in panic disorder. However, as noted already, it would be unwise to argue that because two syndromes respond to the same drug, they are closely related.

Response to behavioural treatment might help to decide the relationship of agoraphobia and panic disorder. If agoraphobia is a secondary development of a biologically determined panic disorder, behavioural treatment would be expected to reduce the secondary symptoms of situational and anticipatory anxiety and of avoidance, leaving the patient with recurrent spontaneous panic attacks. Few follow-up studies have included an adequate assessment of panic attacks, but those that have done so report a marked reduction in panic attacks as well as other symptoms – though not a complete abolition of panics (Clark *et al.* 1985; Lelliott *et al.* 1987; Mitchelson *et al.* 1988; Salkovskis *et al.* 1986). Unfortunately, it is not clear in these studies whether the residual attacks are spontaneous or situational, and further investigation is required.

It can be concluded that although the evidence is consistent with the view that some cases of agoraphobia begin with panic disorder, it does not establish that *all* cases begin in this way. The original panic attacks described by agoraphobics could have different causes in different patients, and epidemiological studies indicate that a proportion of agoraphobics do not have associated panic disorder.

A BIOLOGICAL CAUSE FOR PANIC DISORDER

The claim that panic disorder has a distinct 'biological' (i.e. biochemical or physiological) cause is based on two arguments. First, by definition, if anxiety attacks are not situational the cause must be internal. To some investigators an internal cause must be biochemical or physiological, but this argument neglects internal psychological processes. The second argument is that the response of panic disorder to imipramine indicates a biochemical cause. Attempts have been made to support these arguments by investigating physiological and biochemical processes in panic disorder.

The argument that the lack of external cues for anxiety indicates a 'biological' internal cause, is weakened by evidence that panic disorder patients have a psychological disorder that could cause or contribute to their attacks. They are fearful of visceral sensations (such as palpitations) and these fears are less frequent among patients with generalized anxiety disorder (Hibbert, 1984; Rapee, 1985; Barlow *et al.* 1985; Clark *et al.* 1988). It can be argued that the fears are the consequence of previous panic attacks, but if this is true the fears could still maintain the disorder, even though not the sole cause.

The argument that response to drugs can be used to identify a specific psychiatric syndrome has been considered already, and the same considerations make it unwise to conclude that a specific response to a drug indicates a specific cause for a disorder.

Most investigations of the biochemistry and physiology of panic disorder are difficult to interpret because patients with panic disorder and patients with agoraphobia have been studied together on the assumption (which has been examined above) that the two conditions share the same aetiology. Also, because it is difficult to study spontaneous attacks, panics have usually been provoked with chemical agents. If panic disorder patients are more responsive than other anxious patients to these agents, it is inferred that there is a biochemical abnormality related to the pharmacological properties of the provoking agent.

Of the provoking agents, sodium lactate has been used most often. Infusions of this substance provoke panic attacks in panic disorder patients more readily than in normal subjects (Liebowitz *et al.* 1984; Gaffney *et al.* 1988), social phobics (Liebowitz *et al.* 1985*b*), or depressed patients who do not have panic attacks (McGrath *et al.* 1988). However, subjects with infrequent panic attacks (Cowley *et al.* 1987) and depressed patients with panic attacks (Cowley *et al.* 1986; McGrath *et al.* 1985) respond like panic disorder patients, suggesting that the response relates to the presence of non-situational panic attacks, rather than the syndrome of panic disorder. In any case, the biochemical effects of lactate are complex and it is not possible to infer with certainty what biochemical abnormality might be activated by the infusions.

The response to other provoking agents has been studied. Patients with panic disorder are more sensitive than normal subjects to the anxiety producing effects of both CO₂ inhalations (Fyer *et al.* 1987; Woods *et al.* 1988) and hyperventilation (Rapee, 1986) – procedures which have opposite effects on PCO₂. They are also more sensitive to caffeine (Boulenger *et al.* 1984; Charney *et al.* 1985). The biochemical effects of these procedures are complicated, and it is not certain what abnormal biochemical mechanism they might be affecting in panic patients.

The effects of drugs that act selectively on alpha adrenergic receptors should be easier to interpret. Panic disorder patients react more than other patients to yohimbine, an alpha₂ receptor blocker (Charney *et al.* 1984, 1986). Rather surprisingly, however, these patients also react more than others to clonidine, an alpha₂ receptor agonist (Charney & Heninger, 1986). These two findings are difficult to reconcile with a simple theory of nor-adrenergic over or under activity in panic disorder. They could indicate an instability of mechanisms regulating the sympathetic nervous system. Alternatively, the response to yohimbine might be mediated psychologically because the drug causes changes in visceral sensations of the kind which activate the specific fears of panic disorder patients (referred to above).

There is growing evidence that panic disorder patients are more sensitive to psychological procedures as well as to chemical ones. The procedures that provoke panic seem to activate the fears about physical symptoms described earlier in this review (see Barlow, 1988; Clark *et al.* 1988).

It can be concluded that there is as yet no convincing evidence for a specific biochemical or physiological abnormality in panic disorder, and some evidence that the condition could have psychological causes. The two kinds of cause are, of course, not mutually exclusive.

FACT OR FICTION?

We are now ready to re-examine the four claims about panic disorder. First, to divide all panic attacks into situational and spontaneous types is a convenient fiction which has stimulated research into biological causes of non-situational attacks. However, it is clear that non-situational attacks are of more than one kind: some may have biological causes, but others have psychological causes.

Secondly, as earlier writers recognized, there is a group of patients with frequent panic attacks who do not have agoraphobia, social phobia, severe generalized anxiety or a depressive disorder. In the past it has been difficult to classify these patients and the inclusion in DSM-III and the draft of ICD-10 of a category of panic disorder is useful. However, cases meeting the criteria for panic disorder seem to differ only quantitatively from similar patients with less frequent panic attacks, and the criteria in DMS-III for panic disorder may be too restrictive.

Thirdly, although some cases of agoraphobia may develop from panic disorder, not all cases have been shown to develop in this way. On present evidence, it is more reasonable to regard agoraphobia as a syndrome that has more than one cause.

Finally, the idea that panic disorder has wholly biological causes seems to be another convenient fiction. The idea has been useful in stimulating research but it has now lost much of its value since it implies an unwarranted dichotomy of causes. It is more likely that, as in other psychiatric disorders, psychological and biological causes interact in panic disorder. One possibility is that there is a basic physiological and biochemical disorder affecting autonomic regulation which leads to panic attacks when combined with a fearful attitude to visceral sensations. This idea, which has been developed by Clark *et al.* (1988), may turn out to be another fiction but it is the one that seems particularly likely to generate further fruitful investigations into this intriguing clinical problem.

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