Appendix 1

The behavioural profile of anxiolytic drugs

A1.1 Introduction

A major premise of this book is that the behavioural and neural actions of the anxiolytic drugs can guide us to the psychological nature of, and the neural structures involved in, anxiety. A critical step in our inclusion of the septo-hippocampal system in the structures controlling anxiety was a comparison of the pattern of effects, over a wide range of behavioural tests, of brain lesions of various types with the pattern of effects produced by anxiolytic drugs. In this appendix we provide the detailed justification for the pattern of action which we claimed was shown by anxiolytic drugs in Chapter 4.

There is now a vast mass of literature on anxiolytic drugs (see Nutt 1990 for a review of the human literature). Here we will summarize the animal literature and, because of the volume of the literature, we will depend largely on secondary sources, particularly Gray (1977) for the classical anxiolytics and Griebel (1995) and (Handley 1995) for 5-HT_{1A} and 5-HT_3 selective compounds and imipramine. Where no citation is given for some fact, it should be found in one of these reviews unless some other secondary source is cited as the basis of that particular section.

It is important to note that we will make no attempt to include compounds which are presumed from some animal test or another to be anxiolytic but which have not been tested in human beings. Given the apparent failure of many animal models to detect the more novel clinically effective anxiolytics (see Chapter 4), we would strongly recommend that no compound be treated (or referred to) as 'anxiolytic' until it has been proved so in more than one double-blind, placebo-controlled clinical trial on generalized anxiety.

One important development, since the first edition, is the availability of the novel anxiolytics which, so far as can be told, share none of the side-effects of the classical anxiolytic drugs. We shall be particularly concerned here, therefore, with the relatively few data which allow us to tell whether a particular action is common to both types of anxiolytics. As will be seen, there are a large number of cases where, at first sight, the data not only do not fit our theory but appear to embarrass anyone who uses 'animal models' of anxiolytic action. (The basis for the non-linear dose–response curve found with drugs such as buspirone is considered briefly in Chapter 4, and in more detail at the end of the current appendix.) However, the cases where the immediate similarities between novel and classical anxiolytics are clearest are those (action on septo-hippocampal electrophysiology—Appendix 5; action on the water maze test—see below) which are most consistent with our theory. This has led us, both in this review and in recent laboratory work, to look particularly carefully at the apparently discrepant cases. It is our contention that in all the theoretically critical cases the discrepancies can be resolved.

A second important development, since the first edition, is the analysis (covered in detail in Chapter 2) of the behaviours which are likely to occur in the context of potential threat as paradigmatic of anxiety and as quite distinct from responses to direct threat. But we concluded that the critical feature for such behaviours was the approach–avoidance conflict inherent in the 'potential threat' situation rather than the potentiality of the threat as such. In the present appendix we will deal early on with explicit cases of approach–avoidance and find that, as with the case of predatory defence, the anxiolytic drugs shift the balance of the conflict from avoidance towards approach.

In Chapter 3, we found reason to broaden the notion of approach–avoidance conflict and to treat as 'potentially threatening' novel stimuli of certain kinds, signals of punishment, and signals of reward omission, in addition to the paradigmatic innate anxiety stimuli. In what follows we will deal with all of these cases, and will find reason to emphasize both the role of passive (inhibitory) avoidance in such conflicts and the necessity for true conflict between highly primed (activated) incompatible responses. This leads naturally to the fact that anxiolytic drugs also shift an active avoidance–passive avoidance conflict away from inhibitory avoidance. At the end of this appendix we will find reason to generalize still further. The drugs are effective in a number of tasks which appear, at first sight, to have no aversive component at all, and instead appear to involve memory. However, the tasks do involve conflict—but a conflict between approach and approach. Even here, though, a common thread can be seen. Correct performance of the task requires inhibition of competing responses which are currently inappropriate.

In all of this, we treat the anxiolytic drugs as a single general class. The justification for this and our definition of an anxiolytic drug are given in Chapter 4. The drugs included in our definition are the classical anxiolytics active at the GABA–chloride ionophore complex (alcohol, barbiturates, meprobamate, benzodiazepines) and novel anxiolytics active at 5-HT_{1A} sites (buspirone, ipsapirone, imipramine, etc.). There is probably justification for including beta-blockers such as propranolol under the heading of 'anxiolytic drugs'—but a large part of their action is likely to be peripheral and so we have not taken them as paradigmatic anxiolytics. We have specifically excluded the 5-HT_3 antagonist ondansetron as we believe there is no good evidence that it is an effective clinical treatment for generalized anxiety disorder.

A1.2 Responses elicited by appetitive stimuli

The effects of alcohol on appetite are well known and we are often abjured to 'take a little wine for thy stomach's sake'. Both benzodiazepines and 5-HT_{1A} agonists also increase food intake in a variety of species (see Cooper 1991; where no reference is given in this section, the conclusions are drawn from his review).

‘The fact that benzodiazepines increase food intake was recognized from the first; it is a remarkably robust phenomenon, and behavioural evidence was adduced that it must be distinct from anxiolytic effects of these drugs. Although a hyperphagic effect could, in principle, be secondary to a reduction in fear, stress or anxiety, the main point of interest is that benzodiazepines appear to affect feeding responses relatively directly’ (Cooper 1991, p. 234). They also increase drinking of water and saline.

The effect on food consumption is to increase meal size but not overall food intake—and this probably explains the relative lack of effect of the drugs on acquisition of food-rewarded behaviour. Cooper (1991) argues that the effects of benzodiazepines on drinking compromise the ‘Vogel test’ (see section on punishment below) as the increase in drinking seen in this test with benzodiazepines is similar to the increase seen in unpunished animals.

These effects of the benzodiazepines appear to result from an enhancement of positive ingestive responses as a result of increased palatability with no modification of aversive reactions to flavours (Berridge and Peciña 1995; Parker 1995) as suggested by Cooper (1991, p. 245). Balleine *et al.* (1994) also carried out a series of experiments that suggest that the increase in ingestion produced by benzodiazepines is not the result of an increase in hunger as such.

Buspirone and other 5-HT_{1A} agonists increase intake of food and of *hypertonic* saline in an apparently similar fashion to benzodiazepines; however, they differ in that the 5-HT_{1A} agonists do not increase drinking of water or ordinary saline.

Benzodiazepines and buspirone also produce a reduction in food hoarding behaviour (McNamara and Whishaw 1990; Dringenberg *et al.* 1994). In one sense this might seem to be the opposite of the increased interest in food seen above. However, it can be interpreted in two compatible ways. First, an increase in palatability could increase the probability of immediate eating rather than hoarding. Second, a loss of behavioural inhibition would reduce the probability of the animal switching from the prepotent response of eating to the secondary response of hoarding—provided there can be presumed to be a conflict between the two.

A1.3 Responses elicited by aversive stimuli

There have been surprisingly few studies which investigate the effects of anxiolytic drugs on responses elicited by painful stimuli. Measurement of the threshold electrical current at which flinching or jumping is provoked has failed to reveal any sign of analgesia. In the case of alcohol, there is even evidence of a reduction in the flinch and jump thresholds to shock. This is in contrast to the effects of known analgesics such as morphine.

Similar results are obtained when shock is used to elicit aggression between a pair of animals. At low doses barbiturates and alcohol facilitate aggression (Kršiak 1976; Gray 1977), an effect that can be obtained also with benzodiazepines, although it might be necessary for them to be administered chronically. The 5-HT_{1A} agonists, on the other hand, inhibit shock-induced aggression (De Vry *et al.* 1989).

These results are in contrast (see also Rodgers and Waters 1985) to the reductions in aggression that can be produced when this is elicited by threat—for example, when the animal is provoked by the experimenter. Interestingly, in the Blanchards’ Fear/Defence Test Battery, benzodiazepines ‘reduce only defensive threat while the 5-HT_{1A} agonists (especially gepirone) reduced both defensive threat and attack, and ethanol at low doses potentiated defensive threat and attack, leaving other behaviours largely unchanged’ (Blanchard and Blanchard 1990, p. 188; see also Traber and Glaser 1987; Blanchard *et al*. 1989, 1993). Unfortunately (given the results in the next paragraph), they did not test imipramine. Buspirone is anxiolytic in tests where monkeys are threatened by humans.

Vocalization in many different types of threatening situations appears particularly sensitive to both benzodiazepine and 5-HT_{1A} anxiolytics except for the case of predator-induced vocalization in a colony situation (see Miczek *et al*. 1995 for review). In the case of the 5-HT_{1A} compounds, the action appears to be mediated by somatodendritic autoreceptors in the dorsal raphe nucleus (Remy *et al.* 1996).

Such reductions in threat responses, coupled with the increased incentive value of the reward, probably underlie the increase produced by chlordiazepoxide, buspirone, and benzodiazepine partial agonists in the amount of sweetened milk obtained by subordinate rats in a competitive situation. Imipramine, however, does not appear to reproduce this effect, possibly because of the use of too low a dose (Joly and Sanger 1991).

Threat-induced active avoidance, flight, and freezing are not affected by benzodiazepines, buspirone, gepirone, or low doses of ethanol (Blanchard and Blanchard 1990).

Separation-induced anxiety (as assessed by ultrasonic distress calls) is reduced by both benzodiazepines and 5-HT_{1A} agonists but not by 5-HT_2 agonists (Albinsson *et al*. 1994; see also De Vry *et al.* 1989). The various measures of the Blanchards’ Anxiety/Defence Test Battery are reduced by 5-HT_{1A} agonists, alcohol, imipramine, and benzodiazepines (Blanchard *et al*. 1993). In a mouse variant of the fear and anxiety defence test batteries, anxiolytic agents appear to reduce defensive threat and attack (where the predator must be approached) whereas drugs that are clinically effective at reducing panic reduce the prey–predator distance at which flight and escape is produced (Griebel *et al*. 1995*a*).

The critical conclusion for our later analysis is that anxiolytics clearly do not *reduce* responses to a painful stimulus or to the direct threat of such a stimulus produced by a close and localizable predator. Both theory and the apparent qualitative differences in the effects of the different drugs on shock-induced aggression and on the Fear/Defence Test Battery suggest that here we may be dealing with side-effects of the various drugs.

A1.4 Rewarded behaviour

In terms of our dissection of processes, the experiments in this and the next few sections provide an important foundation of unaffected tasks for our assessment of the processes affected in other tasks. 'Rewarded behaviour' as discussed in Chapter 3 refers to the case where presentation of a stimulus contingent on a behaviour results in the animal performing, at an increased rate, a previously lower frequency behaviour. The stimulus usually takes the form of delivery of food (to a food-deprived animal), or water (to a water-deprived animal), or of some particularly desirable item (e.g. Fruit Loops or chocolate in the case of undeprived rats). In the simplest case this 'reward' is delivered every time the animal produces the behaviour desired by the experimenter. This is termed a continuous reinforcement (CRF) schedule. A key point to note is that if tasks of this type are performed correctly despite some treatment, we can conclude that the treatment does not eliminate perception, motor programming, memory in general, motivation, or the links between any of these processes. This rules out a deficit in any of these as an explanation of any change in behaviour produced by the treatment in some other task.

The anxiolytic drugs are without systematic effect on simple rewarded behaviour or on behaviour maintained by 'rewarding' brain stimulation. This generalization applies across a wide variety of different tasks which use CRF. (Intermittent reinforcement is dealt with later.) It is as true of simple 'spatial' tasks (such as running in an alley, or learning to go to one of two goal arms in a T-maze) as it is true of non-spatial tasks (such as simultaneous discrimination where the animal learns to choose one of two simultaneously presented stimuli). It is even true, to some extent, of performance in the radial-arm maze—which we will consider in the section on maze tasks. This will be important to us later, when we examine the suggestion that the hippocampus is especially concerned with the analysis of spatial information and the control of behaviour in spatially complex environments (O'Keefe and Nadel 1978).

A high frequency of a behaviour which is followed by a reward can be achieved through two quite separate mechanisms. First, given an arbitrary response followed by an arbitrary reward, responding is likely to be supported by instrumental (Thorndikian, operant, Stimulus–Response, S–R) conditioning. Second, with a response such as salivation and a reward such as food, responding is likely to be supported by classical (Pavlovian, respondent, Stimulus–Stimulus, S–S) conditioning. Since the discovery of autoshaping (Brown and Jenkins 1968) it has become clear that any particular response may be maintained by either or both of these mechanisms (see Chapter 2 in Gray 1975).

In the original autoshaping experiments, pigeons were faced with a key which was lit preceding the delivery of a free reward. They came to peck the key despite the lack of any contingency between pecking and food delivery. Note that once they are pecking the key the situation is indistinguishable from the case where there is a response–food contingency—and this raises the possibility that all 'instrumental' conditioning is in fact disguised classical conditioning. That this is not the case is demonstrated by the addition to conventional autoshaping of an omission contingency. The lit key predicts free food as before, but any key peck cancels this food. The classical response elicitation is thus pitted against an instrumental response suppression. The results with this procedure suggests that most pigeons' responding is the result of classical control, whereas rats' responding is more dependent on instrumental control (Williams and Williams 1969; Ridgers and Leslie 1975, cited by Millenson and Leslie 1979).

Since rewarded behaviour is unaffected by anxiolytic drugs over a wide range of appetitive tasks, both nominally classical and nominally instrumental, we may conclude that neither simple classical nor simple instrumental conditioning is affected by anxiolytic drugs in non-human species. This is matched by the fact that, at conventional anxiolytic doses, simple learning is not greatly affected by these drugs in human beings. Buspirone, as an apparent exception to the above rule, tends to decrease responding generally, especially at doses above 1 mg/kg, but in this it simply shows, earlier than do classical anxiolytics, interference from high-dose side-effects possibly mediated by the pituitary–adrenal axis.

A1.5 Responses elicited by frustrative non-reward

Frustration can be viewed as a state elicited by the omission of an expected reward (see Amsel 1992). It is easy enough to see how presentation of food or shock can be eliciting. But omission of food is perilously close to being a non-event, especially if, as a radical behaviourist or an anthropocentric, you do not believe rats can have expectations.

The reality of frustration is demonstrated by the 'frustration effect' in a double runway (Amsel and Roussel 1952). In this experiment, the rat is run in two sequential alleys where the goal box for one alley is the start box for the next. Reward is always available in the second alley but only sometimes in the first. It is found that rats receiving a mixture of rewarded and non-rewarded trials run faster in the second alley after non-reward in the first goal box than after reward. They also run faster than rats who either always receive reward or always receive non-reward (Wagner 1959). It is, therefore, the omission of an expected reward rather than the simple absence of reward which gives rise to this effect.

In a related task, Soubrié *et al.* (1978) trained thirsty rats to drink from a bottle, then presented the bottle empty for a while, and then gave them a full water bottle. Presentation of the empty bottle increased subsequent drinking.

In neither the double runway frustration effect nor this drinking task do anxiolytic drugs have any effect (see Gray 1977). This result proved important when we considered the role of the amygdala in Chapter 4.

One cannot measure a flinch or jump response to non-reward, as one can to shock, but it is possible to measure the aggressive response elicited by non-reward (e.g. Gallup 1965; Azrin 1967). As with shock-elicited aggression

(Weitz 1974), ethanol, the only anxiolytic tested, increased frustration-elicited aggression at low doses (0.5 g/kg) and suppressed it at higher doses (Miczek and Barry 1977).

A1.6 One-way active avoidance and escape

In one-way active avoidance, the animal starts a trial in an area which is always dangerous (i.e. where aversive stimulation such as electric shock to the feet is delivered), while an adjacent area is always safe. If it does not move between the areas in some fixed time such as five seconds, the shock is delivered. (In a pure escape procedure the shock is not delayed.) The animal is then placed back in the dangerous compartment for the start of the next trial. Learning consists of a decreased latency to leave the dangerous compartment, initially resulting in learned escape and then resulting in avoidance. Classical anxiolytic drugs do not impair either one-way active avoidance or escape. By contrast, the 5-HT_{1A} receptor agonists (but not imipramine) do impair active avoidance (Sanger *et al.* 1989). Interestingly, Viana *et al.* (1994), testing rats for their tendency to escape from an open arm of an elevated T-maze (see Zangrossi and Graeff 1997 for behavioural analysis of this test) into a closed arm, found that neither a benzodiazepine *nor* a 5-HT_{1A} agonist reduced the tendency to escape in this situation. It may be that the effect seen by Sanger *et al*. (1989) depends on the use of shock.

Long-term administration of drugs which are clinically effective against panic can reduce escape from a predator—a reaction that might be related to human panic attacks (Griebel *et al*. 1995*b*).

Overall, as with making a response to obtain a reward, making a response to avoid a punishment is unaffected by anxiolytic drugs. In addition, therefore, to perceptual and motor mechanisms, the anxiolytics leave intact both the perception and anticipation of pain—at least where this is demonstrated by a specific avoidance response.

These results in learning experiments are, of course, entirely consistent with the lack of effect of the anxiolytic drugs on predator avoidance reactions which we considered in Chapter 2. However, they contrast to some extent with the reported fear-reducing effects of the drugs on learned escape when electrical stimulation of the central grey is used as the unconditioned stimulus (see Schenberg and Graeff 1978).

A1.7 Classical conditioning of fear

A lack of effect of anxiolytics on instrumental conditioning reinforced by avoidance of a shock might seem to entail a lack of effect on classical conditioning of anticipatory responses to shock. Nonetheless, this possibility can, and needs to, be tested directly. Surprisingly, the data are not clear on this point.

There are four kinds of relevant experiments. The first is the procedure originally used by Pavlov (1927) himself, in which one measures a specific response (e.g. a change in heart rate, defecation, etc.) which is normally elicited by an aversive unconditioned stimulus (UCS) to see to what extent it is elicited by a conditioned stimulus (CS) after pairing with the aversive UCS. The next two employ conditioned suppression procedures in which stimulus–punisher pairing enables the stimulus to suppress a response on which it is superimposed. Finally, there are paradigms in which CS–UCS pairing confers on the CS the capacity to enhance or elicit some innate response. There is no good evidence that the anti-anxiety drugs affect classical aversive conditioning when this is measured by discrete responses directly elicited by the punisher. This is consistent with the results of the previous section and the ethopharmacological analysis of Chapter 2.

In conditioned suppression procedures, the animal (usually a rat) is first trained to make a rewarded response such as lever pressing. It then receives punishment in the presence of a signal, but independently of its bar pressing behaviour; the consequences of this latter conditioning is suppression—the bar-pressing declines in probability in the presence of the signal. The stimulus–punisher pairing may be conducted while the subject performs the instrumental response used to assay the effect of conditioning. This is termed ‘on-the-baseline’ conditioning. Or it may be conducted in a separate experimental situation where the response is impossible. This is termed ‘off-the-baseline’ conditioning.

With simple ‘off-the-baseline’ procedures the data are few and contradictory (Dantzer and Mormede 1976; Dantzer *et al*. 1976; and see references in Gray 1977), but they do not in general show a reduction in conditioned suppression. It is unclear what we would predict here as the effect of the stimulus on baseline responding could be the result either of conditioned escape and avoidance reactions or of a conflict between potential threat and the baseline response. As we will discuss further, in the context of passive avoidance, the key feature of the situation may be the extent to which the conditioning of fear is to a highly discriminable, as opposed to diffuse, source (Blanchard and Blanchard 1970).

By contrast, anxiolytics, including propranolol (Salmon and Gray 1986), and especially benzodiazepines, often show a reduction in conditioned suppression in ‘on-the-baseline’ procedures. We will return to an analysis of the possible differences between these two tasks in Appendix 8, but as with off-the-baseline procedures the key feature of the anxiolytic-sensitive paradigms may be a diffuse, as opposed to discrete, source of threat (Blanchard and Blanchard 1970; see also passive avoidance, below). Of particular note, in relation to data we will be considering on successive discrimination, conditioned suppression is reduced by chlordiazepoxide even after lengthy overtraining and with the drug administered in gradually increasing doses to eliminate state-dependence (McNaughton 1985*a*). Buspirone appears to have relatively reliable effects on conditioned suppression (in contrast to its weak effects on punishment) but imipramine does not appear to have an effect, at least at lower doses (Sanger 1990).

We now come to the fourth type of experiment where fear conditioning elicits or modulates an innate response. There are three cases to consider: conditioned freezing, defensive burying, and fear-potentiated startle.

In the conditioned suppression experiments which we have been considering we might expect there to have been losses of conditioned freezing as a consequence of the increases in the suppressed operant. But anxiolytics can also reduce *conditioned* freezing directly (e.g. Beck and Fibiger 1995) although, as we have seen, they do not affect unconditioned freezing to a direct threat. It is always possible, therefore, that the observed changes in conditioned suppression are consequent on changes in conditioned freezing. As we discussed in Chapter 2, conditioned freezing may, at least in these cases, be the result of particularly high-intensity behavioural inhibition rather than being neurologically the same as predator-induced freezing. Indeed, where conditioning to a specific stimulus has been compared with conditioning to background ('contextual') stimuli, anxiolytics appear to have a much greater effect in the background case (Melia *et al*. 1996)—this distinction will be of some theoretical significance when we come to consider the parallels between anxiolytic drugs and septo-hippocampal lesions.

Defensive burying has been extensively studied by Treit and colleagues and is investigated in the 'shock-probe burying test'.

In this test, rats are shocked from an electrified probe, and the duration of time that they spend spraying bedding material towards the probe (i.e. burying) is the major index of 'anxiety'. Standard anxiolytic drugs suppress this burying behaviour, and abolish the elevations in plasma corticosterone and adrenaline induced by the probe-shock. The suppression of burying by the benzodiazepines does not appear to be secondary to behavioural sedation, associative learning deficits, or analgesia, and can be reversed by benzodiazepine receptor antagonists such as flumazenil. Finally, putative anxiogenic agents increase the amount of time rats spend burying the probe. . . . It is particularly noteworthy that the clinically effective 5HT1A antagonist, buspirone, has produced anxiolytic effects . . . in the shock-probe test, as have other 5HT1A agonists. (Treit *et al*. 1993.)

As noted by Blampied and Kirk (1983, p. 695) 'defensive burying is an interesting behaviour not least because it involves approach to the source of noxious stimulation, and because it is so reliably and strongly elicited by a single aversive experience.' How far it can be classified as a risk assessment behaviour is open to question. However, there are two reasons to link it with risk assessment. First, 'unconditioned burying of novel objects in the absence of shock has also been observed' (Blampied and Kirk 1983, p. 695). Second, it fulfils the major criterion for an anxiety-related reaction (Chapter 2) in that it involves *approach* to a source of potential threat.

In the normal form of this test the drug is present both during acquisition (the initial experience of the shock) and testing (the observation of burying). However, if these two phases are separated (with the consequent risk of state dependency as an explanation for reductions in burying), anxiolytics are effective when given either in the acquisition phase or in the testing phase (Blampied and Kirk 1983; Tsuda *et al.* 1988). In the case of acquisition treatment (Tsuda *et al*. 1988), anxiolytic and anxiogenic drugs produced opposite effects on drug-free testing which reduces the chances that the results are simply due to state dependency.

Defensive burying can be increased by the presence of the odour of a conspecific associated with defeat in a prior agonistic encounter. Both diazepam and buspirone block this potentiation of burying (Hotsenpiller and Williams 1996).

In fear-potentiated startle (M. Davis 1979), a rat's startle response is measured in response to a loud tone. On some trials the tone is preceded by a light which has previously been paired 'off-the-baseline' with footshock. As a result of this pairing, the light increases (potentiates) the startle response to the tone. It might be thought that this represents an output from the fight/flight/freezing system (FFFS; see Chapters 2, 3, and 6) which would contribute to active avoidance. However, benzodiazepines and buspirone (M. Davis 1979; see M. Davis 1992 for review) have little effect on, or even increase, the startle response itself but diminish the potentiation of the startle response produced by the light. This cannot be an effect on the conditioning of fear itself since not only do the drugs not affect active avoidance and learned escape (see above), but their effect on fear-potentiated startle is produced only if they are present in the test session. If they are given only prior to the light-shock pairing they have no effect on potentiation. Tenen (1967) reported similar effects with 'off-the-baseline'[1] conditioned suppression: a blockade of the expression but not the acquisition of conditioned fear (see Gray 1977, for other relevant studies). Alcohol does not appear to reduce fear-potentiated startle, except perhaps at very high doses, whereas non-anxiolytic drugs such as haloperidol and amphetamine do (Hijzen *et al*. 1995).

Perhaps the most surprising failure of effect is with imipramine which is ineffective if given either acutely or chronically (Davis 1992). This lack of effect may be related to the fact that the effect of buspirone on fear-potentiated startle is not reproduced by systemic administration of 8-OH-DPAT or PCPA, nor by dorsal or median raphe lesions, suggesting that its effect on this test is not via 5-HT_{1A} receptors (Davis *et al.* 1988; but see Mansbach and Geyer 1988 for contradictory data). Ipsapirone 'blocked potentiated startle only at a very high dose (40 mg/kg)' (Davis *et al.* 1988, p. 14) and it may be that a higher dose of imipramine would be effective.

A1.8 Passive avoidance, punishment, two-way active avoidance, non-spatial active avoidance

We now come to the paradigmatic case of approach–avoidance conflict: passive avoidance.

Passive avoidance results from the same contingency between response and reinforcer as does rewarded behaviour. The difference is that the reinforcer is a punishment rather than a reward and the behaviour declines in frequency. (It is this increase or decrease in frequency of response which *defines* the stimuli as rewards or punishers, see Chapter 3.)

The response may be spontaneous (e.g. drinking, stepping down from a small platform to the floor of the apparatus) or previously learned (e.g. running along an alley to obtain food). 'Passive avoidance' is used here to cover both spatial and non-spatial tasks, although some prefer to keep it for the former and 'punishment' for the latter. The distinction between passive and active avoidance (see Table 3.1 in the printed text) turns on whether the animal avoids punishment by *inhibiting* a specified response or by *producing* it, respectively.

The importance of this distinction is not self-evident, and theories of learning before the early 1960s usually treated active and passive avoidance as equivalent. The effects of drugs (this section) and lesions (Appendix 8) as well as our analysis in Chapters 2 and 3 suggest that they are quite distinct.

Another distinction which should be important, given the theoretical analysis we have provided so far, reflects the discriminability of the source of shock—and hence the degree of conflict engendered by the procedure. In many cases of passive avoidance, of course, a specific baseline response is punished and here conflict will always be produced. However, in other cases, the shock is associated with a specific object or location. Here, if the animal can detect that a particular object or location is the source of the shock, this should produce active escape from or avoidance of the object and, unless there is some separate reason for approaching the object (e.g. an electrified water spout in the case of a thirsty rat), there will be no conflict. Nonetheless, as emphasized by Blanchard and Blanchard (1970), if the object is poorly discriminable this can result in general behavioural inhibition which is quite different from the discrete avoidance seen with a highly discriminable shock object.

In their experiments:

female rats received shock through objects varying in discriminability. Poorly discriminable objects elicited rapid avoidance acquisition, with suppression of activity and subsequent avoidance of the shock chamber (increased entry latencies). Highly discriminable shock objects also elicited rapid acquisition of avoidance, but without activity suppression or chamber avoidance. This pattern of findings suggests dual mechanisms for passive avoidance, with discriminated avoidance underlying failure to contact highly discriminable shock objects, and response suppression (immobility) underlying avoidance of poorly discriminable sources of threat. (Blanchard and Blanchard 1970, p. 1.)

It should be noted that the issue here is how the animal perceives the situation, rather than how the experimenter views the formal contingencies (an issue we have met before). This distinction between active avoidance, on the one hand, and response suppression, on the other (both being within what is, in formal paradigmatic terms, passive avoidance), is also important for the effects of the anxiolytic drugs. For example, Waddington and Olley (1977) studied the effects of chlordiazepoxide on 'step-down' passive avoidance under two training conditions. The animal's task was to refrain from stepping down from a safe, elevated platform to an electrified grid floor. In the first training condition the rat was removed from the apparatus immediately after it had been shocked and replaced later on the platform. In the second, the rat was shocked until it returned of its own accord to the safe platform. This second procedure, therefore, allowed the animals to solve the problem via an active escape contingency (returning to the safe platform) as well as the passive avoidance contingency (refraining from stepping down). As we would expect, chlordiazepoxide increased the tendency to step down from the platform in the first condition. It failed to produce any effect in the second condition, indicating that in this case the FFFS rather than the BIS (behavioural inhibition system; Chapter 5) was controlling behaviour.

Consistent with this, the anxiolytic drugs (probably including beta blockers) all impair passive avoidance in spatial tasks; that is the drugged animals emit the punished response at a higher rate than controls. This effect is less dramatic with the benzodiazepines than with the barbiturates or alcohol but is directly related to their capacity to bind to benzodiazepine receptors (Lippa *et al*. 1978) and appears to be unrelated to their sedative side-effects (Sanger *et al.* 1995). The 5-HT_{1A} agonists can have equivalent effects to benzodiazepines (Merlo Pich and Samanin 1986; De Vry *et al.* 1989; Albinsson *et al*. 1994; Riekkinen 1994; see Traber and Glaser 1987; Griebel 1995, Table 1) although they often have weak or null effects (see Broekkamp *et al*. 1989; Howard and Pollard 1990; see Griebel 1995, Table 1), except, apparently, when pigeons are used as subjects (Barrett *et al*. 1986, 1994; see review by Barrett and Vanover 1993; but see also Benvega and Leander 1996) or when the drugs are administered chronically before testing (Yamashita *et al.* 1995). In the case of imipramine, chronic administration changes an apparently anxiogenic effect into an anxiolytic one (Fontana and Commissaris 1988).

In operant chambers and other non-spatial tasks the barbiturates and benzodiazepines also reduce passive avoidance. The data on the effects of alcohol are similar, but less clear (Falk 1971; Cook and Davidson 1973; Leander *et al.* 1976). Propranolol only has effects if the shock level is low (Salmon and Gray 1986). 5-HT_{1A} agonists frequently have no effect (e.g. Kuribara 1994; Broekkamp *et al*. 1989); however, tandospirone (a relative of buspirone) has been shown to reduce the suppression of licking in a Vogel-like conflict task (drinking of water simultaneously punished by electric shock) by a direct action on the dorsal hippocampus (Kataoka *et al.* 1991). Acute imipramine is, again, sometimes 'anxiogenic'.

In contrast, therefore, to one-way active avoidance, anxiolytic drugs impair passive avoidance (see also further discussion in Gray 1982, Chapter 2), but the effects of novel anxiolytics are less clear in non-spatial tasks (see for example Table 1 in Barrett and Gleeson 1991) and with acute administration. Benzodiazepines and 5-HT_{1A} agonists

also release responding when this is inhibited by omission of a safety signal (Charrier *et al*. 1994). This is consistent with the analysis of Chapters 2 and 3.

Care must be taken in interpreting some of these data given the effects of many of these drugs on food and water intake (see above and Cooper 1991) and the relative lack of effect of buspirone may in many cases reflect its lesser effect than benzodiazepines on water intake. The effect of buspirone on conditioned suppression of drinking has also been attributed to its action on alpha-2-adrenoceptors (Gower and Tricklebank 1988; see also La Marca and Dunn 1994).

It is important to note here that the effect of the drugs is not simply to prevent the animal from inhibiting a response as such but is a genuine shift of the approach–avoidance conflict in the direction of approach. This reflects an alteration in the motivational consequences of anxiety. Thus Hascöet *et al*. (1994) provided their animals with a choice between reinforcement on a fixed ratio (FR) 1 schedule for food + punishment and an FR8 for food without punishment. Diazepam and a range of 5-HT_{1A} agonists all increased the number of punished responses. Likewise, anxiolytic drugs greatly reduce the occurrence of the stretched approach/stretched attention/flat back approach posture which appears to result from a balance between approach and avoidance behaviour (Molewijk *et al.* 1995). Oddly enough, when given after acquisition of passive avoidance is complete, the 5-HT_{1A} agonists can impair performance under conditions where benzodiazepines and imipramine are without effect (Sanger *et al.* 1989; see also Broekkamp *et al.* 1984; Nabeshima *et al*. 1990; Carli *et al.* 1992*a*), although benzodiazepines can have effects on recall of taste aversion conditioning (Roache and Zabik 1986; but see Delamater and Treit 1988). Given our conclusion, later, that 5-HT_{1A} agonists may be less amnestic than benzodiazepines, and the fact that this effect on passive avoidance cannot be anxiolytic (since it is not produced by the benzodiazepines), it seems likely that it follows some form of state dependency.

Two-way active avoidance is the case in which the dangerous and safe compartments of an apparatus are interchangeable. The main difference between two-way and one-way avoidance is that the animal must shuttle between the compartments, rather than being transferred in one direction by the experimenter. The complexities of this task are discussed in Chapter 2 of the first edition. But, it can be viewed, in the present context, as simply facing the animal, on any one trial, with an active avoidance aspect (to move from the now dangerous compartment) pitted against a passive avoidance aspect (to avoid the previously dangerous compartment). Since one-way active avoidance is unaffected by anxiolytics and passive avoidance is impaired by them, one would predict that two-way avoidance would be improved. This is indeed the case. (In passing it should be noted that this test can be viewed as an avoidance–avoidance conflict rather than an approach–avoidance conflict—but conflict nonetheless it is.)

Rather similar findings have been reported in studies of non-spatial active avoidance. This has usually been studied in operant chambers with Sidman avoidance schedules. Such a schedule is defined by two parameters, the shock–shock and the response–shock intervals. The former is usually substantially shorter than the latter. In the absence of a response, shocks occur regularly at the shock–shock interval; each response postpones the next shock by the time defined by the response–shock interval. Note that there is no explicit warning signal in this procedure. Time since the last response or since the last shock provides the only predictor. Low doses of anxiolytic drugs, given to animals which have learnt to bar press on this schedule, improve performance. This is particularly the case in animals which performed poorly in the undrugged state. Bignami *et al*. (1971) suggest that this results from a reduction in the response–suppressant effects of the secondary aversive stimuli constituted by the general experimental environment—a direct analogue of the situation in two-way active avoidance and also of the situation analysed by Blanchard and Blanchard (1970).

To our knowledge, buspirone has not been tested on two-way avoidance, and the results are difficult to predict given its capacity to impair active avoidance and its somewhat weaker effects on passive avoidance than classical anxiolytics.

The recurrence of diffuse or spatial stimuli as a factor in making tasks drug sensitive is something to which we will return in later appendices.

A1.9 Reward omission, successive discrimination, and related schedules

In passive avoidance, presentation of a response-contingent punisher inhibits a spontaneous or previously learned response. We have already seen that omission of an expected reward has many of the properties of a punisher. However, in addition, it carries a virtual guarantee of conflict since the same response which previously generated the expected reward is that which, by definition, gives rise to the omission of the expected reward. As we might expect from this, when injected during extinction, the anxiolytic drugs reduce the rate of extinction in both operant chambers and runways. Interestingly, benzodiazepines can still have this effect on extinction if they are administered for 12 days, not administered for 4 weeks during which they should wash out of the animal's system, with the animal then being both trained and extinguished with no further drug administration (Shemer *et al.* 1984). Novel anxiolytics do not appear to have been tested on extinction.

Extinction can be thought of as the simplest case of both successive discrimination and a variety of schedules of reward omission. In all of these a requirement to respond under some circumstances is pitted against an explicit or implicit requirement to inhibit responding under others.

The closest relative to extinction is reversal of a simultaneous discrimination. As we noted in the section on reward, simultaneous discriminations are unaffected by anxiolytic drugs. The reversal of such a discrimination (where the old S– becomes S+ and vice versa) is impaired by barbiturates (Bindra and Reichert 1967; Caul 1967). It is unfortunate that more experiments of this kind have not been reported, since, as we shall see, reversal learning is particularly sensitive to septal and hippocampal lesions. This effect on reversal learning occurs whether the reinforcer is a reward or a punisher (Bindra and Reichert 1967).

In successive discrimination the positive (S+) and negative (S–) stimuli are presented separately in time, and the animal's task is to respond in the presence of S+ and to refrain from responding in the presence of S–. In stark contrast to the lack of effect of anxiolytic drugs on *simultaneous* discriminations, and as with extinction and reversal, anxiolytic drugs almost always impair successive discriminations in both spatial and non-spatial apparatus. Propranolol is effective in operant successive discrimination (Salmon and Gray 1986) and buspirone has similar effects but only in a narrow dose range (Panickar and McNaughton 1991*a*; see also Stanhope and Dourish 1996). An interesting exception to this rule occurs when well-trained animals are given an anxiolytic drug in increasing doses. With conventional delivery (e.g. doses of 0, 5, 5, 0 mg/kg chlordiazepoxide on successive days) anxiolytics decrease successive discrimination. However, with modestly graded delivery (0, 2.5, 5, 5, 5 . . . mg/kg) no effect is obtained unless the drug is given during acquisition of the schedule (Vachon *et al.* 1982; McNaughton 1985*a*; see also review by Cole 1986). This suggests that the effects of anxiolytics, *provided that they are given once successive discrimination has become well learned*, are due to state dependency (i.e. the fact that the drug state has changed rather than the presence of the drug itself). We thus have the situation that the drugs can affect acquisition of successive discrimination in a non-state-dependent manner and, as we saw earlier, they affect both acquisition of, and well-learned, conditioned suppression in a non-state-dependent manner. But they do not affect well-learned successive discrimination except through state dependency. This pattern of results is consistent with the explanation we presented in Chapter 3 for the persistence of active avoidance. Let us consider the case with shock as opposed to non-reward. In well-trained successive discrimination the animal no longer receives regular shocks and will feel no fear. Its lack of responding will have become dependent on habit in exactly the same way as the presence of responding in active avoidance. However, in the conditioned suppression case, delivery of shock is not altered by the reduction in responding; shock will occur with as great a frequency after extended training as it did at the start of training, and so the animal will remain fearful. Given the equivalence of shock and omission of expected reward for which we have argued, the same argument should hold for successive discrimination based on non-reward.

Intermittent schedules of reinforcement can be considered as varieties of successive discrimination in which time or reward, as opposed to an explicit neutral stimulus, provides the continuing cue for response inhibition. In single alternation, the relevant cue is the outcome of the previous trial. The animal learns that reward signals non-reward and vice versa. On a fixed interval (FI) schedule, delivery of reward is a reliable signal that, for the period of the interval (typically 1 min) responses will not be rewarded (Staddon 1970, 1972). Similarly, in 'differential reinforcement of low rates of response' (DRL) the making of a response, whether it is rewarded or not, delays the next reward by the DRL interval (typically 15–20 s). Thus the making of the response is a reliable signal of a non-reward period. With both FI and DRL, response rates in control animals are much lower after the event which signals the start of the interval and, in well-trained animals, responding peaks at the end of the non-reward period. In each of single alternation and DRL, classical anxiolytic drugs increase responding more in the non-reward period than they do in the reward period. In FI more general increases are observed, possibly because of the difficulty of separating reward from non-reward periods. Buspirone has been tested on both FI and DRL and can produce similar effects to classical anxiolytics, but only in a narrow dose range (Panickar and McNaughton 1991*b*, 1992). Interestingly, the newer partial benzodiazepine agonists, which lack the major side-effects of the full agonists, also appear to have rather weak effects on DRL (Stephens and Voet 1994) as may propranolol (Salmon and Gray 1985*a*,*b*). In a DRL72 task (which is often viewed as a screen for antidepressant rather than anxiolytic drugs) buspirone has similar effects to diazepam except on burst responding (responses with very short inter-response intervals), where they have opposite effects (Richards *et al.* 1994). The effects of buspirone on FI become much more like those of the benzodiazepines if it is given for a long period before the start of training (Zhu and McNaughton 1995) or if corticosterone levels are held constant (McNaughton *et al.* 1996). In pigeons, gepirone and 8-OH-DPAT have the opposite effect to buspirone, increasing rather than decreasing FI responding, suggesting that the DA2 antagonist properties of the latter may be masking its anxiolytic effects (Barrett *et al.* 1988).

Similar considerations apply to fixed ratio (FR) schedules. On these the animal must make a specified number of responses for reward to be obtained. With large ratios, reward necessarily signals a period of non-reward and a pronounced pause in responding develops. Anxiolytic drugs increase responding on these schedules, but it is not clear that they shorten the post-reinforcement pause.

The anxiolytic drugs also antagonize the behavioural effects of non-reward when reward is not removed completely, but merely reduced in quantity. Large rewards sustain higher levels of performance than small rewards. If animals that are accustomed to receiving large rewards are unexpectedly switched to a small reward, their performance drops to a level lower even than that sustained by accustomed low reward. This undershoot, 'contrast effect', or 'depression effect' (Crespi 1942; Baltzer and Weiskrantz 1979) is blocked or attenuated by barbiturates and benzodiazepines (Baltzer *et al.* 1979; and references in Gray 1977) even when the contrast effect depends on safety

signals rather than reward (Torres *et al*. 1994), but not, surprisingly, by 5-HT_{1A} agonists given either acutely or chronically (Flaherty *et al*. 1990).

A variable interval (VI) or random interval (RI) schedule is similar to FI and DRL schedules except that the precise length of the interval is uncertain. This has the important consequence that the animal no longer has a reliable signal of periods of low probability of reinforcement. In consequence, response rates remain fairly high and stable, with no pause after reward is delivered. The anxiolytics have no consistent effects on response rate in these schedules but on occasion produce a mild increase in responding.

The data reviewed in this section, taken with the earlier data on rewarded tasks and simultaneous discrimination and on active versus inhibitory avoidance conditioning, lead to the conclusion that animals treated with anxiolytic drugs over-respond at times when control animals are actively inhibiting some prepotent response as a result of conflicting response tendencies. They provide quite different evidence, then, for the existence of the behavioural inhibition system, which was postulated on purely behavioural grounds in Chapter 3. They also reinforce the view that the anxiolytic drugs (as a global class, excluding side-effects) can be used as markers or probes for the operation of the BIS.

In the following sections we will allow the anxiolytic drugs to take us into territory which, at first sight, seems unrelated to the threat systems we have been considering up to this point. However, as we noted at the beginning of the appendix, while not involving any clear threat, except that involved in loss of food, when anxiolytic drugs have effects in these tasks we will be able to discern involvement of the BIS in the fact that they involve approach–approach conflicts in which a previously appropriate response must be inhibited.

A1.10 Maze learning

The effects of anxiolytic drugs in mazes are of particular interest in relation to the spatial view of the hippocampus (see Chapter 7 of the printed text). It is unfortunate, therefore, that very few experiments have been done with complex mazes (none are reported in Gray 1977).

The logically simplest type of maze is the T-maze, in which there are only two possible choices—one correct and one incorrect. As with other simultaneous discriminations, anxiolytic drugs do not impair simultaneous spatial discrimination—when one arm of the T is always correct.

The next level of complexity is represented by spatial alternation. While there are no direct tests reported with learned alternation, studies have been undertaken with spontaneous alternation. In this procedure the animal is simply placed in the stem of a T-maze and allowed to explore freely. The first choice of arm (left or right) is recorded, and the procedure is repeated. On the second trial about 70 to 80 per cent of normal animals typically choose the arm opposite to the one chosen on the first trial. Animals treated with anxiolytics choose at random (Douglas and Truncer 1976; Gray 1977). A detail to which we will return when we consider the radial-arm maze is that with the benzodiazepine chlordiazepoxide, a high dose (20 mg/kg, Granjean and Bättig 1962; Iwahara *et al*. 1972) eliminates spontaneous alternation, but it is ineffective at a dose (5 mg/kg; Panickar and McNaughton, unpublished data) which would be effective in tasks such as successive discrimination, FI, DRL, and many others. Alternation in normal animals is in part due to a tendency to vary the goal arm chosen (‘stimulus alternation’) and in part a tendency to vary the direction of body turn (‘response alternation’). Anxiolytics appear to affect response alternation but not stimulus alternation (McNaughton and Feldon 1980).

In a radial-arm maze task, the rat is placed in the centre of a maze in the shape of a star burst where there are typically 8 or 16 arms. In the simplest version of this task all arms contain a piece of food at the beginning of any one trial and the most efficient performance is for the rat to visit each arm only once. This might seem very simple in that this outcome can be achieved by a rule such as ‘turn sharp left as you come out of each arm’. In practice, rats do not solve the task in this way, tending to choose arms roughly opposite to that which they have just visited. They must, therefore, maintain in working memory information (possibly spatial information) about the arms they have visited. We discussed different types of memory more in Chapter 6. Suffice it to say here that a normally anxiolytic dose of chlordiazepoxide (5 mg/kg) is without effect in this task (data from Rawlins cited by McNaughton *et al*. 1980) but, as with spontaneous alternation, a high dose (20 mg/kg) is effective (Rawlins, personal communication). The 5-HT_{1A} agonists also impair performance in the radial-arm maze (Winter and Petti 1987). Interestingly, if only four arms are baited, and these are cued with pieces of sandpaper which are changed in spatial position from trial to trial, then 5 mg/kg of chlordiazepoxide is sufficient to produce a deficit in acquisition of this task (Hodges and Green 1986; Olaman and McNaughton, in preparation). This task is discussed in more detail below.

Probably the quintessential test of spatial navigation, and nowadays the most commonly used maze in relation to temporal lobe lesions, is the Morris water maze (Morris 1981, 1984). This consists of a circular featureless swimming pool which contains a submerged, and hence invisible, platform which is always located in the same spatial position. The rat is placed in the pool at different positions on different trials and control rats quickly learn to find the platform and to swim almost directly to it. The invisibility of the platform also allows for the use of transfer tests to determine what the rat has learnt. In the transfer test, at the end of acquisition of the task, the rat is placed in the water as usual, but there is no platform to swim to. Control rats show that they know the precise position at which the platform should have been located. They swim to this position and then swim in very tight circles on the spot where the platform would have been (Fig. 4.2).

Chlordiazepoxide, buspirone, the 5-HT_{1A} agonist 8-OH-DPAT, ethanol, and other anxiolytic drugs eliminate *acquisition* of spatial navigation in the water maze (McNaughton and Morris 1987, 1992; Devenport *et al.* 1989; Rowan *et al.* 1990; McNamara and Skelton 1991, 1992; Carli and Samanin 1992; Keith and Galizio 1997) while leaving intact non-spatial (or less accurate) strategies for finding the platform. It is of note that in this task, unlike those we have considered above, buspirone has a purely linear dose–response curve (McNaughton and Morris 1992). The 5-HT_{1A} agonist 8-OH-DPAT also impairs the capacity of rats to learn a spatially-based discrimination between a real and a false platform when injected both systemically and into the hippocampus (Carli and Samanin 1992; Carli *et al*. 1992*b*) and its systemic effect can be blocked by injection of a 5-HT_{1A} antagonist into the hippocampus (Carli *et al*. 1995). An exception to this general pattern is the report that even high doses of pentobarbitone do not affect acquisition in the water maze in mice (Beaudin and Lalonde 1997).

There are two features of the effects of anxiolytics in the water maze which are particularly important for our analysis of behavioural inhibition. These are discussed more fully in Chapter 4, but will be mentioned here.

First, it is clear that the rats are motivated to learn the task and are capable of at least some learning. On successive trials in the apparatus, they reduce the distance they swim markedly and towards the end of acquisition appear, on the basis of path length, to be solving the task nearly as well as controls. However, in the transfer test, they swim straight through the position at which the platform would have been (Fig. 4.2) and show little indication that they know where it is. This shows they have a simple rule which allows them to bump into it.

Second, while this task could be viewed as involving aversive motivation (specifically a desire to escape from the water), it should be noted that it is formally an escape or active avoidance task *not* one involving passive avoidance. However, we concluded above that it is only passive and not active avoidance tasks which anxiolytic drugs normally impair.

The deficit produced by anxiolytic drugs in this task cannot therefore be attributed to the use of a negative reinforcer. Nor can it be attributed to a general failure of memory, since respectable learning occurs but accuracy is reduced by a failure to determine the position of (or at least correctly approach) the platform. Nor can it be attributed, except ad hoc, to a loss of specifically spatial capacities since many of the other tasks we have considered (FI, DRL, etc.) are not distinguished by specifically spatial requirements. Furthermore, administration of buspirone only during the probe trial at the end of acquisition has no effect (Rowan *et al*. 1990) and diazepam has no effect on performance (McNamara and Skelton 1991; see also Kant *et al*. 1996) or even on acquisition if the rats have first been habituated to swimming in the maze (Zanotti *et al*. 1994) as a result of the elimination of interfering strategies such as thigmotaxis (Cain 1997). Sufficiently long (30 day) pre-treatment with diazepam can also induce tolerance (McNamara and Skelton 1997).

This point is emphasized when we view spatial tasks as a whole. In this section we have seen a progression from simple to complex tasks. In the simplest, there was little effect of the drugs; in the more complex (alternation and radial-arm maze), there was a clear effect only at high doses; finally, in the most complex (spatial navigation as opposed to other solutions of the water maze), there was total abolition of the capacity. This emphasis on complexity, as opposed to space, is underscored by two facts. First, an increasing sensitivity to drugs with increasing complexity of task characterizes the data in all the previous sections—in tasks which have no obvious spatial component. Second, as noted above, if the radial-arm maze is modified to be more complex, but less spatial, anxiolytics become effective even at low doses. Instead of putting food in all eight arms of the maze, one can place food in only four *and* signal which four by placing, for example, a piece of sandpaper at the end of each baited arm. The arms containing the food are changed from trial to trial. Chlordiazepoxide at 5 mg/kg significantly impairs acquisition of this task (Hodges and Green 1986; McNaughton and Olaman, in preparation).

Complexity is a rather elastic term and does not seem to relate very well to the idea of conflict which has been at the root of all our analysis so far. In the case of the water maze, we can make some progress to closing this gap. As we will discuss later (Appendices 8 and 9), septo-hippocampal lesions produce an even larger deficit in spatial navigation in the water maze than do anxiolytic drugs. However, there are a number of data that suggest that space, qua space, is not the critical factor in determining the lesion deficit. For example, Eichenbaum *et al.* (1990) found that rats with fimbria–fornix lesions (which disconnected the septum from the hippocampus) could perform the task nearly as well as controls, but only if they started from the same position on every trial, and yet a probe trial showed that they were solving the problem using spatial cues and not some simpler rule. The main cause of the drug deficit in the standard form of the maze may be due to an inability to inhibit conflicting response tendencies when starting from different positions on each trial.

A1.11 Responses to novelty

Almost always when an experimenter studies an animal, the latter will instantly be faced with novel stimuli. In almost all cases, also, the animal must first react appropriately to these novel stimuli and classify them correctly before it can decide how it should then behave. It may seem surprising, therefore, that we have left discussion of novelty so late.

Unfortunately, both motivationally speaking and in terms of experimental control of critical variables, novelty is complex and in many respects intractable. Animals will both approach novel stimuli in order to explore them and avoid novel situations if the intensity of novelty is too great. This latter effect may be analogous to the situation with ‘neutral’ stimuli where a sufficient increase in intensity will render them aversive. The ‘intensity’ of novelty is, of

course, a function of the experience which the animal has had with the stimuli concerned. As a result, starting at an unpredictable value, the balance shifts from avoidance to approach with repeated or continued exposure to a specific set of stimuli (until all novelty is totally lost and the stimuli become neutral). Of particular concern is that it may be difficult to determine whether any specific behaviour observed in a novel situation (as opposed to that to an introduced novel stimulus in a situation to which the animal is habituated) is the result of approach, avoidance, or the risk assessment which can result from a conflict between the two. Furthermore, in many situations used to test anxiolytic drugs, the aversive components can give rise to both active and passive avoidance components (see for example Viana *et al.* 1994). As we saw above, we would expect the active avoidance to be insensitive and the passive avoidance to be sensitive to anxiolytic drugs.

Responses to 'high intensity' novelty have played a substantial role in investigations of individual differences in fearfulness and their genetic (Broadhurst 1960), ontogenetic (Levine 1962), and hormonal (Gray 1971*b*) bases (see Gray 1987 for a review).

In the high-stress open-field test, for example, the animal is taken from its home cage and placed in a large arena, usually brightly lit and sometimes located under a source of loud noise. Measures are taken of its exploratory behaviour (ambulation and rearing on the hind legs) and of its level of defecation and urination. There is good evidence that high fearfulness is accompanied by high defecation scores (Broadhurst 1960, 1975; Gray 1971*a*, 1979). The relation between ambulation and fearfulness is more complex. Ambulation is positively related to fearfulness when the animal is first exposed to the open field, but subsequently this relation becomes negative (see Gray 1982, Section 2.10). We will return to this issue in Appendix 10 (and see Chapter 12 for recent genetic analyses).

The effects of anxiolytic drugs on open-field behaviour are complicated. There is no good evidence that they produce a reduction in responses, such as defecation, directly elicited by aversive aspects of novelty. They increase ambulation under some conditions, but the pattern of results does not suggest that this is necessarily mediated by changes in fear (Gray 1982, Section 2.10). These results are consistent with the lack of effect of anxiolytics on responses directly elicited by punishers. 5-HT_{1A} agonists actually induce defecation under conditions in which control rats do not defecate (Croci *et al.* 1995). Anxiolytic drugs, including buspirone, decrease the tendency of mice to keep to the walls of an open field (thigmotaxis) independently of whether they increase or decrease ambulation itself (Simon *et al.* 1994).

Anxiolytic drugs usually produce a reduction in rearing (Iwahara and Sakama 1972; Thiébot *et al.* 1973, 1976; McNaughton 1985*b*; Griebel *et al.* 1992). However, these results must be placed in the context of the Blanchards' analysis of risk assessment (e.g. Blanchard *et al.* 1991). As will be remembered (Chapter 2), they found an inverted U-shaped relationship between rearing and the intensity of potential threat. That is, at high levels of potential threat rearing was low (and could be increased by anxiolytic drugs), while at intermediate levels of potential threat rearing was high and was reduced by anxiolytic drugs. In both cases, of course, the effect of the anxiolytic drugs was to move the behaviour in the direction of lower perceived threat. Consistent with this, while McNaughton found that an anxiolytic decreased rearing in a low-stress version of the open field (McNaughton 1985*b*), he found it increased rearing in a high-stress version (McNaughton *et al.* 1984). Likewise, Fukuda and Iwahara (1974) found that anxiolytics increased rearing in the first few minutes of their test, when anxiety might be presumed to be highest, and this was followed by a decrease in rearing subsequently when anxiety was likely to have moderated (see also Rodgers and Shepherd 1993). All of these data are consistent with the view that (a) rearing is an integral part of environmental scanning and risk assessment behaviour and (b) anxiolytics reduce the level of perceived risk or conflict (Blanchard *et al.* 1990; see also Griebel *et al.* 1997 on the relative effectiveness of 5-HT_{1A} agonists as opposed to other 5-HT subtypes on risk assessment behaviour).

Interestingly, rearing in the low-stress open field is a second case (the first being the water maze) where buspirone has a linear dose–response curve (Panickar and McNaughton 1991*a*) as does 8-OHDPAT (Broekkamp *et al.* 1989). This prompts the speculation that the reduction in rearing in response to novelty could be related to the deficits seen in the water maze. On reaching the safe platform, undrugged rats in this apparatus spend considerable time rearing (N. McNaughton, anecdotal observations). It may be then that the reduction in rearing in the open field is a sign of a more general loss of the capacity to gather information to resolve conflicts.[2]

Defecation, ambulation and rearing are all, in one sense or another, responses *elicited* by novelty. A range of other tests appear to reflect (as in the Visible Burrow System, Chapter 2) concurrent behavioural inhibition: eating, drinking, emergence, social interaction, the black–white box, and the elevated plus maze. In all these cases, novelty suppresses prepotent behaviour. In some, stimulus manipulations, such as the use of bright lights and noise in the open field test, bright lights in the social interaction test (File and Hyde 1978; File 1980), or other stimuli (omission of side walls in the elevated plus maze, openness and whiteness in the black–white box), can be used to increase stress and increase inhibition. *Classical* anxiolytic drugs reduce inhibition in all these situations (Gray 1982, Section 2.10). However, buspirone is often reported to be without effect in the elevated plus maze (see Table 5 in Rodgers and Cole 1994) and the social interaction test (see Barrett and Vanover 1993) although buspirone's effects may be somewhat more robust in the latter (File and Andrews 1994). Imipramine is effective in neither test and propranolol is only occasionally effective. Buspirone, and other 5-HT_{1A} compounds and antidepressants also, with acute administration, appear to be ineffective with novelty-suppressed eating (Bodnoff *et al.* 1989). Theoretically this is surprising, given the clear basis for linking such inhibition with the behavioural inhibition seen in response to

potential threat and may depend on the precise procedures used to test the animals (Hogg 1996). However, buspirone's effects may be clearer with the more recent use of ethologically derived measures in the plus maze (Rodgers and Cole 1994; Rodgers and Dalvi 1997; see Dawson and Tricklebank 1995 for a contrary opinion; and Rodgers *et al.* 1997 for a review) and (as with fixed interval responding) if it is administered chronically before testing (Cole and Rodgers 1994). Chronic administration also results in 'anxiolytic' effects on novelty-suppressed eating (Bodnoff *et al.* 1989) as it does with other antidepressant drugs (Bodnoff *et al.* 1988).

One possibility (Johnston and File 1988) is that the release of corticosterone by buspirone blocks its anxiolytic effects and that this effect occurs even at the lowest effective doses in these two tests because of particularly marked endogenous release of corticosterone (e.g. File *et al.* 1994). If this speculation is the case, anxiolytic effects of buspirone would be seen in these tests if adrenalectomized rats were used (preferably with exogenous replacement of normal basal corticosterone levels—see McNaughton *et al.* 1996 for an example of this type of result with a fixed interval schedule). Certainly, stress can interact with drugs in strange ways in the elevated plus maze. Different stressors which elevate corticosterone to similar amounts can produce quite different effects from each other on baseline responding (perhaps because of the different time course of the raised corticosterone levels) and such stressors can reverse the effects of 5-HT_{1A} agonists (McBlane and Handley 1994).

Buspirone also appears to differ from the purer 5-HT_{1A} agonist, 8-OH-DPAT, both in not having an anxiolytic effect in this test and in producing its anxiogenic effects through receptors other than 5-HT_{1A} (Collinson and Dawson 1997). File *et al.* (1996) suggest that the weak effects of 5-HT_{1A} agonists could be due to opposite actions on median raphe autoreceptors (producing an anxiolytic effect) and on hippocampal terminals (producing an anxiogenic effect) with reductions in hippocampal 5-HT transmission being anxiolytic. If this is true then a subtle difference in the type of the 5-HT_{1A} receptors in the two areas could explain the differences between 8-OHDPAT and buspirone.

By contrast to the effects of buspirone on the elevated plus maze, ipsapirone, like diazepam, increases emergence in the elevated T-maze (Viana *et al.* 1994). It seems likely that this is due to the fact that this test has isolated the passive avoidance component from other aspects (e.g. active avoidance) of the plus maze, rather than there being a major difference between buspirone and ipsapirone.

A disadvantage of the tests we have looked at so far in this section is that the experimenter places the animal in an environment which contains both novel and non-novel features and simply observes behaviour—with little experimental control of the changes observed. It is then difficult to distinguish approach to one stimulus from avoidance of another or from behaviour designed to assess risk given the conflict inherent in the situation. One way to approach this problem is to measure exploratory behaviour that is evoked by discrete novel elements in a non-novel environment (as distinct from locomotion in a generally novel environment). Behaviour of this kind is generally decreased by the anxiolytic drugs.

Hughes (1972; Hughes and Syme 1972; Hughes and Greig 1975), for example, put rats into one-half of a two-compartment box, then removed them and injected them with chlordiazepoxide or placebo before returning them to the apparatus with both halves now open. The drug reduced entries into the novel side of the box even though it increased overall locomotion. In a similar experiment with sodium amylobarbitone, Ison *et al.* (1966) placed rats in the stem of a T-maze separated by glass partitions from the two arms, of which one was black and one was white. After 3 min the rat was removed, one of the arms was changed so that they were now both black or both white, and the rat was returned to the stem of the T-maze. As in other experiments using this technique, normal rats chose to enter the changed arm about 75 per cent of the time; the rats drugged with sodium amylobarbitone chose at random.

A lone experiment by McGonigle *et al.* (1967) has taken this type of analysis further by measuring the degree to which a drugged animal *learns* about a novel element in its environment. They trained rats on a random 50 per cent partial reinforcement (PRF) schedule to choose the positive cue (black or white) in a choice box. Choice of the negative cue was never rewarded. The rats were then shifted to a combined-cue discrimination (black versus white and horizontal versus vertical stripes, both types of cue being presented together) in which the original positive cue (e.g. black) remained positive. During this stage of the experiment, half the animals received sodium amylobarbitone and half received placebo. Finally, transfer tests were conducted with only horizontal versus vertical stripes and no drug. Controls chose correctly on 80 per cent of transfer trials, but the animals which had received the drug showed no learning about the novel cue. This suggests that the drugs impair the capacity of a novel cue to gain control of behaviour. However, it is possible that the use of a PRF schedule could be as important as novelty in inducing switching in the control animals (see next section).

It is unfortunate that other workers have not followed the lead set by McGonigle *et al.* (1967). Not only is there a need to eliminate the confounds noted above, but there is a rich theoretical and experimental literature on the role of attention in animal learning (e.g. Sutherland and Mackintosh 1971; and see McGaughy *et al.* 1994 for effects of chlordiazepoxide on 'divided attention'), from which many tests of learning about novel cues similar that of McGonigle *et al.* might easily be derived.

The analysis of novelty is procedurally much more difficult than the analysis of rewards and punishers (which is one reason why we have left its consideration until now). However, if we take the findings obtained with the latter as our guide, some semblance of order can be detected in the results reviewed in the present section.

First, let us consider the immediate eliciting effects of novel stimuli. Startle, defecation, and, at least in low-stress cases, ambulation, are, like the eliciting effects of rewards and punishers, unaffected by anxiolytic drugs. Of these, the theoretically least tractable is ambulation. If this were taken as a risk assessment behaviour, it should be (in

general) reduced by anxiolytic drugs. However, ambulation could involve both risk assessment and avoidance of aversive stimuli. In this context it is interesting that while the effects of the anxiolytic drugs are, in one sense, inconsistent, they appear to remove a source of variation in the control data. Thus high levels of ambulation are reduced and low levels are increased across different experiments with varying control groups so that all the experiments show the same behaviour in the drugged groups (McNaughton 1985*b*).

Second, let us consider the behavioural inhibition produced by novel stimuli. Like the inhibitory effects of punishers, these are reduced by anxiolytic drugs (although there may be some question about this in the case of the effects of buspirone on the elevated plus maze and social interaction test). In this context, it is interesting to note that the conditioned suppression produced by a stimulus paired with food is *not* affected by chlordiazepoxide (Miczek 1973). There are a variety of reasons for treating this 'positive conditioned suppression' as a special case (Davison *et al.* 1980; McNaughton 1989, Section 9.8). But the key issue is (as we have emphasized before) not the specific arrangement of stimuli, nor the specific direction of behavioural change, but the extent to which the observed behavioural inhibition depends on conflict.

Third, let us consider approach to novelty. At first sight, the reduction produced by anxiolytics in the approach to novelty is surprising. After all, anxiolytics do not decrease appetitive behaviour in general. This is of particular interest since, up until this point, the effects of the drugs could be characterized as a decrease in the effective aversiveness of the situation. This cannot be the case here since a decrease in the aversiveness of a novel stimulus with no change in its attractiveness would increase rather than decrease approach. One possible explanation of this result is that the anxiolytic drugs produce a decrease in the capacity to detect novelty which, in this case, elicits approach, at least in the sense of risk assessment, as well as behavioural inhibition. A second possible explanation is that the approach to the novel stimulus is an example of risk assessment, and hence is reduced by the drug.

A1.12 Counterconditioning and toughening up

So far we have dealt with situations which involve a single reinforcer either alone or in combination with a neutral stimulus. In this section we will consider tasks in which one reinforcer predicts another.

In the simplest case a reinforcer such as shock can predict a reinforcer such as food, 'off-the-baseline'. The subsequent eliciting effects of the shock, or its capacity to inhibit responding back 'on-the-baseline', are reduced by shock–food pairing compared to controls which receive similar numbers of shock and food deliveries, but with no correlation between the shock and food. This reduction in the effect of the shock is referred to as counterconditioning. Chlordiazepoxide has absolutely no effect on simple 'classical' counterconditioning of shock with food (McNaughton and Gray 1983), nor does it appear to affect the similar 'off-the-baseline' counterconditioning by food of a stimulus which predicts shock (McNaughton and Gray, unpublished observations).

The 'partial punishment effect' (PPE) is, formally speaking, quite similar to simple classical counterconditioning. To demonstrate the PPE, one takes two groups of rats. One group is trained to run down a runway for food on a CRF schedule, and receives no shocks. The second group, like the first, always receives food, but also, on a random 50 per cent of trials, receives shock (partial punishment). In a final phase of the experiment both groups of rats receive shock on all trials. This produces much less suppression in the previously shocked group—evidence for some kind of counterconditioning or at least tolerance. Anxiolytic drugs, of course, reduce suppression in CRF animals (see section on passive avoidance); but they *increase* suppression in the partially punished group, eliminating the counterconditioning. This effect is produced, in a non-state-dependent manner, only if a 24-hour intertrial interval is used—an issue to which we will return in later appendices (see also McNaughton 1989, Chapter 7).

Given the similarities which we have already discovered between the effects of punishment and the effects of reward omission, it should come as no surprise that the same pattern of results is obtained in relation to the partial reinforcement extinction effect (PREE). As with the PPE, there are two groups of rats, one of which is trained with CRF. The second group receives reward on 50 per cent of trials and non-reward on the other 50 per cent. Through a chain of conditioning processes (Amsel 1992), partial reinforcement can be viewed as counterconditioning the aversive effects of frustration. As a result, partially non-reinforced rats when faced with continuous non-reinforcement (extinction) show less suppression than CRF rats.

The links between the PREE and PPE go beyond this formal similarity since partial non-reinforcement increases resistance to continuous punishment and partial punishment increases resistance to continuous non-reinforcement (Brown and Wagner 1964). As with the PPE, anxiolytic drugs abolish the PREE in a non-state-dependent manner with a 24-hour intertrial interval (Feldon *et al.* 1979; Feldon and Gray 1981) but not with a short intertrial interval (Ziff and Capaldi 1971). At intermediate intertrial intervals and with large numbers of training trials intermediate effects are observed (Feldon 1977; Willner and Crowe 1977; Feldon *et al.* 1979; Feldon and Gray 1981; see references in Gray 1977; see also McNaughton 1989, Chapter 7).

A theoretically related effect of reward omission is seen towards the end of acquisition of running in an alley with intermittent reward. Here, partially rewarded rats run faster towards the goal box than continuously rewarded rats, particularly in the early parts of the alley (Goodrich 1959; Haggard 1959). This 'partial reinforcement acquisition effect' is abolished by classical anxiolytic drugs, but has not been tested with novel ones.

Both the behavioural phenomena and the drug effects which we have considered here have been subjected to complex theoretical analysis (Amsel 1962, 1992; Capaldi 1967; Macintosh 1974; Gray 1975; McNaughton 1989). For the moment, we will merely note that, as with the other paradigms we have considered, there is the suggestion

that anxiolytic drugs have greater effects as the situation involves greater degrees of conflict or, given the role of intertrial interval, as it places a greater load on memory systems. We will turn now to the issue of the extent to which anxiolytic drugs affect memory.

A1.13 Conditional and delayed discriminations

We have already touched on one class of task favoured by those who study memory—mazes, and the water maze in particular. There, it will be remembered we suggested that the apparent impairments in memory were a secondary consequence of an inherent approach–approach conflict—that is, a failure to inhibit competing response tendencies. We will make essentially the same argument here.

There is a more complex variant of the successive discrimination known as a 'conditional discrimination'. An example will bring out the essential features of this paradigm. It comes from a report by Iwasaki *et al*. (1976), who made an explicit comparison of the effects of chlordiazepoxide between simultaneous and conditional discrimination learning. For this purpose, they used a choice-box in which, for the simultaneous task, the rat had to choose between black and grey doors. In the conditional task, both doors were the same brightness on any given trial (either black or white) and the animal had to learn to go left when they were one brightness and to go right when they were the other. Animals injected with saline as a control found the two tasks equally difficult. (Had the two tasks used stimuli of the same brightness, say black and white in both cases, the conditional discrimination would have been harder than the simultaneous one.) Animals injected with chlordiazepoxide were no different from controls on the simultaneous task, but were impaired on the conditional discrimination.

Perhaps one of the purest tests of memory is the delayed matching-to-sample task. In this a sample stimulus (with pigeons this would be either red or green displayed on a centre key which they must peck) is followed by a variable delay and the presentation of two alternatives (for example a red key on the left and a green key on the right). The pigeon is then rewarded for pressing whichever key displays the colour which was first presented as the sample. Behaviour in this task is often reported in terms of per cent correct choices. However, it can be seen that (as in a number of other tasks) errors could arise from two different sources: a true failure to discriminate between the alternatives; and response bias. These different sources can be isolated using methods based on signal detection theory (Davison and Tustin 1978). Provided this is done, it is found that in excess of 95 per cent of the variance in performance across delay intervals can be accounted for by an exponential function with two parameters, the discriminability at nominal zero delay and the rate of the exponential decay of discriminability with delay (White 1985). Anxiolytic drugs impair performance in this type of task by reducing 'discriminability' without increasing the rate of decay. In the special case of delayed matching to position, the 5-HT_{1A} agonist ipsapirone has no effect (Jansen and Andrews 1994), while benzodiazepines and ethanol affect rate of decay and not 'discriminability' (Melia *et al.* 1990; see also Givens and McMahon 1997).

Results similar to standard delayed matching have been obtained in rats using a combination of the conditional and delayed matching procedures. The rats were presented with a high tone or a low tone and, after a delay in which they had to make a nose poke response to prevent them taking up a fixed position in the apparatus, they had to make a response on one of two retractable levers. The rule to be used was of the form: low tone go left, high tone go right. Chlordiazepoxide reduced discriminability and did not increase rate of memory decay (Tan *et al*. 1996; see also Herremans *et al*. 1995*a*). Ipsapirone (a close relative of buspirone) has similar effects (Herremans *et al.* 1995*b*). The vigilance task of McGaughy and Sarter (1995) is very similar in design and also showed a clear effect of chlordiazepoxide.

It should be noted that the effects of the anxiolytic drugs on delayed matching and conditional discrimination cannot be accounted for in quite the same way as we accounted for their effects on successive discrimination. In delayed and conditional tasks, the animal has to choose trial by trial between competing responses, not choose between responding and not responding. Simple disinhibition of responding as a whole cannot, therefore, account for errors—but nor can the simple requirement to choose between competing responses. Simultaneous discriminations share with conditional discriminations the requirement to choose between alternative responses trial by trial. But simultaneous discriminations differ in two respects: (i) the correct response (or in some cases the correct stimulus) does not change from trial to trial and, consequently, (ii) the correct response rapidly develops a stronger excitatory potential than any competing response. In conditional discrimination and delayed matching, by contrast, the correct response does change from trial to trial (e.g. left and right responses will be rewarded equally often); with the consequence that the excitatory potentials of the two competing responses are likely to be roughly equal. Thus to perform efficiently in a conditional discrimination, the animal must be able to suppress interference from the response which, on a given trial, happens to be incorrect. In the case of delayed matching the same will be true of the correct stimulus, unless trial-unique stimuli are used. This conclusion is of particular importance for the detailed mechanisms which we ascribe to the behavioural inhibition system. A similar kind of explanation may be appropriate for the amnestic effects of the drugs in humans which appear to be linked with changes in attention (Preston *et al*. 1989; see also McGaughy *et al.* 1994 for an animal example) and encoding processes (Gorissen *et al*. 1995).

A1.14 Conclusions

We have now completed our review of the data on the behavioural profile of the anxiolytic drugs. A summary of the profile is provided in Table 4.2 in the printed text, and an overview of the theoretical implications of this profile for the concept of the behavioural inhibition system can be found at the end of Chapter 4. Our main conclusion is that anxiolytic drugs as a class (including classical and novel anxiolytics) appear to act specifically to impair the functioning of the behavioural inhibition system (Chapter 5). We also conclude that we should be able to use these drugs as markers for the location in the brain of the networks which subserve the functions of the behavioural inhibition system. Our search for these locations, given that anxiety is a defensive behaviour, requires close inspection of the networks controlling defensive behaviour in general. The latter is summarized in Chapter 6 and dealt with in detail in the following appendices.

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Notes

1. Tenen's (1967) experiment is wrongly described by Gray (1977) as using an 'on-the-baseline' design. We are grateful to P. Salmon for pointing this out to us.

2. An apparent exception to the above is the data of Cruz *et al.* (1994). They carried out an 'ethopharmacological' analysis of the plus maze coupled with a factor analysis. They concluded that rearing and risk assessment did not load on conventional anxiety measures (see also Rodgers and Johnson 1995) and were not affected by benzodiazepines. It is difficult to square this with the Blanchards' analysis (and in the case of 'risk assessment' is at variance with the conclusions drawn in a review of the plus maze by Rodgers and Cole 1994)—but it seems possible that this could be the result of a failure to manipulate 'defensive distance' coupled with a production in the + maze of a high level of anxiety. The anxiolytic drugs might then have had no apparent effect as a result of a shift from one side to the other of the U-shaped rearing-anxiety function (this would also affect the factor analysis—which in any case had a very small N). A similar analysis by File (1993) concluded that the behaviour on the first and second trial in the plus maze depended on quite different factors and that 'during the first 5 minutes in the elevated plus-maze the rats are acquiring a fear of heights and it is this phobic anxiety state that is measured during the second 5-minute trial' and which is insensitive to benzodiazepines (File 1993, p. 199).