

BIOLOGICAL MODELS OF PANIC DISORDER AND AGORAPHOBIA—A REVIEW

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Summary—Biological models have had major consequences for the therapy and theory of panic disorder and agoraphobia. Authors such as Klein and Sheehan propose a qualitative biological distinction between panic attacks and other types of anxiety. Central arguments for their models include drug specificity, panic induction, family data, spontaneity of panic attacks and separation anxiety. A look at the evidence, however, shows surprisingly little empirical support for these arguments. In spite of the great heuristic value of Klein's and Sheehan's models, alternative approaches focusing on an interaction of physiological and psychological factors seem more capable of integrating the relevant findings.

INTRODUCTION

In the last few years anxiety disorders have moved into the focus of interest in psychiatry. The recent overview of psychiatric progress in the *Journal of the American Medical Association* was almost exclusively devoted to anxiety disorders, especially panic disorder and agoraphobia with panic attacks (Freedman and Glass, 1984). Several journals have published special supplements on the topic. The next revision of the *Diagnostic and Statistic Manual* of the American Psychiatric Association (DSM-III-R; to be published in 1987) will place even more emphasis on the role of panic attacks in the classification and etiology of anxiety disorders (Spitzer and Williams, 1984).

The major impetus for this development has come from Klein's model of panic disorder and agoraphobia, which is based on his conception of the role of spontaneous panic attacks (Klein, 1980, 1981). His theory postulates a basic distinction between panic attacks and other types of anxiety. This is congruent with the approach currently favoured by much of the psychiatric research on anxiety. Sheehan, for example, argues for a biological explanation for panic disorder (Sheehan, 1982a, b; Carr and Sheehan, 1984). He divides pathological anxiety into 'endogenous' and 'exogenous' subtypes (Sheehan and Sheehan, 1982a, b, 1983; Sheehan, 1984). Endogenous anxiety is defined by the occurrence of spontaneous panic attacks and is a 'metabolic disease' (Carr and Sheehan, 1984).

In our discussion of current biological models of panic disorder and agoraphobia we will primarily focus on Klein's model, since it is the prototype for current biological approaches. However, we will also present Sheehan's model and discuss the evidence for the major assumptions of both Klein's and Sheehan's approaches. In spite of the great heuristic value of these models, the empirical basis for many of their central postulates is surprisingly weak. At present a purely biological model seems to be incapable of integrating many of the relevant findings. Alternative models that focus more on interactions between psychological and physiological factors will be discussed briefly. Further etiological considerations can be found in the recent reviews by Foa, Steketee and Young (1984), Rachman (1984a) and Roth (1984).

SEPARATION, PANIC AND AGORAPHOBIA

In spite of Freud's (1895) early vivid and accurate description of panic attacks (Angstanfaelle), psychoanalysis, psychiatry and psychology did not attach any special importance to this form of anxiety until recently. Like other major changes in the clinical sciences, change in this attitude was

triggered by a therapeutic discovery. In the 1960s Klein and his coworkers noticed a therapeutic effect of tricyclic antidepressants on patients suffering from recurrent attack-like anxiety (Klein and Fink, 1962; Klein, 1964; Mendel and Klein, 1969). Subsequently Klein formulated a new theory of pathological anxiety (e.g. Klein, 1980, 1981) based on a *qualitative* distinction between what he termed panic anxiety and chronic or anticipatory anxiety. Panic anxiety is characterized by an acute, attack-like course of a specific group of predominantly somatic symptoms. In Klein's view panic attacks often occur spontaneously, 'out of the blue.' They represent a specific biological dysfunction. In contrast, anticipatory anxiety is triggered by specific stimuli or their anticipation and thus occurs primarily in feared situations or while anticipating such situations. Anticipatory anxiety has a more chronic course, fewer and slower fluctuations and more cognitive symptoms.

This qualitative distinction between panic and anticipatory anxiety facilitates a new view of agoraphobia: Klein explains the chronic anxiety and avoidance of agoraphobic patients as consequences of their experience of spontaneous panic attacks. What the patients fear primarily is the recurrence of these attacks rather than the environmental setting itself. This is similar to the position of several other authors who have understood agoraphobia as 'fear of fear' or 'phobophobia' (e.g. Westphal, 1871; Frankl, 1975; Beck and Emery, 1979; Chambless, 1982; Griez and van den Hout, 1983). However, these authors assume a quantitative rather than a qualitative difference between panic and anxiety, a view shared by many others (e.g. Lader, 1975, 1982; Mefferd, 1979).

Even though a biological nature of qualitatively distinct panic attacks would not imply that they must be treated pharmacologically, Klein and Sheehan consider psychotherapy including behavioural approaches secondary or even irrelevant in the treatment of panic attacks (Klein, 1981; Sheehan, 1982a, b). The treatment of anticipatory anxiety alone (e.g. by exposure therapy or diazepam) should not result in lasting improvement of panic disorder or agoraphobia with panic attacks, since spontaneously recurring panic attacks would make a relapse very probable.

Klein relates panic attacks to separation anxiety. The help-seeking, dependent behaviour of panic patients reminds him of the reactions of young animals or children who were separated from their mothers. He refers to an innate mechanism in both animals and humans that is activated by separation from attachment stimuli. This unlearned alarm mechanism consists of a protest and a despair component, conceived by Klein as parallel to Bowlby's (1969, 1973) first two stages of the response to separation. The protest component of the alarm mechanism includes the elicitation of panic (active, help-seeking behaviour); the despair component includes the elicitation of depression. Klein assumes that in panic patients this alarm mechanism is activated by minimal triggers or without triggers because their threshold for alarm is chronically lowered. He speculates that "the sole function of all antidepressants is simply to raise thresholds throughout this apparatus . . . and that their beneficial effects on anxiety attacks and/or depression result from this normalization of function" (Klein, 1981, p. 248). Note that his concept of alarm mechanism activation does not specify the conditions determining whether panic or depression will predominate.

A schematic representation of Klein's (1981) model is given in Fig. 1. It shows what Klein considers to be the typical sequence of childhood separation anxiety, spontaneous panic attacks and agoraphobia. This last stage does not occur in patients with uncomplicated panic disorder and separation anxiety does not have to precede the development of panic disorder in all cases.

Klein advances five major arguments for the validity of his model:

- (1) *Drug specificity.* Different drugs are therapeutic for panic and anticipatory anxiety. Tricyclic antidepressants and MAO inhibitors specifically treat panic but not anticipatory anxiety. Sedatives and minor tranquillizers, especially benzodiazepines, on the other hand do not affect panic but treat anticipatory anxiety.
- (2) *Panic induction.* Panic attacks can be experimentally induced by a biological agent (sodium lactate infusion) in panic patients but not in normal controls.
- (3) *Family data.* Family and twin studies show a strong genetic factor for panic that is independent from anticipatory anxiety.
- (4) *Spontaneity of panic attacks.* The majority of the attacks especially at the onset of the disorder occur spontaneously, that is, not in response to specific stimuli.

Model	Evidence adduced
<i>Possible predisposing antecedent:</i>	
Separation from specific social stimuli to which attachment had developed	Research by Bowlby (1969, 1973); observations in children with school 'phobia'; therapeutic effect of tricyclics on distress caused by separation in children and animals
↓	
Innate (unconditioned) protest, help-seeking behaviour and panic (innate alarm mechanism)	
<i>Development of panic attacks:</i>	
Pathologically lowered biological threshold leads to the activation of the innate alarm mechanism independent of external stimulation = spontaneous panic attacks	Family studies; panic-induction studies with sodium lactate; blockade of natural and lactate induced panic by tricyclics
↓	
<i>Development of agoraphobia:</i> (not inevitable)	
Experience of panic attacks leads to anticipatory anxiety and avoidance of situations in which attacks occurred	Clinical observation of the development of symptoms; blockade of anticipatory anxiety but not panic attacks by benzodiazepines
↓	
Generalization of anticipatory anxiety and avoidance to many situations	

Fig. 1. Schematic representation of Klein's (1981) model of the development of panic attacks and agoraphobia.

- (5) *Separation anxiety*. About half of all agoraphobic patients have a childhood history of separation anxiety. Separation anxiety in young animals and children ('school phobia') responds to treatment with tricyclic antidepressants.

ENDOGENOUS AND EXOGENOUS ANXIETY

In a way similar to Klein, Sheehan (1982a, 1984; Sheehan and Sheehan, 1982a, b, 1983) asserts that 'spontaneous panic attacks' are an entity distinct from other anxiety states. He proposes a classification of anxiety disorders based on the presence or absence of these attacks. Phobias that occur in the presence of panic attacks are classified as 'endogenous phobic anxiety' (in contrast to 'exogenous'). Sheehan claims a purely metabolic cause for panic attacks (Sheehan and Sheehan, 1983; Carr and Sheehan, 1984). He acknowledges the role of general stress, but considers it to be non-specifically aggravating rather than causal. Learning processes are also secondary: spontaneous panic attacks can become elaborated by learning into phobic avoidances such as agoraphobia.

Sheehan and Sheehan (1983) describe the natural history of panic disorder as follows:

In the 'subpanic symptom stage' the patient experiences some panic symptoms for no apparent reason. Later on, the first 'full blown panic attacks' occur with a host of anxiety symptoms and a desire to flee. In the next stage, the patient becomes increasingly hypochondriacal and is preoccupied with the search for an (organic) cause of the attacks. Depersonalization and derealization are common symptoms at this stage. Subsequently, simple and social phobias can develop by association of panic attacks and specific situations (classical conditioning). This may progress so that the patient increasingly restricts his or her lifestyle and becomes severely disabled by agoraphobia or polyphobias. As a final stage, a reactive depression may occur.

The major arguments for Klein's model are used by Sheehan as well, with the exception of the analogies with separation anxiety. The status of empirical support for these arguments will be

discussed in the next section. Sheehan's biological orientation leads him to an undervaluation of behavioural treatment. A statement like "agoraphobics and social phobics respond best to tricyclics and MAOI's and poorly to behaviour therapy alone" (Sheehan and Sheehan, 1983, p. 248) implies that behaviour therapy has an inconsequential role in the treatment of these disorders. However, nearly two decades of sound research have convincingly demonstrated the efficacy of behavioural approaches for social anxiety and at least for the avoidance behaviour of agoraphobics (Twentyman and Zimering, 1979; Brehony and Geller, 1981; Marks, 1981, 1983a, b; Mathews, Gelder and Johnston, 1981; Chambless and Goldstein, 1982; Keefe and Agras, 1983; Thorpe and Burns, 1983; Foa *et al.*, 1984). Authors such as Hand, Lamontagne and Marks (1974), Mathews, Teasdale, Munby, Johnston and Shaw (1977), Emmelkamp and Kuipers (1979), Chambless and Goldstein (1980; cf. Goldstein, 1982), McPherson, Brougham and McLaren (1980), Munby and Johnston (1980), Burns, Thorpe, Cavallero and Gosling (1983), Michelson, Mavissakalian and Marchione (1985), Fiegenbaum (1986) and Hand, Angenendt, Fischer and Wilke (1986) have developed and tested highly effective treatment packages for agoraphobia that do not include medication and lead to improvement lasting up to 9 years.

STATUS OF EMPIRICAL SUPPORT FOR THE BIOLOGICAL MODEL

Drug specificity

The majority of drug treatment studies do not support the drug specificity argument. The claim that benzodiazepines are ineffective in treating panic is challenged by the efficacy of alprazolam, a new triazolobenzodiazepine, in the treatment of both anticipatory and panic anxiety (Chouinard, Annable, Fontaine and Solyom, 1982; Shader, Goodman and Gever, 1982; Sheehan, 1982b). One may object that this efficacy is a consequence of the special chemical structure and antidepressant properties of alprazolam, but even the standard benzodiazepine, diazepam, recently has been shown to reduce the frequency of panic attacks in a double-blind comparison of diazepam, propranolol and placebo (Noyes, Anderson, Clancy, Crowe, Slymen, Ghoneim and Hinrichs, 1984). This is the only study in which high doses of diazepam were administered to panic attack patients at regular intervals. The second claim, that antidepressants are not effective in treating anticipatory anxiety, is still largely untested. There are as yet no published studies on the effects of antidepressants to anxiety in patients with a chief complaint of generalized anxiety. A study in press (Kahn *et al.*, cited in Klein, 1984) apparently finds that these drugs reduce anxiety in anxious patients without panic attacks. In several studies of patients with other primary diagnoses, tricyclic antidepressants significantly reduced generalized anxiety (cf. Matthews *et al.*, 1981, pp. 57-59; Marks, 1983a). Marks (1983a) concludes in his review that tricyclics have a broad spectrum of effects not limited to dysphoria or panic attacks.

Several problems remain concerning the efficacy of antidepressants (tricyclics and MAO inhibitors) in panic attacks. While these drugs are beneficial at least in the range of weeks to months (Grunhaus, Gloger and Weissturb, 1981; Matuzas and Glass, 1983; Telch, Agras, Taylor, Roth and Gallen, 1985), it is unknown whether they retain their effects after years of continued treatment and relapse rates after discontinuation may be high (Pohl, Berchou and Rainey, 1982; Keefe and Agras, 1983; Marks, 1983a). Furthermore, the mechanism of their action is unclear. There are at least two other hypothetical mechanisms in addition to Klein's postulation of direct blockade of the attacks by an (as yet unknown) biological mechanism:

- (a) the depression-mediation mechanism (Marks, 1983a)—antidepressants relieve depressive symptoms, which secondarily results in a reduction of panic attacks;
- (b) the exposure-facilitation mechanism (Telch *et al.*, 1985)—antidepressants facilitate exposure to the feared situations, which results in a reduction in panic frequency; mechanisms A and B may not be independent.

Panic induction

Klein and Sheehan claim that about 65-100% of panic patients respond to sodium lactate infusions with panic attacks, while controls never or only very rarely do so. They conclude from

this that panic patients have a specific biological vulnerability (Klein, 1981; Shader *et al.*, 1982; Carr and Sheehan, 1984). However, the empirical support for this conclusion is far from unequivocal. In a recent review we documented severe methodological problems in the 13 published studies of sodium lactate infusions that limit their interpretation (Margraf, Ehlers and Roth, 1986a). Demand characteristics of the experimental situation and expectancy bias often were not adequately controlled. Relevant intervening cognitive variables were not taken into consideration. The similarity of the effects of lactate infusions and naturally occurring panic attacks has not been adequately assessed. Aside from these problems, the results of these studies indicate that lactate infusion is not a sensitive and specific way to diagnose panic disorder. If differences in baseline levels of subjective anxiety and physiological arousal are taken into consideration, the responses of patients and controls to lactate do not seem to differ.

In our laboratory we found that lactate infusions induce increases in subjective anxiety and physiological arousal that were approximately equal in panic patients and normal control Ss (Ehlers, Margraf, Roth, Taylor, Maddock, Sheikh, Kopell, McClenahan, Gossard, Blowers, Agras and Kopell, 1986c). The level of anxiety and physiological arousal that Ss reached depended more on their baseline levels rather than their diagnoses. Patients had higher levels of anxiety throughout the experiment. Their response to lactate, however, did not differ from that of the controls. Overall the effects of lactate appeared to be rather moderate in intensity. These data and the data summarized in our literature review are not compatible with the interpretation of the response to lactate as a biological marker for panic attacks.

As of today, none of the proposed biological mechanisms seems to explain the effects of lactate infusions sufficiently. A more comprehensive model that includes the interaction of perceived physiological changes, environmental cues, and, depending on individual learning experiences, the appraisal of this information as dangerous is probably more realistic (Ackerman and Sachar, 1974; Margraf *et al.*, 1986c). The same applies to CO₂ inhalation which has been put forward as an alternative challenge to lactate (van den Hout and Griez, 1982, 1984; Gorman, Askanazi, Liebowitz, Fyer, Stein, Kinney and Klein, 1984; Ehlers, Margraf and Roth, 1986a, b).

Family data

There are considerably fewer twin and family studies of anxiety disorders than of psychoses. Most of the data are based on older diagnostic schemes that did not divide anxiety patients on the basis of panic attacks, and the description of the patients is generally not sufficient to divide them retrospectively (McInnes, 1937; Brown, 1942; Wheeler, White, Reed and Cohen, 1948; Cohen, Badal, Kilpatrick, Reed and White, 1951; Slater and Shields, 1969; Noyes, Clancy, Crowe, Hoenk and Slymen, 1978; Carey and Gottesman, 1981; Cloninger, Martin, Clayton and Guze, 1981). There are several family studies of agoraphobia (Solyom, Beck, Solyom and Hugel, 1974; Buglass, Clarkem, Henderson, Kreitman and Presley, 1977; Burns and Thorpe, 1977; Harris, Noyes, Crowe and Chaudhry, 1983; Moran and Andrews, 1985). Only the most recent studies are based on DSM-III diagnoses and report data on panic disorder (Raskin, Peeke, Dickman and Pinsker, 1982; Crowe, Noyes, Pauls and Slymen, 1983; Leckman, Weissman, Merinkangas, Pauls and Prusoff, 1983; Torgersen, 1983).

In general these studies find an increased familial risk for anxiety disorders, including panic disorder, as well as higher concordance rates for monozygotic than dizygotic twins, but there are inconsistencies and exceptions. There are data on both sides of the question of whether generalized anxiety is familially transmitted (Slater and Shields, 1969; Carey and Gottesman, 1981; Crowe *et al.*, 1983; Leckman *et al.*, 1983; Leckman *et al.*, 1983; Torgersen, 1983). Similarly, the data on agoraphobia are contradictory (Solyom *et al.*, 1974; Buglass *et al.*, 1977; Burns and Thorpe, 1977; Harris *et al.*, 1983; Moran and Andrews, 1985). The claim of a genetic factor for panic independent of anticipatory (generalized) anxiety seems to be supported by Torgersen (1983). However, Raskin *et al.* (1982) did not find differential incidences of panic and generalized anxiety in families of patients with one or the other disorder. The data of Leckman *et al.* (1983) from depressed and anxious patients also do not support independent familial transmission of panic and generalized anxiety. Finally, several studies found a significantly increased risk for anxiety disorders only or mainly in female relatives (Solyom *et al.*, 1974; Burns and Thorpe, 1977; Cloninger *et al.*, 1981; Crowe *et al.*, 1983; Harris *et al.*, 1983; Moran and Andrews, 1985).

The results in family and twin studies depend strongly on the criteria used for determining concordance and diagnosis. Carey and Gottesman (1981) found that if one twin was phobic, there was a higher probability that a dizygotic rather than a monozygotic co-twin had received psychiatric or general medical treatment for 'nervous' problems (DZ 46% vs MZ 25%). However, they were able to reverse this result by classifying the co-twins on a looser, more poorly specified criterion of being psychiatrically 'noteworthy' (they use the German word 'auffällig' (DZ 38% vs MZ 88%).

In addition, there are contradictions between twin and family studies: different groups of relatives that share similar genetic risks are reported to have widely differing rates of panic disorder or other anxiety disorders. For example, lower rates are reported for dizygotic twins (Slater and Shields, 1969; Torgersen, 1983) than for siblings in general. Similarly, the concordance between siblings is less than between parents and children (Brown, 1942; Cohen *et al.*, 1951; Crowe *et al.*, 1983; Moran and Andrews, 1985). Furthermore, the rates for monozygotic twins are within sampling error of the rates for other first-degree relatives (Slater and Shields, 1969; Carey and Gottesman, 1981; Torgersen, 1983).

In spite of these problems, the evidence supporting a familial risk of anxiety and panic disorder is consistent with the claimed genetic factor for panic disorder. However, whether the familial risk is a genetic one can only be determined from adoption studies, which are currently lacking. In addition, we cannot yet say whether the familial risk for panic is independent of the risk for generalized anxiety. Finally, the large percentages of non-concordant monozygotic twins (59–69%) and non-affected first-degree relatives (averaging about 85%) show the strong influence of non-genetic factors.

Spontaneity of panic attacks

The claim by most proponents of biological models that panic attacks are spontaneous is based entirely on clinical impressions as is the psychoanalytic notion that panic attacks are triggered by unconscious ideas. Klein and Sheehan quote no studies of the spontaneity of panic attacks and fail to specify the notion of spontaneity sufficiently. Commonly, it is referred to in two ways. First, a significant proportion of panic attacks appear unpredictable to the patient. This seems to be confirmed by clinical impressions and recent data by Barlow, Vermilyea, Blanchard, Vermilyea, Di Nardo and Cerny (1985), Taylor, Sheikh, Agras, Roth, Margraf, Ehlers, Maddock and Gossard (1986) and Margraf, Taylor, Ehlers, Roth and Agras (1986c). Second, the term 'spontaneous' is used to indicate that panic attacks are due to a biological dysfunction and represent an autonomic discharge that is independent of psychological, perceptual and situational factors. This notion of spontaneity has not been approached empirically by biologically oriented researchers.

There is little argument that at certain times in a clinical course, non-specific psychological or physiological stress can contribute to the overall frequency of panic attacks (Brehony and Geller, 1981; Mathews *et al.*, 1981; Raskin *et al.*, 1982; Tearnan, Telch and Keefe, 1984; Uhde, Boulenger, Roy-Byrne, Graci, Vittone and Post, 1985). Klein (1964) himself originally quoted 'endocrine fluctuations' (such as those associated with birth, menopause, gynecological surgery etc.) as a context for the onset of panic disorder in a subgroup of patients. In addition, there is one study that suggests a degree of specificity of life events related to panic disorder. Finlay-Jones and Brown (1981) demonstrated a greater frequency of 'danger'-related events preceding the onset of anxiety and panic symptoms or their exacerbations. 'Loss'-related events were more likely to lead to depression. It remains to be determined why some people are resistant to stressors that are pathogenic in others.

In addition, it is quite clear that precipitating events operating in a time frame of days or hours can be important (Brehony and Geller, 1981; Mathews *et al.*, 1981; Raskin *et al.*, 1982). These precipitants can be a feared situation or anticipation of a feared situation, or non-specific stress. Rachman and Levitt (1985) for instance, were able to induce panic attacks by exposing claustrophobic Ss to an enclosed room. When panic attacks occur in feared situations, they can be said to be spontaneous only in the sense that their exact time of occurrence within the larger time frame or context cannot be predicted.

However, most central to the validity of current biological models of panic attacks is whether immediate external or internal triggers for individual panic attacks exist. If such triggers are

regularly present, the distinction between 'spontaneous' panic (as defined above) and other kinds of anxiety is vitiated. The most promising candidates for such triggering events are internal cues, either bodily sensations interpreted as dangerous or anxiety-inducing thoughts and images. Beck, Laude and Bohnert (1974) and Hibbert (1984) found specific cognitions preceding or accompanying panic attacks or anxiety episodes in all investigated patients. The panic patients' cognitions were more intrusive, clear and dramatic, and were centred more on death, illness and loss of control than those of patients without panic attacks. This is consistent with the data quoted above by Finlay-Jones and Brown (1981) on the specific relevance of 'danger' for this patient group.

External and internal cues are more likely to be perceived and appraised as threatening by anxious patients. Selective information processing of threat cues in these patients was demonstrated in a series of studies by Mathews and coworkers (Butler and Mathews, 1983; Mathews, 1984; Mathews and MacLeod, 1985) who took objective measures such as reaction time in addition to self-reports. Hibbert (1984) found that the most frequent sequence of events in panic attacks was the perception of an unpleasant bodily sensation (e.g. sweaty palms, dyspnea or palpitations), followed by anxious catastrophizing cognitions and the full-blown clinical picture of a panic attack. In the same vein, Ley (1985) recently reported that in the majority of patients fear is preceded by the perception of somatic symptoms. Thus, investigations more systematic than ordinary clinical interviews, suggest that definite events and cognitions are related to at least some individual panic attacks.

Separation anxiety

Indirect evidence for Klein's belief that childhood separation anxiety involves the same biological mechanism as adult panic attacks comes primarily from his own investigations. In an unstandardized retrospective study without a control group, in which the interviewers were not blind to the patients' diagnoses, Klein (1964) found a history of childhood separation anxiety in 50% of the panic attack patients. In another retrospective study, Gittelman-Klein and Klein (1984) report that 50% of their female agoraphobic patients [a subgroup of the sample of Klein, Zitrin, Woerner and Ross (1983)] had a history of childhood separation anxiety, as opposed to only 27% of the patients with specific phobias. The two patient groups differed similarly for current complaints of separation anxiety (47% vs 22%). For male patients these differences were not present.

In contrast, in a series of standardized and controlled studies there were no differences between agoraphobics and control Ss or other anxiety patients in the frequency of permanent or longer-term separation from the parents before age 15 yr, the death of a parent, signs of separation anxiety during shorter separations from the mother or difficulties in attending school ('school phobia') (Berg, Butler and Pritchard, 1974; Solyom *et al.*, 1974; Buglass *et al.*, 1977). Similarly, the comparison of panic disorder and generalized anxiety disorder patients yielded no significant differences for childhood separation anxiety, longer-term separation before age 10 yr or the number of separations experienced before onset of the anxiety disorder (Raskin *et al.*, 1982). Coryell, Noyes and Clancy (1983) found no difference in early loss or divorce of the parents between patients with panic disorder and primary unipolar depression. It is uncertain whether agoraphobic families differ in stability from other families [for a review, see Tearnan *et al.* (1984)].

Klein refers to 'school phobia' data in his arguments for separation anxiety as a vulnerability factor. However, family studies of school phobia do not support the genetic transmission of a tendency to separation anxiety from agoraphobic parents to their children. While Berg (1976) found in an uncontrolled study that 7-14% of the offspring of agoraphobics were school phobics, the same group (Berg *et al.*, 1974) had reported no more psychiatric problems in the parents of school phobic children than in the parents of a control group. Similarly, Gittelman-Klein (1975) did not find a single case of agoraphobia among the parents of 45 school phobic children. In addition, considering the extent of school phobia as an operationalization of separation anxiety is not without problems, since there are diverse reasons for school 'phobic' behaviour in children.

The success of tricyclic antidepressants in treating school phobia is not yet well established. Gittelman-Klein and Klein (1973, 1980) found a positive effect of imipramine in doses of up to 200 mg, while Berney, Kolvin, Bhate, Garside, Jeans, Kay and Scarth (1981) found no effect of a lower dose of up to 75 mg of clomipramine. In animal studies, positive effects of imipramine on distressed behaviour following separation were observed (Suomi, Seaman, Lewis, Delizio and

McKinney, 1978; Scott, Stewart and DeGhett, 1973). However, according to Gittelman-Klein and Klein (1984), a previous or current history of separation anxiety does not correlate with therapeutic success of imipramine in the treatment of agoraphobic patients.

Thus, the claimed relationship between childhood separation anxiety and adult panic attacks, which often occur 'spontaneously' without the stimulus of separation, is tenuous. Experiences of separation do seem to precede the first occurrence of agoraphobic symptoms in a subgroup of patients (cf. Tearnan *et al.*, 1984). However, separation is only one of many stressors, and other interpersonal problems are reported more often. Furthermore, separation as a stressor does not precede panic disorder more often than generalized anxiety disorder (Raskin *et al.*, 1982). The strongest association between childhood separation and adult psychiatric problems is not with anxiety at all, but with depression (Tennant, Smith, Bebbington and Hurry, 1981; Tennant, Hurry and Bebbington, 1982). All conclusions, however, based on the studies cited in this section, are tempered by the fact that all of the studies were retrospective: no prospective studies have been conducted.

ALTERNATIVE APPROACHES

Other models of panic attacks and panic disorder are currently less comprehensive and less developed. The most relevant approaches question the spontaneity of panic attacks and generally postulate an interaction of psychological and physiological factors in the development and maintenance of panic disorder. Several authors assume a positive feedback loop between physiological changes and the person's response to perceiving these changes (Beck and Emery, 1979; Mathews *et al.*, 1981; Margraf *et al.*, 1986a; Clark, 1986; Barlow, 1986). Possible cognitive processes involved have been mentioned above in the section on spontaneity of panic attacks. Some authors specify possible physiological components or antecedents involved in panic attacks. Most often suggested are hyperventilation, vestibular dysfunction and cardiovascular events.

Hyperventilation

The role of hyperventilation in panic attacks and agoraphobia is emphasized by a group of British researchers (Lum, 1981; Clark and Hemsley, 1982; Bonn, Readhead and Timmons, 1984; Clark, Salkovskis and Chalkley, 1985; Salkovskis, Jones and Clark, 1986a). According to them, the cause of seemingly spontaneous panic attacks is very often chronic or episodic hyperventilation of which the patient generally is not aware. Standardized hyperventilation procedures produced symptoms similar or identical to panic attacks in the majority of panic patients (Bonn *et al.*, 1984; Clark *et al.*, 1985; Salkovskis and Clark, 1986; however, cf. Gorman *et al.*, 1984). Similar but less intense symptoms were produced in normal controls and other patient groups (Lum, 1981; Clark and Hemsley, 1982). In one study 67% of the panic patients, but only 4% of the normal controls were unable to complete a hyperventilation procedure requiring 60 breaths/min for 3 min (Bonn *et al.*, 1984)—20 of the 21 patients rated the effects of this procedure as similar to naturally occurring panic attacks, although less intense. Bonn *et al.* (1984) also found a high resting respiration rate (28 cycles/min) in these patients. However, they do not report values for the control group. Consistent with hyperventilation Salkovskis *et al.* (1986a) found significantly lower $p\text{CO}_2$ -values at rest in panic patients whose attacks were rated as similar to the effects of hyperventilation than in matched normal controls. The $p\text{CO}_2$ -values correlated significantly with the perceived similarity of panic and hyperventilation. In several treatment studies involving rather small samples but up to 2 yr of follow-up, both panic frequency and agoraphobic behaviour could be controlled or eliminated by a combination of respiration training, cognitive restructuring and, in some cases, exposure to feared situations (Bonn *et al.*, 1984; Salkovskis and Clark, 1986; Clark *et al.*, 1985; Salkovskis *et al.*, 1986a). The $p\text{CO}_2$ -values were increasingly normalized with successful treatment. At follow-up, the combination of respiration training and exposure was significantly better than exposure alone [further improvement vs mild worsening (Bonn *et al.*, 1984)]. The results of hyperventilation procedures, $p\text{CO}_2$ -values and therapy effects argue strongly in favour of a role for hyperventilation in at least some panic attacks. In addition, there are now a few case reports that show hyperventilation in naturally occurring panic attacks by ambulatory monitoring of transcutaneous CO_2 and measurement of blood gases (Salkovskis, Warwick, Clark and Wessels,

1986b). However, it is unclear in what percentage of panic patients hyperventilation may be involved, since respiratory complaints are not primary for all patients (cf. Garszen, van Veenendaal and Bloemink, 1983).

Vestibular dysfunction and cardiovascular events

Vestibular dysfunction could play a role in panic patients whose main complaints are dizziness and feelings of unsteadiness. Jacob, Moller, Turner and Wall (1985) found that a high frequency of such patients showed abnormal vestibular or auditory function without specific neurological disorders being present: 67% of the patients showed positional or spontaneous nystagmus, 56% had abnormal responses to caloric stimulation, 35% to rotational tests and 32% to posturography. Pure tone audiograms were abnormal in 26% and acoustic reflexes in 44% of the patients. These results are consistent with the finding of a high prevalence of anxiety neurosis (41%) in patients referred with vestibular disorders who turned out to have an abnormal response to caloric stimulation (Hood, 1975). In the same vein, Hallam and Stephens (1985) recently found that tinnitus sufferers complaining of dizziness show much higher somatic and phobic anxiety scores on a standardized test of psychopathology.

Ambulatory monitoring of heart rate and physical activity in our laboratory (Taylor, Telch and Havvik, 1983; Taylor *et al.*, 1986; Margraf *et al.*, 1986b) and by Freedman, Ianni, Etedgui and Putezhath (1985) has shown that many self-reported panic attacks (diaries) are accompanied by clear-cut increases in heart rate. Cardiovascular symptoms are reported by nearly all panic patients and number among their most distressing and frequent symptoms. An elevated cardiovascular mortality for male panic patients was found by Coryell, Noyes and Clancy (1982), although another recent study did not find this elevation (Martin, Cloninger, Guze and Clayton, 1985; cf. Black, Warrack and Winokur, 1985). In addition, a higher incidence of mitral valve prolapse has been found in several studies (Pariser, Jones and Pinta, 1979; Kantor, Zitrin and Zeldis, 1980; Venkatesh, Pauls, Crowe, Noyes, van Valkenburg, Martins and Kerber, 1980; see Klein and Gorman, 1984, for a discussion), but not in two others (Hartman, Kramer, Brown and Deveraux, 1982; Shear, Deveraux, Kramer-Foz, Mann and Frances, 1984). Similarly, Tzivoni, Stern, Keren and Stern (1980) found abnormalities such as sinus tachycardias and other arrhythmias in the ambulatory EKG of patients with 'neurocirculatory asthenia'. An anti-anxiety effect of controlling sinus tachycardia in panic patients by having them increase their vagal tone with the Valsalva manoeuvre has recently been shown by Satory (1985).

Critique and integration

At present, it appears unlikely that any single one of these physiological antecedents is implicated in all panic attacks. Other mechanisms associated with special disease states would have to be included in any complete theory (MacKenzie and Popkin, 1983, McCue and McCue, 1984). Estimates of the percentage of panic patients whose attacks might be due to any one of these mechanisms or syndromes are lacking. In any case, there is probably a common final pathway for these different physiological mechanisms in that a perception of unpleasant bodily feelings and their appraisal as dangerous leads to panic. The probability of noticing deviant somatic events and their appraisal as dangerous depends on factors such as the current anxiety level, environmental cues, available explanations for bodily sensations, uncertainty and perceived control, possible coping strategies and the presence of safety signals (Beck, Emery and Greenberg, 1985; Rachman, 1983, 1984a, b). It is also relevant whether the specific bodily sensations and environmental cues have been associated with anxiety states earlier in the individual's learning history. Elsewhere we have specified these processes in greater detail in a cognitive psychophysiological model of the anxiety-provoking effects of lactate infusions (Margraf *et al.*, 1986a). Barlow (1986) also describes a 'psychological' model of panic that relies on interoceptive conditioning as one of its central mechanisms. Recently, Clark (1986) has proposed an excellent formulation of what he terms the 'cognitive approach' to panic. Clark concludes his paper by giving three experimentally testable predictions that follow from a cognitive or psychophysiological model of panic. Another such test is discussed below.

Central to all of the above approaches is the hypothesis of a positive feedback loop between bodily sensations and response to their perception. Even though this hypothesis is directly

amenable to experimental testing, empirical studies are scarce. One way of testing the hypothesis is to give the *S* false feedback of sudden heart rate increases, thus manipulating perceived but not real physiological arousal. The hypothesis predicts a stronger response in panic patients than in normal controls if the feedback is perceived as accurate. Preliminary results from a study currently in progress in our laboratory show this pattern (Ehlers, Margraf, Roth, Taylor and Birbaumer, 1985; Margraf *et al.*, 1986b). Among *Ss* who believe that the feedback is accurate, the panic patients respond with significant increases in physiological arousal (heart rate, systolic and diastolic blood pressure), while normal controls do not show increased arousal and thus do not show a positive feedback pattern.

Additional evidence shows that panic patients specifically are more aware of anxiety-related somatic events in that they report such events more often than patients with generalized anxiety (Hoehn-Saric, 1981, 1982; Anderson, Noyes and Crowe, 1984; cf. Tyrer, 1973, 1976). We have recently demonstrated significant somatization in panic attack patients and a substantial overlap with somatization disorder (King, Margraf, Ehlers and Maddock, 1986). Chambless (1982) and Foa *et al.* (1984) quote several studies showing hypochondriacal attitudes in agoraphobic patients with panic attacks. Perhaps anxious and hypochondriacal patients are more capable of accurate perception of their bodily functions than other persons and therefore are more sensitive to changes [see Tyrer, Lee and Alexander (1980) for cardiac awareness]. That anxiety patients respond selectively to the preception of verbal somatic threat cues has been shown by Mathews and MacLeod (1985) using a modified Stroop colour-naming task. This result has been replicated with other paradigms (MacLeod, Mathews and Tata, 1986; Mathews and MacLeod, 1986). The work of this group bears implications for the feedback loop suggested by Margraf *et al.* (1986a) and Clark (1986). These studies demonstrated that selective attention towards threat cues can occur long before the *S* is aware of the stimulus material. If the same is true in panic, selective attention allocation towards bodily changes might start the positive feedback loop at a much earlier stage of information processing than the models currently under discussion proposed.

CONCLUSIONS

Current biological models have had major consequences for the theory and therapy of panic attacks and agoraphobia. While drawing needed attention to the special features of panic attacks and the patients suffering from them, authors such as Klein and Sheehan are able to garner surprisingly little evidence for some of their central assumptions. Our review of the literature found no support for the claim of drug specificity for panic vs other types of anxiety. The so-called panic-induction studies provide no basis for Klein's or Sheehan's models. Genetic transmission of proneness to panic independent of generalized anxiety has yet to be demonstrated. Although the question of spontaneity of panic attacks has only recently begun to be studied adequately, there is some evidence for internal cues immediately triggering individual panic attacks. Finally, the relationship between childhood separation anxiety and adult panic attacks is tenuous, possibly due to the purely retrospective nature of the studies carried out so far. We conclude that models focusing entirely on the effects of biological on psychological states are not compatible with the complexity of the phenomena studied and with the majority of the empirical data. An interactive view that includes the role of cognition and learning seems more able to cope with the data. Such a model has to specify the physiological antecedents or components of panic. Several such mechanisms were presented, although it is unlikely that any one of them can completely explain the complexities of panic attacks.

One of the major implications of models such as those of Klein and Sheehan is that the panic attacks themselves should be a focus of treatment. This is a positive step since, even though the attacks are an important source of suffering and their alleviation may be crucial for permanent recovery, previous treatment approaches tended to neglect them. The poor prognosis of agoraphobia as opposed to simple phobias (Marks, 1970) as well as the relapses of agoraphobics occurring even after successful behaviour therapy (Munby and Johnston, 1980; Emmelkamp and van der Hout, 1983; Thorpe and Burns, 1983; Bonn *et al.*, 1984) may be due to recurring panic attacks. In addition, there may be theoretical reasons for considering panic attacks to be a separate phenomenon from avoidance behaviour, regardless of whether there are qualitative differences

between panic and other types of anxiety (Rachman and Hodgson, 1974; Eysenck, 1980). A model that explicitly takes panic attacks into consideration is better suited to explain the multiple phobias of agoraphobic patients than are pure conditioning models, but perhaps not better than more refined conditioning models that make use of Seligman's (1971) 'preparedness' hypothesis (cf. Öhman, 1979). In addition, it seems desirable for any complete theory to include the role that safety signals play in anxiety processes. The safety signal hypothesis originally proposed by Mowrer (1960) and developed by Gray (1971) and Seligman and Binnik (1977), has recently been adapted to agoraphobia by Rachman (1984a, b). The potential value of the safety signal perspective for the modification of agoraphobic behaviour has been discussed by Rachman (1983).

Both drug and psychologically-based treatments have been successful in treating panic attacks (Sheehan, 1982b; Bonn *et al.*, 1984; Clark *et al.*, 1985; Salkovskis *et al.*, 1986a). Goldstein (1982) was able to achieve improvement or complete remission in 71.4% of his agoraphobic patients and a nearly total elimination of panic attacks (1-year follow-up) using non-drug methods. However, the efficacy of different methods for treating panic attacks must be determined independently of any inferred etiology of those attacks. Many authors seem to think that a biological (or psychological) cause necessitates a biological (or psychological) therapy. This conclusion does not follow logically (Freedman, 1982). The same criticism applies to the attempt to infer necessary causes from successful treatments.

The attractiveness of the DSM-III classification of anxiety disorders hinges in part on whether the theory that there are two qualitatively different types of anxiety is confirmed by further evidence. There are also problems in the clinical application of this classification in that DSM-III and probably DSM-III-R (Spitzer and Williams, 1984) make distinctions that are not reasonable for every patient and every clinical course (cf. Hallam, 1978; Marks, 1983a; Sheehan and Sheehan, 1983; Foa *et al.*, 1984). Many patients with generalized anxiety disorder show (less frequent) panic attacks and patients with panic disorder or agoraphobia with panic attacks have in general a high level of generalized anxiety. The overlap of anxiety and depressive disorders, explicit in Klein's theory and confirmed clinically and experimentally (e.g. Finlay-Jones and Brown, 1981; Boyd, Burke, Gruenberg, Holzer, Rae, George, Karno, Stoltzman, McEvoy and Netsadt, 1984; Breier, Charney and Henninger, 1984; Mathews, 1984), is another problem for future classification systems.

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