British Journal of Psychiatry (1986), **149**, 346–352

Panic Attacks: New Approaches to an Old Problem

M. G. GELDER

Anxiety attacks were included in the first descriptions of the syndrome of anxiety neurosis. Recently it has been suggested that such attacks (now usually called panic attacks) characterize a distinct form of anxiety disorder—panic disorder. It has also been proposed that panic attacks result from a biochemical disorder and require pharmacological treatment. Some of the evidence for these ideas is presented, and two other explanations for panic attacks are reviewed: that they are caused by hyperventilation, and that they result from a cognitive disorder. It is concluded that although it is not possible on the present evidence to choose between the three theories, there is strong indirect support for the cognitive theory and good reason to investigate cognitive factors more thoroughly. Future work on biochemical causes of, and pharmacological treatments for panic attacks should take account of such factors.

The syndrome of anxiety neurosis was first described by Freud (1985) in a paper published in a neurological journal under the title "The justification for detaching from neurasthenia a particular syndrome: the anxiety-neurosis." Freud described all the features that we recognise today, and drew attention to one feature in particular: anxiety attacks. Although this was the first description of anxiety neurosis, similar attacks had been noted by da Costa (1871) in his description of 'soldiers' heart'. However, da Costa ascribed the symptoms to a cardiac rather than a nervous disorder—a view shared by many patients today.

A description of panic attacks

Freud's description of the symptoms of an anxiety (or, as it is now usually known, panic) attack is closely similar to that incorporated in the current American diagnostic system, DSM-III (American Psychiatric Association, 1980), under the rubric for Panic Disorder. An attack consists of a rapid onset both of intense symptoms of autonomic arousal and of mental symptoms. Physiological recordings reflect the disturbance, showing increased skin conductance, muscle blood flow, and heart rate (Lader & Mathews, 1970). The mental symptoms were well described by Freud (1895), who drew attention to the interplay of the two kinds of disturbance:

> "An anxiety attack may consist of a feeling of anxiety alone, without any associated ideas, or accompanied by the interpretation that is nearest to hand such as ideas of the extinction of life, or a stroke, or the threat of madness . . . or the feeling of anxiety may have linked to it a disturbance of one or more of the bodily functions—such as respiration, heart action, vasomotor innervation or glandular activity. From this combination the patient picks out in particular now one, now another, factor. He complains of 'spasms of the heart', 'difficulty in breathing', 'outbreaks of sweating' . . . and such like; and in his description, the feeling of anxiety often recedes into the background."

Panic attacks are of two kinds. The first kind are provoked by a stimulus that the patient recognises; in other words, they are a particularly intense form of phobic anxiety. The second kind appears to arise spontaneously; to quote Freud (1895) again, they "erupt into consciousness without being called forth by any train of thought." Nowadays it is generally assumed that the two kinds are equivalent, and they are studied together. However, they could arise in quite different ways, and might respond to different treatments. Indeed, there is a strong clinical impression (though the evidence is still incomplete) that panic attacks which occur in phobic situations and are accompanied by avoidance respond to exposure treatment, while those occurring spontaneously do not but respond instead to imipramine. This account is mainly concerned with the second kind—the apparently spontaneous attacks of panic.

Do panic attacks define a separate disorder?

Freud described panic attacks as a general feature of anxiety neuroses. For many years most psychiatrists shared this view, but it is now commonly suggested

https://doi.org/10.1192/bjp.149.3.346 Published online by Cambridge University Press

that anxiety neuroses with panic attacks are a separate entity, and this idea is now incorporated in DSM–III. The alternative view—that panic attacks are merely an index of the severity of an anxiety disorder—is still held by many psychiatrists, and it is appropriate to examine briefly the strength of the evidence for the opinion that there is a separate panic disorder.

The idea that panic attacks indicate a distinct form of anxiety disorder was originally proposed by Klein (1964). He based this claim mainly on the observation that panic attacks respond to treatment with imipramine and that the background of generalized anxiety does not. Many of Klein's patients appear to have been agoraphobic, showing avoidance as well as panic attacks; they thus belonged to the first of the two types noted above. Because Klein regards avoidance behaviour as secondary to panic attacks, he has considered it appropriate to combine in his studies patients who avoid (agoraphobics) and those who do not (generalized anxiety neuroses). While this is a tenable position, it is important to be aware of it, because the treatment in the major clinical trial by Klein and his colleagues included both exposure, directed at avoidance, and imipramine, directed at panic (e.g. Zitrin *et al*, 1983). Since there is evidence that exposure alone can reduce the panic attacks of agoraphobic patients (e.g. Hibbert & Chan, 1986) it is necessary, in order to support Klein's position, to show that imipramine alleviates panic attacks in generalised anxiety neurosis. To date this has not been proved beyond doubt, since the evidence published so far is based only on a small group of patients (Garakani *et al*, 1984). However, further evidence on this issue should be available soon from trials now in progress.

Do patients with panic attacks differ from those with generalised anxiety disorder in ways other than their response to treatment? Several authors have reported differences in symptoms. However, these differences are directly related to the symptoms of the panic attacks themselves and are therefore not helpful in answering the question. They include more somatic symptoms (Hibbert, 1985; Hoehn-Saric, 1982; Anderson *et al*, 1984) and more preoccupations with ideas about illness and dying (Hibbert, 1985) among panic attack patients.

Are there any differences not directly due to the panic attacks? The evidence on this point is confounded by the inclusion of agoraphobic patients in the panic attack groups, so that the observed differences may be due, at least in part, to differences between agoraphobia and general anxiety neurosis rather than between panic disorder and general anxiety neurosis. Thus Raskin *et al* (1982) found that panic attack patients reported more disturbances in their childhood environment, but not difference in loss or separation. They also found that the panic disorder group reported more previous depressive disorders. Crowe *et al* (1983) studied the relatives of probands with panic disorder and found an excess of panic disorder among their first degree relatives, but no increase of generalised anxiety disorder. These family differences suggest the possibility of genetic differences between panic disorder and generalized anxiety disorder, but these differences might only be in the degree of genetic loading, with a greater genetic influence in severe anxiety neuroses than mild ones. It can be concluded that there is as yet no strong evidence that panic attacks mark out a different disorder, rather than a more severe degree of the same one. However, whatever the truth of this issue, the causes of panic attacks still need to be explained.

Causes of panic attacks

The normal responses of fear and anxiety are the final result of a complicated series of physiological and psychological mechanisms. Panic attacks must result from a disorder of some of these mechanisms, and this disorder might be the same in every case, or differ between cases.

A discussion of the causes of panic attacks requires a broad understanding of the mechanisms of anxiety: there are physiological and psychological components, and each has several elements. The physiological mechanisms include control centres in the brain and effector systems in the periphery. The central mechanisms include the locus ceruleus, a nucleus involved in the control of sympathetic activity and in the regulation of arousal. The peripheral physiological mechanisms include autonomic arousal, increased tension in skeletal muscles, enhanced respiration, and the release of adrenaline and noradrenaline.

Peripheral noradrenergic mechanisms

Many of the most obvious symptoms of a panic attack reflect overactivity of the sympathetic nervous system. This overactivity might arise in two ways: from heightened sensitivity of end organs, or from increased activity in sympathetic nerves. The first possibility was suggested by Wearn and Sturgis (1919) who gave intramuscular injections of adrenaline to patients with 'irritable heart' (a condition now generally thought to be identical with severe anxiety disorders). They observed that the same amount of adrenaline produced more symptoms in the anxious patients than in normal controls. This finding might

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indicate that anxious patients are unusually sensitive to the effects of adrenaline. However, the differences could be due to variations in absorption from the injection site, and the crucial experiment requires an intravenous infusion of adrenaline. This was done by Fraser & Wilson (1918) and by Hume (1918), and when Wood (1941) combined their results he found that anxiety neurosis patients and controls responded equally.

Since that time, it has been shown that these peripheral sympathetic effects depend on β-adrenergic mechanisms. Nesse *et al* (1984) examined the effect in anxious patients and controls of the specific β-adrenergic agonist, isoproterenol. They found no evidence of increased β-adrenergic receptor responses in panic anxiety patients; indeed, there was an indication that the response was slightly decreased, a finding that could reflect down-regulation of receptors in response to sustained high levels of noradrenaline. Thus although some of the symptoms of panic discorder are undoubtedly related to increased sympathetic activity, this does not seem to be due to hypersensitivity of post-synaptic β-adrenergic receptors.

Central autonomic regulatory mechanisms and panic attacks

The central regulatory mechanisms for a xiety are complicated, but for the purpose of this r view they can be simplified by focusing attention o a single important structure: the locus ceruleus. which is situated in the floor of the fourth ventricle. In animals, ascending noradrenergic pathways can be traced from the locus ceruleus to the hippocampus and forebrain, where they probably modulate arousal levels. Descending pathways from the locus ceruleus affect peripheral sympathetic activity.

Three kinds of evidence point to the importance of the locus ceruleus in the regulation of anxiety in animals (Redmond & Huang, 1982). Firstly, stimulation of cells in the locus ceruleus leads to behaviour like that produced by anxiety-provoking stimuli. Secondly, lesions in the locus ceruleus abolish the behavioural response to anxiety-provoking stimuli. Thirdly, the drugs piperoxan and yohimbine, which increase activity in cells of the locus, produce anxiety-like behaviour in animals. Not all the evidence points in the same direction; for example, the drug buspirone increases activity in the locus but reduces anxiety (Sanghera *et al*, 1983).

If a control mechanism of this kind exists in man, panic attacks could arise from excessive stimulation of neurons on the locus ceruleus or from inadequate inhibitory mechanisms. At present most interest is centred on possible failures of the inhibitory mechanisms. The noradrenergic neurons in the locus ceruleus have receptor sites for several inhibitory neurotransmitters, notably α_2 adrenoceptors, and receptors for gamma-aminobutyric acid (GABA) and encephalins (see Redmond & Huang, 1982). In this review only the α_2 adrenergic autoreceptors will be considered (see Grant *et al*, 1980, for the possible role of GABA-benzodiazepine receptors).

If these poorly-functioning autoreceptors are a cause of panic attacks, yohimbine (a drug which penetrates the blood/brain barrier and inhibits these receptors) should reduce their activity more readily than in generally anxious or normal subjects. Removing an inhibitory mechanism on these cells will increase autonomic activity and arousal. It should also result in a greater increase in plasma 3-methoxy-4-hydroxy-phenylethylene glycol (MHPG), which seems to reflect central noradrenergic turnover.

Charney *et al* (1984) gave yohimbine orally to drug-free anxious patients and to healthy controls. The drug produced greater increases in tremors, palpitations and systolic blood pressure in the patients than in the controls. Anxiety also increased more, and patients reporting the most panic attacks before the test showed the greatest rise in plasma MHPG in response to yohimbine. These findings are consistent with the view that panic attacks develop when there is an abnormal balance between excitation and inhibition at the locus ceruleus (and perhaps other areas of the brain), possibly due to abnormal α_2 receptor function. However, the findings could also be explained if the direct effects of yohimbine are restricted to increases in the physiological symptoms of tremor, pulse rate and blood pressure, while the feelings of panic result from the patient's psychological response to these physical changes. Furthermore, yohimbine is a less selective α_2 adrenoceptor antagonist than certain recently discovered compounds; to be certain that noradrenergic changes are of primary importance this work needs to be repeated with these more specific agents.

Clonidine is another drug that acts on α_2 autoreceptors. Because clonidine is an α_2 agonist it stimulates the autoreceptors, thereby reducing activity in the noradrenergic neurons of the locus. If α_2 receptors are underfunctioning in the patients with panic attacks, clonidine would not be expected to be a powerful way of controlling the attacks. Ko *et al* (1983) gave clonidine to panic attack patients and found only a weak anxiolytic effect, although there were definite effects in lowering blood pressure and producing sedation. These findings are compatible

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with the α_2 hypothesis of panic attacks, but certainly cannot be taken as strong evidence for it.

Imipramine and panic attacks

The revival of interest in panic attacks can be traced to the observation by Klein (1964) that imipramine seemed to have a specific effect on this aspect of anxiety disorders. A subsequent clinical trial (Zitrin *et al*, 1983) appears to confirm this observation, although the size and generality of the effect is difficult to assess due to the high drop-out rate from both the imipramine-treated group (29%) and the control group. Also, patients had phobias with panic attacks rather than generalized anxiety with panic attacks.

If imipramine does suppress panic attacks, how might this come about? Two clinical observations are relevant. Firstly, many anxious patients complain of unpleasant side-effects when they first take imipramine even in small doses (Zitrin *et al*, 1978). Although the point has not been tested formally, it is reported that these side-effects are more severe than those experienced by most depressed patients; thus Zitrin (1983) states that some patients are exquisitely sensitive to the drug, developing insomnia, irritability, unusual energy and apprehension with doses as low as 10 mg/day. Secondly, it appears that the anti-panic effect is slow to develop, taking up to four weeks before panics cease (Zitrin, 1983). This contrasts with the early onset of side-effects.

These clinical observations can be compared with pharmacological findings about imipramine and related antidepressants. The immediate effect of these drugs is to block the re-uptake of noradrenaline, thereby increasing the amount of noradrenaline acting post-synaptically. This action could account for the side-effects noted early in treatment. The subsequent changes are quite complex. Long-term administration of tricyclic antidepressants reduces post-synaptic β-adrenergic receptor function and increases post-synaptic α_2 adrenergic function (Charney *et al*, 1981). Also, chronic administration of some tricyclic antidepressants decreases α_2 adrenergic autoreceptor function (Charney *et al*, 1981). The net effect of these changes on noradrenergic function is extremely difficult to predict. One way around this difficulty is to assess overall transmission through the synapse. Cowen *et al* (1985) have studied transmission through adrenergic synapses using the release of melatonin as an index of this (the release of melatonin in the pineal depends on noradrenergic transmission). These experiments show that in normal subjects after desmethylimipramine has been taken there is an initial increase of adrenergic transmission which lasts for at least a week; after three weeks of treatment it returns to the pre-treatment level. This return to normal despite continuing treatment suggests some kind of compensatory mechanism that overcomes the effect of the initial rise in noradrenergic transmission. If, as seems likely, imipramine has effects similar to those of desmethylimipramine this compensatory mechanism might have an effect that stabilizes adrenergic synapses. If that were the case, it might also account for the anti-panic effect.

Cowen *et al* (1985) studied normal subjects, and comparable data are not available from patients with panic attacks. However, Charney & Heninger (1985) have reported decreased MHPG concentrations in the plasma of such patients after 8–12 weeks of imipramine. This finding suggests that central noradrenergic function has been reduced by the drug. The mechanism is not understood, but Charney & Heninger suggest that it is not mainly due to changes in α_2 receptors, since responses to yohimbine (which acts on these receptors) are unchanged.

As yet these ideas are speculative, because we do not know how this compensation is brought about. However, this is an obvious area for research, and the answer might increase our understanding not only of the actions of imipramine in patients with panic attacks but also the abnormality in nervous regulation that is present in these patients.

Hyperventilation as a cause of panic attacks

An increase of respiratory activity is part of the normal 'fight or flight' response. Patients with anxiety neurosis increase their breathing as well as their level of sympathetic arousal and, since they engage in neither fight nor flight, they may breathe off more CO_2 than they produce (i.e. hyperventilate). Hyperventilation produces symptoms resembling those of panic anxiety, as can be seen when the symptoms of the two conditions are listed in parallel (Table). It is possible that panic attacks occur when the symptoms of hyperventilation occur alone or when they are added to the other manifestations of an anxiety response which would otherwise produce less intense symptoms.

The most direct way of deciding whether panic attacks are caused by hyperventilation is to estimate concentrations of carbon dioxide in arterial blood ($paCO_2$) during a panic attack. These concentrations can be estimated indirectly in a laboratory by measuring end-tidal CO_2 or directly by intra-arterial sampling. However, panic attacks seldom occur in the controlled conditions of the laboratory.

Until recently it was not possible to make measurements of $paCO_2$ during panic attacks occurring

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TABLE I
Comparison of symptoms of panic attacks and hyperventilation

Diagnostic criteria for panic attacks[1] *(at least four required)*	*Symptoms of hyperventilation*[2]
Dizziness, light-headedness or unsteady feelings	Dizziness
Depersonalization or derealization	Unreality
Faintness	Faintness
Paraesthesiae	Paraesthesia
Trembling and shaking	Tremor and coarse twitching
Shortness of breath or smothering sensations	Shortness of breath
Palpitations or tachycardia	Palpitations
Chest pain or discomfort	Atypical chest pain
Apprehension	Apprehension
Choking	
Sweating	
Nausea and abdominal distress	
Hot flushes or chills	
Fear of dying	
Fear of going crazy or of doing something uncontrolled	

1. From DSM III-R (American Psychiatric Association, 1985)
2. From Lewis (1954)

outside the laboratory, but a method has now been described which can estimate $paCO_2$ indirectly in ambulant patients. Hibbert (1986) has combined a miniaturized method for measuring transcutaneous CO_2, developed at University College Hospital, with the Medilog recorder, which was originally developed for 24-hour monitoring of ECG. The principle is this: the rate at which CO_2 leaks through the skin depends on $paCO_2$, skin metabolism and skin blood flow. The last two can be held constant in the skin under a pH electrode by warming that skin to a constant temperature. Under these circumstances measurements of pH reflect transcutaneous CO_2 leakage, and have been shown to be highly correlated with $paCO_2$ (Clutton-Brock & Rithalia, 1984). Using this method, Hibbert has shown that some patients hyperventilate during panic attacks. Not all do this, however, and it is not yet certain what proportion of panic attack patients do. On the present evidence it seems that although hyperventilation may contribute to panic attacks in some patients, it is not likely to be the principal cause in the majority.

Psychological causes of panic attacks

The psychological mechanisms involved in anxiety are no less complicated than the physiological ones. However, for the present discussion it will be enough to consider one important psychological component: the cognitive changes.

Paradoxically, the psychological theory of panic attacks begins with the results of pharmacological experiments. It has been explained that panic attacks can be provoked by voluntary overbreathing and that yohimbine, an alpha-adrenergic blocker, has a similar effect. It is also well-known that infusions of sodium lactate provoke panics, and do so more readily in anxious patients than in normal subjects (Pitts & McClure, 1967). The mild stimulant caffeine has a similar effect (Boulenger *et al*, 1984). These observations could be explained if the various agents have the common pharmacological property of stimulating activity in the locus ceruleus (or some other structure controlling anxiety). However, there is an equally plausible alternative explanation, which is worth considering because not all panic attack patients who receive these provoking agents respond by developing a panic: psychological factors may account for the variability in response.

This psychological explanation starts with observations on individual differences in response to one of the provoking agents—hyperventilation. Clark & Hemsley (1982) asked volunteers to overbreathe and recorded three variables: the symptoms experienced, the pCO_2 level reached, and the neuroticism score of each patient. Physical symptoms, especially

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palpitations, were quite highly correlated with the lowering of pCO_2 achieved during hyperventilation, while psychological symptoms were related more to measures of neuroticism. Clark & Hemsley suggested that there might be a two-stage process in which overbreathing leads to physical symptoms, which in turn give rise to worries that increase the level of anxiety further. They pointed out that a response of this kind could readily give rise to a vicious circle leading to a panic attack.

Neuroticism is a broad concept; can the psychological component be identified more precisely? It was noted earlier that Freud (1895) stressed the anxious patient's preoccupation with fears of dying, a stroke, or loss of sanity. Beck *et al* (1974) drew attention to similar symptoms, and added fears of heart disease and fainting. Hibbert (1985*a*) assessed all these fears in a standardized way and confirmed the earlier observations. Of course, the fears might be a consequence of the panic attacks rather than a cause. This problem can be addressed most readily by attempting to treat panic attacks by changing the cognitions with a psychological treatment.

Clark *et al* (1985) have described a treatment in which cognitions are changed by combining voluntary hyperventilation, intended to provoke symptoms, with cognitive restructuring in which it is explained how panic attacks can result from the misinterpretations of bodily sensations resulting from overbreathing and other innocuous causes. Patients then practise controlling these attacks both in subsequent occasions of treatment and during panic attacks arising occurring in everyday life. Two clinical trials have shown that this treatment leads to a substantial improvement in panic attacks in patients who did not improve during a preliminary waiting period (Clark *et al*, 1985; Salkovskis *et al*, 1985). A stricter test of a randomized comparative trial will have to be carried out before these findings can be evaluated fully. However, the existing evidence does seem to give quite strong, although necessarily indirect, support to the cognitive theory of panic attacks.

Conclusion

The various mechanisms for the cause of panic attacks which have been reviewed are not mutually exclusive: they are concerned with different stages of a complicated psychophysiological process which could go wrong in more than one way. Just as we now recognise more than one cause of hypertension or diabetes, so we may need to recognise more than one cause of panic attacks.

There is no support for the theory that peripheral β-adrenergic mechanisms are hypersensitive in patients with panic attacks. Although there are interesting pointers to a possible disorder of the central mechanisms controlling sympathetic activity, there is as yet insufficient firm evidence to support this hypothesis strongly. Nevertheless, this is clearly one of the more promising lines for future research. There is no convincing evidence that the majority of attacks are principally caused by hyperventilation, though overbreathing may play a part in some attacks—it is still not known how many.

The psychological hypothesis that cognitions are abnormal in people who experience panic attacks and that these cognitions amplify the anxiety response is quite strongly supported by evidence, albeit mostly indirect evidence. The idea receives further support from the effects of a cognitive treatment, though the specificity of the effect has not yet been established beyond doubt.

We are still some way from solving the problem of panic attacks which Freud drew to our attention. Nevertheless, much progress has been made in recent years towards a better understanding of the causes, and it seems likely that the eventual solution will to be of a particularly interesting kind, integrating pharmacological, physiological and psychological approaches to the problem.

Acknowledgements

I am grateful to David Clark and David Nutt for their helpful comments. The paper is based on a lecture first given at the MRC Clinical Research Centre, Northwick Park.

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(*Accepted 12 November 1985*)

https://doi.org/10.1192/bjp.149.3.346 Published online by Cambridge University Press