1. Emotional Behaviour and the Limbic System

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Introduction

As the old slogan had it, 'no psychosis without neurosis'. The meaning of these words has now changed, so that a translation into contemporary English is needed: no mental illness without disturbance in brain function. This principle remains valid today, and its validity extends to the field of psychosomatic diseases: psyche affects soma by way of its material substrate, the brain (and soma, of course, affects psyche by the same route). One further act of translation is needed to bring this preamble up to date: by 'psyche' is meant the systems that control behaviour. There are therefore four terms in the interactions that concern us: the body (soma), behaviour, the systems that control behaviour (psyche), and the brain. An earlier fashionable contrast for the last two of these terms (psyche and brain) qualified them as the 'conceptual' and the 'real' nervous systems; a more recent one contrasts them as 'software' and 'hardware'.

The mental states that have most often been implicated in the genesis and maintenance of psychosomatic illness are the emotions. It would seem therefore that full understanding of psychosomatic illness will require a successful analysis of the brain mechanisms that mediate the emotions and of their input-output relations with the body. We are still a long way short of possessing such an analysis -- so far short, indeed, that any attempt even to list the different emotions (assuming that they can eventually be differentiated one from the other) would be at the moment a highly speculative enterprise. In this chapter, therefore, I shall concentrate on those aspects of the emotions and emotional behaviour about which one can say something concrete. This strategy will narrow my scrutiny to anxiety, depression and the development of tolerance for stress; and even in this
foreshortened list, as we shall see, there is doubt as to whether one can distinguish the brain mechanisms that underlie anxiety and depression respectively.

Anxiety is probably the emotion that has most often been related clinically to psychosomatic symptoms; it is also, I believe, the emotion whose neurology is at present most fully understood. It is therefore the most natural place at which to start.

The Neurology of Anxiety

An obvious problem in studying the neural basis of any mental state is that one cannot do experiments with the only organisms – people – that can attempt to describe their mental states (though, to be sure, such descriptions are in any case notoriously fallible). We can glean what information we can from the random insults to the brain that accident and disease cause our fellows; but, for systematic research, we have no alternative but to make use of animals. However, we then face the equally difficult problem of determining what mental states the subjects of our experiments experience. Stated this way the problem is not merely difficult, it is apparently intractable. But it can be reduced to manageable proportions by making use of the translation rules we have just established. A mental state is a state of the systems that control behaviour. Furthermore, such a state is inferred from observations of behaviour and used to account for and predict behaviour – a formulation that is as true when applied to people as when applied to rats, cats or monkeys. It is thus no harder (and, given the relatively greater simplicity of their behaviour, may even be easier) to do this for animals than for people. We can at the very least subject our inferences about the emotional states of, say, a laboratory rat to systematic and rigorous experimental test – something rarely if ever possible with human beings in or out of the laboratory. So the problem lies, not in the ascription of mental states to animals, but in determining the equivalence of the states so ascribed to those experienced by people. In short, the question that must first concern us here is: Is it possible to ascribe to experimental animals a state sufficiently similar to the human state of anxiety to allow one to study the neurology of anxiety in animals?

I have posed and answered this question at some length elsewhere [Gray, 1982a, b]. The solution to our problem turns on the use as an experimental tool of the anti-anxiety drugs (including principally the benzo-
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Inputs
- Signals of punishment
- Signals of nonreward
- Novel stimuli
- Innate fear stimuli

Behavioural inhibition system

Outputs
- Behavioural inhibition
- Increment in arousal
- Increased attention

Anti-anxiety drugs

Fig. 1. The behavioral inhibition system. This responds to any of its adequate inputs with all of its outputs, and comprises the hypothetical substrate on which the anti-anxiety drugs act to reduce anxiety.

diazepines, the barbiturates and alcohol [Gray, 1977]. These drugs appear to be effective in the acute control of anxiety in man [Rickels, 1978]. Can we then use them to ask (by studying their mode of action in the brain) what neural mechanisms mediate anxiety? The answer to this question is a conditional ‘yes’ – but the condition is a hard one to meet: we must first show that the behavioural effects of the anti-anxiety drugs in animals are consistent with the hypothesis that animals possess a mental state similar to human anxiety and that this state is reduced by the action of the drugs. (The same condition, mutatis mutandis, applies to the use of all psychotropic agents as probes of animal mental states, but it is one that is normally more honoured in the breach than in the observance.)

In an attempt to see whether this condition can be met, I have reviewed some 400 experiments in which one or other of the anti-anxiety drugs have been administered to species ranging from goldfish to chimpanzees [Gray, 1977]. The results of the very diverse procedures that have been used in these experiments yield to a satisfyingly simple set of generalisations (summarised in fig. 1). One may account for the great majority of the experimental findings by the following rules. First, three kinds of stimuli are functionally equivalent in the types of behavioural change they elicit; these are stimuli associated with pain or punishment, stimuli associated with nonreward (i.e. the non-occurrence of anticipated reward) or failure, and novel stimuli (left-hand side of fig. 1); other kinds of stimuli (including pain and nonreward as such) do not elicit same types of behavioural change. Second, the types of behavioural change elicited by these stimuli consist in inhibition of ongoing behaviour, increased level of
arousal (so that the next initiated behavioural act is performed harder or faster than usual), and increased attention to the environment and especially novel elements in the environment (right-hand side of fig. 1). Third, all these types of behavioural change in response to any of the appropriate stimuli are reduced by administration of any of the anti-anxiety drugs.

One can interpret these findings by supposing (1) that the brain contains a special-purpose system (the behavioural inhibition system in fig. 1) whose behavioural outputs (listed to the right of fig. 1) occur in response to any of the inputs listed to the left, and (2) that activity in the behavioural inhibition system is counteracted by the anti-anxiety drugs. We next go one step further and postulate (3) that activity in the behavioural inhibition system constitutes the mental state of anxiety. We can now state that anxiety is (in every-day language) a state produced by the threat of pain, punishment, nonreward or failure, or by an encounter with a novel or uncertain environment; and that, in a state of anxiety, one 'stops, looks and listens' and prepares for hard and rapid action. This, I think, would be recognised by the proverbial man on the Clapham omnibus as a plausible account of human anxiety, yet it is entirely based upon experiments with animals. It is this fact which gives me courage to suppose that animals possess a state of anxiety that is closely similar to the human state bearing that name.

If this conclusion is accepted, several others flow from it. First, note that the generalisations summarised in figure 1 appear to apply equally well to all the species tested, from goldfish to chimpanzees (although the great bulk of the data have come from experiments with rodents). This implies that anxiety is phylogenetically old and depends neither on the great growth of the neocortex in man nor on the recognition of one's own mortality nor on the stresses of modern life nor yet on the Oedipus complex. This conclusion is backed up by biochemical evidence, which demonstrates that the high-affinity specific benzodiazepine receptor recently shown to be located on neuronal membranes [Mohler and Okada, 1977; Braestrup and Squires, 1977] is present in the same form in higher bony fish and in mammals including man [Nielsen et al., 1978]. Phylogenetic longevity in turn implies that anxiety is functionally useful – it is not there to bring some of us into hospital but because, in our evolutionary past, it has helped all of us to survive. The same line of argument leads to a further important conclusion: we may seek in the brains of animals for a phylogenetically stable neural substrate of anxiety and have some hope of finding it.
These considerations guide our search towards structures older than that late-flowering plant (phylogenetically speaking), the neocortex. Other sign-posts point in the same direction: a wealth of evidence from experiments in which the brain has been lesioned in diverse manners, or stimulated electrically or chemically, implicates as the heartland of emotional experience the complex of interconnected structures that make up the limbic system [Isaacson, 1974] perhaps together with the hypothalamus [Panksepp, 1982]. It is here, therefore, that we should start searching for the neural substrate of anxiety.

There are two rather different ways of going about this search. The first and obvious way is to ask directly of the anti-anxiety drugs what they do in the brain - to membranes, synapses, receptors, transmitters and the like. But this direct approach runs into difficulties. Like all drugs, anti-anxiety drugs have more than one kind of effect: besides reducing anxiety, they are (among other things) muscle relaxants, sedatives and anti-convulsants. Discovery, therefore, that anti-anxiety drugs have such-and-such an effect on, say, a receptor fails to tell us that this effect is related to anxiety reduction, because it could equally well underlie some other 'side effect' (from our point of view) of the drug. While this problem is general in the analysis of drug action, it is particularly acute in regard to the anti-anxiety drugs, since their best-documented biochemical effect (clear for both benzodiazepines and barbiturates and possibly involved also in the action of alcohol) is to enhance the synaptic efficacy of the inhibitory neurotransmitter, g-aminobutyric acid (GABA) [Costa, 1983]. The benzodiazepines do this by way of their specific receptor, which is closely coupled to GABA receptors [Bowery, 1984], the barbiturates perhaps by way of yet another receptor forming part of the same supramolecular complex [Olsen, 1981]. But GABA (and benzodiazepine) receptors are distributed throughout the central nervous system, including the spinal cord, so this fact about the neurochemical actions of anti-anxiety drugs barely narrows at all the range of possible sites at which the brain might mediate anxiety. What we have instead is an excellent means of anti-convulsant action - the deepening of a general inhibitory blanket on the brain.

In the absence of more specific indications of the neural basis of anxiety from the direct approach, we must supplement our search by an indirect approach to the problem. This is the approach favoured by psychologists, to whom it is natural to ask (fig. 1): 'What can I do to the brain which will mimic the actions of the anti-anxiety drugs in behavioural tests that are sensitive to the functions of the behavioural inhibition system?'
Or: ‘What can I do to the brain which will produce effects in such tests that are diametrically opposed to those of the anti-anxiety drugs?’ Answers to these questions should pin-point those regions of the brain that are crucial to anti-anxiety behavioural action (though, to be sure, we shall also need to demonstrate how the known neurochemical actions of the drugs can give rise to altered functioning in these regions of the brain).

These too are questions that I have considered extensively elsewhere [Gray, 1982a, b]. Before I outline the conclusions I reached, a word of caution is in order. We should not expect to uncover any simple one-to-one mapping between structures in the brain and concepts in our psychology. If we are correct in delineating a separate psychological state, e.g. that of anxiety, it follows that there are structures in the brain which mediate that state; but it does not follow either that these structures will themselves be neatly separable from other brain structures nor that they discharge only one set of functions corresponding to only one psychological state. There is almost bound to be, in other words, only partial overlap between psychological concepts and anatomical boundaries: a given psychological function will require many structures for its discharge, and the structures may themselves vary in relation to the exact manner in which the function is discharged; and a given structure will play a role in the discharge of many different functions. These important caveats must not be lost from sight in the dogmatic summary of conclusions that follows.

Chief among these conclusions is that a central role in the neuro-psychology of anxiety is played by the septo-hippocampal system [Elliot and Whelan, 1978]. The major (but not the only) item of evidence upon which this conclusion rests is the remarkable similarity that exists between the behavioural syndrome observed after administration of the anti-anxiety drugs [Gray, 1977], on the one hand, and lesions to the septal area or hippocampal formation [Gray and McNaughton, 1983] on the other. The extent of this similarity is so great that it is difficult to believe that the anti-anxiety drugs do not include an impairment in the functioning of the septo-hippocampal system as one of their major paths of action. This conclusion is in no way inconsistent with the evidence that the mode of action of these substances includes an enhancement of GABAergic inhibition. There are many routes by which such enhanced inhibition might give rise to reduced activity in the septo-hippocampal system, including increased efficacy of GABA within the hippocampal formation or septal area themselves. One particular route, however, appears to be especially important (though not necessarily to the exclusion of others). Ascending monoaminergic inputs
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![Diagram of information processing](image)

Fig. 2. The kinds of information processing required for the successful functioning of the hypothetical comparator (see text for further information).

(both noradrenergic and serotonergic) to the septo-hippocampal system appear to increase the efficiency with which this system processes afferents from the neocortex (via the entorhinal area) [Segal, 1977]. These inputs are especially active under conditions of stress, and this stress-induced increment in their activity is reversed by the anti-anxiety drugs [Lidbrink et al., 1972]. Blockade of the noradrenergic input to the septo-hippocampal system by these drugs could be secondary to enhanced GABAergic inhibition at the cell bodies in the locus coeruleus (in the brain stem) or at terminals within the septal area or hippocampus [Gray et al., 1984]; similarly, blockade of the serotonergic input could be secondary to enhanced GABAergic inhibition at the cell bodies in the median raphe nucleus or at septo-hippocampal terminals.

Knowledge of the brain regions that mediate a psychological state is an important step forward. But it is an incomplete step unless one can supplement this information with an understanding of the particular functions discharged by these brain regions and the manner in which they contribute to the psychological state in question. We do not yet possess such an understanding for anxiety (or for any emotion). However, speculation is possible, and I have indulged in it elsewhere [Gray, 1982a, b]. The central tenet of this speculation is that the septo-hippocampal system, together with its neocortical input (from the entorhinal area) and its connections to Papez' [1937] circuit (subicular area, mammillary bodies, anteriomedial thalamus and cingulate cortex), discharges the function of a comparator (see fig. 2), matching (1) sensory inputs describing the current state of the organism's world to (2) predictions (generated within the same system) as to what those inputs should be. When sensory inputs and predicted inputs...
can be successfully matched, this system confines itself to a monitoring function and behaviour is controlled by other regions of the brain. When a ‘mismatch’ occurs (something happens that is not predicted, something that is predicted fails to happen, or something that is predicted is aversive) then the septo-hippocampal system takes control of behaviour and operates the outputs of the behavioural inhibition system (fig. 1). It would take us too far afield to go into the details of this model of septo-hippocampal function here; its flavour is to some extent captured in figure 3.

Within the framework of this model, anxiety can be conceptualised in two ways. One way is to treat the degree of anxiety as proportional to the number of items that the comparator selects for processing (that is, for
prediction and matching to the world). Viewed in this manner, a high level of anxiety corresponds quite well to the kinds of symptoms displayed by patients with the obsessive-compulsive syndrome: an over-zealous checking of the environment and one's own behaviour, and vigilance for the dangers that may be attendant on both. The second way treats anxiety as proportional to the case with which the comparator declares 'mismatch' and operates the outputs of the behavioural inhibition system. Viewed like this, anxiety corresponds to the kind of symptom displayed by patients with wide-ranging phobias (e.g. agoraphobia). These two ways of looking at anxiety are not mutually exclusive - rather the reverse, since the more items that are monitored the greater is the likelihood (other things being equal) that some discrepancy will be noticed. The frequent co-existence, clinically, of obsessional and phobic symptoms, therefore, is to be expected, given the model. The monoaminergic (especially the noradrenergic) inputs to the septo-hippocampal system (whose activity is boosted by stress) appear to increase the degree to which the comparator selects items (originating from neocortical sensory systems via the entorhinal area) for processing; it is in this way that they increase anxiety. Conversely, the anti-anxiety drugs reduce anxiety by limiting the degree to which these monoaminergic inputs enhance the capacity of the comparator to process information, thus impairing both checking behaviour and the consequent detection of mismatch or the threat of mismatch.

Figure 2 illustrates the psychological functions that must be discharged for such a comparator to work; it can be regarded as a flow-chart of the main 'software' of anxiety. The 'hardware' that instantiates this software is presented diagrammatically in figure 3, with tentative labels attaching particular functions (e.g. the comparator function itself) to particular pathways or regions (e.g. the subicular area) [for details, see Gray, 1982a]. Note that this approach to the psychology of anxiety has come up with a distinctively cognitive theory of its subject matter. This is not altogether surprising, since cognitive processes are necessarily conducted in the brain, and it is by way of an analysis of brain function that the theory has been constructed. But somehow cognitive processes must eventuate in behaviour and in the signs and symptoms of anxiety that the physician observes. So we must next ask; 'How does the system displayed in figure 3 affect the organism in which it is housed?'

In answering this question - and again I must be dogmatic, relying on previous publications [Gray, 1982a, b] - it is useful to refer back to the outputs illustrated to the right of figure 1. (This figure can now be seen as
an earlier 'behaviourist' version of the more fully developed and more cognitive theory shown in figure 3.)

The inhibition of ongoing behaviour that is such a prominent feature of anxiety is most likely mediated by projections that link the septo-hippocampal system (by way of the subicular area) to the basal ganglia and cingulate cortex; a further possible route is provided by afferents to the hypothalamus descending from the septal area. In either event, the inhibition of behaviour is not a direct blockade of motor systems, but seems rather to be executed at the level of programs for action, which are interrupted by messages from the comparator system. There is possibly a difference between the subiculo-cingulate and septo-hypothalamic projections, with the former interrupting learned motor programs and the latter innate ones. The serotonergic projection to the septohippocampal and other systems appears to facilitate the inhibition of motor programs [Williams and Azmitia, 1981].

The increased attention shown as a second output of the behavioural inhibition system (fig. 1) is an integral part of the software depicted in figure 2. Heightened activity in the comparator necessarily requires increased neocortical sensory input via the entorhinal area. Under conditions of mismatch this process probably comes under the direct control of the septo-hippocampal system (allowing selection of significant items for checking) via the projection from the subiculum to the entorhinal cortex (fig. 3). Selection of items for checking is further enhanced (as noted above) by the ascending monoaminergic inputs to the septo-hippocampal system, especially the noradrenergic afferents from the locus coeruleus [McNaughton and Mason, 1980].

Two other features of anxiety appear not to involve the septo-hippocampal system directly but to depend upon the activation of other noradrenergic projections from the locus coeruleus [Redmond, 1979]. The first is the increased readiness for rapid and vigorous action which occurs concurrently with increased behavioural inhibition (and which may be masked by the latter) – i.e. the ‘increased arousal’ of figure 1. This feature of anxiety appears to reflect a rather general effect of locus coeruleus projections throughout the brain. However, a particularly important role is probably played by the projection to the hypothalamus, in which action patterns for innate emotional behavioural routines appear to be stored [Panksepp, 1982]. Noradrenergic projections to the hypothalamus from other brain-stem nuclei besides the locus coeruleus may also play a part in elevating arousal.
The remaining feature of anxiety is often particularly prominent clinically, yet it has so far not been mentioned here and does not even appear as one of the outputs of the behavioural inhibition system depicted in figure 1. This feature consists of the well-known autonomic signs of anxiety (cardiovascular, respiratory, electrodermal, etc.) [Lader, 1975]. Its absence from figure 1 carries no deep significance; it is due simply to the fact that the animal experiments which form the data base for that figure have almost never included measurements of such autonomic responses. However, data summarised by Redmond [1979], in an impressive and wide-ranging review of the neurology of anxiety, allow an easy integration between this feature of anxiety and the others considered already: the autonomic signs of anxiety appear to be mediated largely by efferents from the locus coeruleus that descend into the spinal cord. There is evidence that such autonomic responses are susceptible to blockade by opiate drugs, probably acting upon opiate receptors in the locus coeruleus [Redmond, 1979]. This effect of the opiates contrasts with their failure to exert anxiolytic-like action in well-validated behavioural tests of anxiety [Geller et al., 1963]. I have considered this problem elsewhere and suggested a possible solution [Gray, in press].

This discussion of the neurology of anxiety took as its starting point the action of anti-anxiety drugs. However, some patients fail to respond to these drugs or any other method of treatment. In such cases, a treatment of last resort is provided by psychosurgery. Both prefrontal leucotomy and damage to the cingulate cortex have been shown to reduce anxiety in patients who have suffered severely for many years and who have failed to benefit from either pharmacological or other treatments [for a review, see Powell, 1979]. Further elaboration of the theory of anxiety outlined here is clearly necessary to take account of such drug-resistant anxiety disorders and the role played in them by the prefrontal and cingulate cortices. This elaboration [Gray, 1982a] has taken the form of attributing to the prefrontal cortex a role in establishing control over the functioning of the septo-hippocampal comparator by verbal systems located in the language areas of the neocortex. The route by which such prefrontal control is exerted includes projections to the cingulate and entorhinal areas. According to the theory, control of the comparator by language systems, exercised by this route, is of particular importance in cases in which the source of threat has become largely internalised (e.g. in the form of verbally formulated standards of behaviour that an obsessive patient attempts to meet). It is patients of this kind who appear to benefit most from psychosurgery.
The Neurology of Depression

The brain mechanisms that mediate depression are less well understood than those that mediate anxiety. There are several reasons for this. First, there is still confusion clinically as to whether depression is a unitary condition varying principally in severity or whether it can be subdivided; and, if subdivision is possible, it is still uncertain whether this should be carried out categorically or by ranking patients and/or symptoms along one or more continua [for a discussion of these problems, see Roth, 1979]. Second, almost equally plausible cases can be made for the views that anti-depressant drugs (tricyclics and monoamine oxidase inhibitors) act by increasing or decreasing net monoaminergic (and perhaps especially noradrenergic) synaptic transmission [Stone, 1983]. (Notice that on the former view anti-depressants act in the opposite manner to anti-anxiety drugs, but on the latter view they act in the same manner. This might then imply either that depression is the opposite of anxiety or that it is the same condition as anxiety. If there are two different kinds of depression, the former inference would apply well to 'psychotic' depression, the latter to 'neurotic' depression. These amply complexities are discussed in detail by Gray [1982a].) Finally, there are no clear-cut behavioural tests of depression in animals which might allow the construction for depression of a model equivalent to that shown for anxiety in figure 1.

The research which has so far come closest to providing such tests is related to the concept of 'learned helplessness' [Seligman, 1975]. If an animal is exposed to uncontrollable aversive stimuli (e.g. footshock, forced swimming in cold water) and is then given an opportunity to avoid or escape from such stimuli, there is observed an impairment in the animal's ability to carry out appropriate avoidance or escape behaviour relative to controls initially exposed to controllable or no aversive stimuli. This is the basic phenomenon termed by Seligman [1975] as 'learned helplessness'; however, since there is considerable controversy as to whether the observed behaviour in fact reflects any learning [Weiss et al., 1976], it is safer to term it simply 'helplessness'.

Several arguments support the relevance of helplessness in animals to human depression. There is evidence that, in both conditions, lack of control over aversive events is an important precipitating factor, and that inability to exercise control even when it is possible to do so is an important symptom [Seligman, 1975]. A more wide-ranging similarity of symptoms of the two conditions has been noted by Weiss et al. [1982] and is repro-
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duced here as table I. Pharmacological data, showing that helplessness in animals can be reversed selectively by anti-depressants, have been adduced by Sherman and Petty [1982]. Further, Weiss's group [Weiss et al., 1976, 1982] have demonstrated an important role in helplessness in the rat of the same noradrenergic mechanisms that have been implicated in human depression [Van Praag, 1978]. However, there is a major problem in integrating these diverse strands of evidence into a single coherent story: there is almost certainly more than one kind of helplessness in animals, and the evidence summarised above does not all relate to the same kind.

The demonstration that helplessness comes in more than one form comes from Glazer and Weiss [1976]. These workers showed, in rats, that exposure to high-intensity, short-duration, uncontrollable shock gives rise to a form of helplessness that is closely related to changes in the levels of noradrenaline in the brain, whereas exposure to low-intensity, long-duration, uncontrollable shock gives rise to helplessness that appears not to relate closely to noradrenergic mechanisms in the brain. The two forms of helplessness differed also in other ways: 'noradrenergic' helplessness was of shorter duration than 'non-noradrenergic' helplessness (so that Glazer and Weiss called the two phenomena 'short-term' and 'long-term' interference effects, respectively); and prolonged initial exposure to uncontrollable shock caused helplessness to disappear (an effect termed 'toughening up') in the case of noradrenergic but not non-noradrenergic helplessness. (We shall return to the phenomenon of toughening up in the final section of this chapter.) Given the relevance of noradrenergic mechanisms to human depression [Stone, 1983], it is Weiss's short-term interference effect that one is tempted to relate to the clinical condition. To be able to make this step with any confidence, however, we would need to know which form of helplessness responds to anti-depressant medication. Unfortunately, Sherman and Petty [1982], who have provided most of the pharmacological data, have used their own behavioural paradigm and this cannot (in the absence of relevant experiments) be aligned with either Weiss's short-term or long-term interference effect.

If we nonetheless assume for the moment that Weiss's short-term, noradrenergic interference effect is a model for human depression, we come up against two other intractable problems.

First, though it seems clear that the short-term interference effect depends in some manner on changes in noradrenergic transmission, it is uncertain whether these changes give rise to an increase or a decrease in
Table 1. Comparison of the effects of uncontrollable shock with symptomatic indications of depression from the third edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-III).

<table>
<thead>
<tr>
<th>Uncontrollable shock as a model of depression</th>
<th>DSM-III criteria for depression: four of the following</th>
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<tbody>
<tr>
<td>Uncontrollable shock produces the following symptomatology</td>
<td></td>
</tr>
<tr>
<td>1. Decreased food and/or water consumption</td>
<td>1. poor appetite and significant weight loss</td>
</tr>
<tr>
<td>Brady, Thornton, and Fisher, 1962 [ref. 17]</td>
<td></td>
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<tr>
<td>Pare, 1964 [18]</td>
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<tr>
<td>Pare, 1965 [19]</td>
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<tr>
<td>* Weiss, 1968 [12]</td>
<td></td>
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<tr>
<td>2. Weight loss</td>
<td>2. psychomotor alterations</td>
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<tr>
<td>Pare, 1965 [19]</td>
<td></td>
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<tr>
<td>* Weiss, 1968 [12]</td>
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<tr>
<td>3. Poor performance in tasks requiring active motor behaviour</td>
<td>3. loss of energy or fatigue</td>
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<td>(Shuttle avoidance-escape, lever-press escape, water-escape, open-field activity, etc.)</td>
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<tr>
<td>Overmier and Seligman, 1967 [1]</td>
<td></td>
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<td>*Seligman and Maier, 1967 [2]</td>
<td></td>
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<td>Overmier, 1968 [20]</td>
<td></td>
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<tr>
<td>Weiss, Glazer, Pohorecky, Brick, and Miller, 1975 [21]</td>
<td></td>
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<tr>
<td>Weiss, Bailey, Korzeniowski, and Grillone, 1980 [22]</td>
<td></td>
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<tr>
<td>* Sutton, Coover, and Lints, 1981 [23]</td>
<td></td>
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<tr>
<td>4. loss of interest in usual activities</td>
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<td>5. sleep changes</td>
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noradrenergic transmission (the same ambiguity that clouds current understanding of the mode of action of anti-depressant drugs).

The data reported by Weiss's group in 1975 suggested that noradrenergic transmission was decreased in animals made helpless by high-intensity uncontrollable shock. Whole-brain levels of noradrenaline were lowered in such animals at the time that they displayed behavioural...
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<table>
<thead>
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<th>Table 1. (cont.) Uncontrollable shock as a model of depression</th>
<th>DSM-III criteria for depression: four of the following</th>
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<tbody>
<tr>
<td></td>
<td>* Maier, Anderson, and Leiberman, 1972 [25]</td>
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<td></td>
<td>* Corum and Thurmond, 1977 [26]</td>
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<td></td>
<td>6. indecisiveness, evidence of decreased ability</td>
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<td></td>
<td>to think</td>
</tr>
<tr>
<td>5. Loss of normal grooming or play activity</td>
<td>* Redmond, Maas, Dekirmanjian, and Schlemmer, 1973 [27]</td>
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<tr>
<td></td>
<td>Stone, 1980 [14]</td>
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<tr>
<td></td>
<td>* Weiss, Goodman, Losito, Corrigan, Harry, and</td>
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<td></td>
<td>Bailley, 1981 [15]</td>
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<td></td>
<td>7. <em>Feelings of worthlessness</em></td>
</tr>
<tr>
<td>6. Decreased sleep</td>
<td>* Weiss, Goodman, Losito, Corrigan, Harry and</td>
</tr>
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<td></td>
<td>Bailley, 1981 - unpubl. observation [16]</td>
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<tr>
<td></td>
<td>8. Recurrent thoughts of death and suicide</td>
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</tbody>
</table>

For references in this table see Weiss et al. [1982].

* Denotes study demonstrating that the effect depends on uncontrollability of shock

helplessness; and prolonged exposure to uncontrollable shock, causing toughening up, eliminated the fall in noradrenaline levels, apparently by increasing the activity of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of noradrenaline. This pattern of results was consistent with the hypothesis that helplessness was due to a reduction in the availability of noradrenaline for release at neuronal terminals.

However, subsequent research [Weiss et al., 1982] showed that both the fall in noradrenaline levels due to exposure to uncontrollable shock, and the subsequent rise in noradrenaline levels with prolongation of this exposure (together with increased activity of tyrosine hydroxylase), were confined to the region of the locus coeruleus and did not occur in terminal regions of the locus coeruleus projection. Weiss et al. [1982] interpret these findings in the light of the presence on locus coeruleus cell bodies of alpha-adrenergic auto-receptors, that is, receptors which, when stimulated by noradrenaline released by local recurrent collaterals, act to inhibit further firing of noradrenergic axons destined for the forebrain. Their hy-
hypothesis now supposes that, during helplessness, there is a reduction in stimulation of these auto-receptors (consequent upon lowered availability of noradrenaline) and so an increase in the activity of noradrenergic terminals in the forebrain. In short, far from helplessness reflecting lowered noradrenergic transmission as in the 1975 hypothesis, it now reflects increased noradrenergic transmission.

The second problem that we must face in interpreting Weiss's findings is this: supposing that the short-term interference effect is a model of some kind of depression, and supposing also that there is more than one kind of depression, is it a model of psychotic or neurotic depression? Weiss et al. [1975] believed that they were studying a model of psychotic depression, and this view is supported by the symptoms gathered together in table I. However, now that their data have forced them to the hypothesis that helplessness reflects an increase in forebrain noradrenergic transmission, they prefer the view that they have a model of neurotic depression, i.e. the form of depression that is closest to (and perhaps identical with) anxiety [Roth, 1979]. Again, pharmacological data, of the kind gathered by Sherman and Petty but using Weiss's short-term interference effect, might resolve this problem.

Having indicated all the complexities and possibilities for double vision in this field [see also Gray 1982a; Stone, 1984], I shall now indicate my own view of the data. If we assume, with Weiss et al. [1982], that their short-term interference effect is due to increased forebrain noradrenaline release, and if we take into account the analysis of the neurology of anxiety with which this chapter began, then we must conclude (again with Weiss et al. [1982]) that the short-term interference effect is a model of either anxiety or something very close to anxiety (since anxiety too depends on increased release of noradrenaline). This leaves open the possibility that Weiss's long-term interference effect (and Seligman's original observation of helplessness in animals, which rather resembles the long-term than the short-term interference effect) is a model of psychotic depression. But since we know nothing of the neurology of the long-term interference effect, this tells us nothing of the neurology of depression. In short, we are left with the neurology of anxiety as outlined in the first section of this chapter, now supplemented by the very interesting data reported by Weiss et al. [1975, 1982]. Whether this is the neurology of anxiety, of neurotic depression or of both depends upon a prior judgement as to whether these two conditions truly differ; my own view is that they do not, but that psychotic depression is different from both [Gray, 1982a].
The Neurology of Tolerance for Stress

As noted in the previous section, the behavioural effects of exposure to uncontrollable footshock or cold swims or other such aversive events vary with the duration of exposure. Exposure on relatively few occasions disrupts behaviour, but exposure on many occasions eliminates the disruption. As an example (but there are many others), Weiss et al. [1975] found that rats tested in a two-compartment apparatus (a 'shuttlebox') in which they could escape from shock by jumping from side to side behaved differently depending on whether they had previously been exposed to a single session of uncontrollable footshock or to 15 daily sessions of this kind. In the former case, they were unable to escape the shock when tested in the shuttlebox, in the latter they were like unshocked controls. As we also saw, this 'toughening-up' effect of prolonged exposure to uncontrollable shock is apparently due to changes in the capacity of noradrenergic neurons to synthesize their transmitter, noradrenaline [Weiss et al., 1982].

Given the conclusion, reached in the previous section, that the initial disruption of shuttlebox performance studied by Weiss's group is probably related to anxiety, it is natural to ask whether the brain systems responsible for anxiety are involved also in the development of tolerance for repeated stress.

Evidence that this is indeed the case comes from a series of experiments in my own laboratory. These experiments have employed tasks which, while differing from those used by Weiss's group in many respects, have in common the feature that the animal's tolerance for events that normally disrupt behaviour is increased by exposure to those events. Two phenomena in particular have engaged much of our attention – the partial punishment effect (PPE) and the partial reinforcement extinction effect (PREE). Both of these phenomena are observed in a straight alley which the rat has to traverse to obtain, in the goalbox, a food reward. Three basic training schedules are used. The first, a continuous reinforcement (CRF) schedule, involves simply the delivery of the food reward on each occasion (a trial) that the rat runs down the alley. The second, a partial punishment (PP) schedule, adds to the food reward a footshock delivered on a randomly chosen 50% of trials just as the rat enters the goalbox and just before it takes the food. The third, a partial reinforcement (PRF) schedule, employs no shock, but omits the food reward on a randomly chosen 50% of trials. (This is the event of nonreward, which we encountered in the discussion of the behavioural inhibition system depicted in
figure 1. The stressful nature of nonreward is demonstrated by its capacity to elicit a rise in plasma corticosterone, [Goldman et al., 1973.] The PPE consists in the fact that, if animals initially trained on CRF and PP schedules are tested with food and shock given on every trial (continuous punishment), the PP-trained animals show more resistance to punishment (that is, they continue to run to the goalbox for longer and run faster) than the CRF-trained animals. Similarly, the PREE consists in the fact that, if CRF- and PRF-trained animals are tested with nonreward on every trial (an extinction schedule), the PRF animals show more resistance to extinction than CRF animals. That these two phenomena share common mechanisms is suggested by the demonstration [Brown and Wagner, 1964] of cross-tolerance between them: that is, animals trained on a PRF schedule display increased resistance to punishment and animals trained on a PP schedule display increased resistance to extinction, in both cases relative to animals trained on CRF.

The first indication that the brain systems mediating these phenomena might be related to those that mediate anxiety came from the demonstration that, under certain conditions, both the PPE [Davis et al., 1981] and the PREE [Gray, 1969; Feldon et al., 1979; Feldon and Gray, 1981] are abolished if animals are trained after administration of an anxiolytic dose of a barbiturate or a benzodiazepine. Given the general evidence, outlined earlier in this chapter, that anxiety is a function of the septo-hippocampal system, we followed up these findings by investigating the effects of damage to this system on the PREE and PPE. While initially our experiments yielded evidence that strongly supported a role for the septo-hippocampal system in the PREE [Gray et al., 1978], our most recent findings show that this role is constrained by temporal parameters that are clearly different from those that determine the effects of the anti-anxiety drugs [Rawlins, in press]. In other experiments we have demonstrated a role in behavioural tolerance for stress for the ascending noradrenergic (but not serotonergic) fibres that innervate the septo-hippocampal system [Owen et al., 1982; Davis and Gray, 1983; Tsaltas and Gray, in preparation]. Again, however, the parameters that constrain the effects of lesions to the dorsal noradrenergic bundle (carrying the ascending noradrenergic efferents from the locus coeruleus) differ from those that constrain the effects of anxiolytic drugs, resembling rather the parameters applicable to damage to the septo-hippocampal system [Owen et al., 1982; Tsaltas and Gray, in preparation; Gray and McNaughton, 1983]. Thus, present data from lesion experiments permit the conclusion that the septo-hippocampal system and its
noradrenergic afferents are in some way involved in the development of tolerance for stress, but fail to indicate a clear mechanism for the action of anti-anxiety drugs in blocking the development of such stress tolerance.

Further evidence for the involvement of the septo-hippocampal system in the development of tolerance for stress comes from experiments in which we have, via chronically implanted electrodes, stimulated the septal area in conscious rats. It is well known that the medial septal area contains the pacemaker cells that control (via a diffuse cholinergic projection travelling in the fornix and fimbria) the slow, high-voltage electrical waves in the hippocampal formation known as the ‘theta rhythm’ [for a review, see Gray, 1982a]. If one stimulates the septal area using short (ca. 0.5 ms) pulses at a frequency lying within the natural theta range (6–12 Hz in the rat) one can artificially drive the hippocampal theta rhythm at the imposed frequency. We have recently shown that a course of ten days’ stimulation of this kind (a total of 90 s of stimulation per day) alters the rat’s behaviour several weeks later in a manner that is consistent with the hypothesis that the animal has been rendered behaviourally more tolerant of stress. Relative to unstimulated controls the stimulated rats show more resistance to extinction, to punishment and to disruption of responding (pressing a bar for food reward) by stimuli associated with footshock [Holt and Gray, 1983a, in press]. These results are obtained even though the barpressing response is not acquired until the period of septal stimulation is over.

These intriguing findings suggest that septal stimulation in some way mimics the neural consequences of exposure to aversive stimuli (though the stimulation is not aversive in its own right) [Ball and Gray, 1971]. We cannot yet be sure that the critical feature of the stimulation is its driving of the hippocampal theta rhythm, but several findings clearly point in this direction. First, if high-frequency electrical stimulation is applied to the septal area, this disrupts rather than drives the theta rhythm; such stimulation proactively reduces resistance to extinction [Holt and Gray, 1983b] – the opposite effect to that observed after theta-driving stimulation. Second, the frequency of septal stimulation that increases tolerance for stress is 7.7 Hz [Gray, 1972]. This is an important finding, since anti-anxiety drugs raise the threshold for septal driving of hippocampal theta selectively at this same frequency of 7.7 Hz [McNaughton et al., 1977]. Thus, the increase in tolerance for stress produced by septal stimulation appears to depend upon activation of the same mechanism (i.e., an input to the hippocampal formation eliciting 7.7-Hz theta) which is blocked by anti-anxiety drugs when they reduce tolerance for stress.
Resistance to Cancer

Now, the latter effect—elevation of the threshold for 7.7-Hz theta driving by anxiolytic drugs—is almost certainly due to a reduction in the noradrenergic input to the septo-hippocampal system from the locus coeruleus [Gray et al., 1975; McNaughton et al., 1977]. Thus, one might perhaps expect the increased tolerance for stress caused by repeated 7.7-Hz theta driving to be accompanied by signs of increased noradrenergic input to the septo-hippocampal system. We have indeed observed such signs. After the same regime of septal stimulation that produces increased tolerance for stress there is increased activity of tyrosine hydroxylase in the hippocampus [Graham-Jones et al., in press]. This finding is reminiscent of the report by Weiss’s group that the regime of exposure to uncontrollable footshock which gave rise to behavioural toughening up was accompanied by increased tyrosine hydroxylation in the brain. However, as noted in the previous section, this biochemical change was confined to the region of the cell bodies in the locus coeruleus [Weiss et al., 1982]. The significance of this discrepancy in the location of the increased activity of tyrosine hydroxylase in the two sets of experiments is at present unclear. But both sets of experiments concur in suggesting that increased activity of the rate-limiting enzyme in noradrenaline synthesis, i.e. tyrosine hydroxylase, may contribute to the development of behavioural tolerance for stress.

The central concern of this book is with psychosomatic medicine. However, the role of the brain in psychosomatic disorders is still very obscure [Fauman, 1982]. It is for this reason that I have confined my attention to more general issues related to the role of the brain in emotion and reactions to stress. Nonetheless, it is perhaps appropriate to bring this chapter to a close with an attempt—no matter how speculative—to relate behavioural tolerance for stress to a classic psychosomatic problem: resistance to cancer.

The role of psychological factors in the progress of human cancers is now well established, as is the corresponding role of stress and behavioural factors in cancers in animals [Riley, 1981; Sklar and Anisman, 1981]. For our present purpose, one particular feature of the experiments with animals demands attention. Recall that, in Weiss’s experiments, it was shown that exposure to a single session of uncontrollable (but not controllable) shock disrupted subsequent behaviour in the shuttlebox, whereas exposure to repeated sessions of uncontrollable shock eliminated this be-
havioural disruption. Anisman's group, working with mice, has demonstrated a closely similar pattern of change in the rate of growth of cancer cells: a single session of uncontrollable (but not controllable) shock causes experimentally induced tumours to grow faster, whereas repeated shock sessions causes them to grow slower [Sklar and Anisman, 1981].

These observations suggest that the same brain mechanisms that mediate the development of behavioural tolerance for stress may also mediate resistance to cancer. If this is so, and if it is correct (as argued above) to implicate the septo-hippocampal system and ascending noradrenergic fibres in behavioural tolerance for stress, then it is possible that these structures also play a role in determining resistance to cancer. We are currently investigating this hypothesis, by measuring the rate of tumour growth in animals that have previously been subjected to septal driving of the hippocampal theta rhythm. If one may extrapolate from our earlier behavioural observations [Holt and Gray, 1983a], such stimulation should retard the growth of a tumour implanted after the period of stimulation is over. Such an outcome of our experiments is, of course, inherently unlikely; but it would not be without parallel, since there is already evidence that lesions to the brain (principally the hypothalamus, with which the septal area has intimate reciprocal connections) can affect the immune system [Fauman, 1982].

Conclusion

The role played by the brain in the control of emotional behaviour is still obscure, but islands of clarity are beginning to emerge. The structures that mediate anxiety (at least some of them) have been marked out, and their function in processing information is yielding to analysis. Although the major advances in our understanding of the neuropsychology of anxiety have come from animal experiments, recent observations on patients suffering from panic disorder (using the new brain imaging technique of positron emission tomography) have confirmed the importance of the hippocampal formation and its connections with the temporal lobe [Reiman et al., 1984]. There is evidence that the structures concerned with the development of tolerance for stress are closely related to those that mediate anxiety. The hippocampus (once more) and other systems connected to it have been demonstrated in several experiments from my own laboratory to play a key role in determining behavioural tolerance for stress. It is in-
terestingly, it is interesting to note that this structure contains many of the physiological elements found also in peripheral systems involved in stress responding: cholinergic and noradrenergic afferent pathways, and cells that avidly bind adrenocortical hormones [McEwen et al., 1969]. Thus, it may yet turn out that the principles that govern the role of peripheral structures in responding to stress are applicable also to the central nervous system. But much experimental work remains to be done before we can see these (or any other) principles at all clearly.

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