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Conditioning and Sensitisation in the Longitudinal Course of Affective Illness

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Few biological theories of manic-depressive illness have focused on the longitudinal course of affective dysfunction and the mechanisms underlying its often recurrent and progressive course. The authors discuss two models for the development of progressive behavioural dysfunction—behavioural sensitisation and electrophysiological kindling—as they provide clues to important clinical and biological variables relevant to sensitisation in affective illness. The role of environmental context and conditioning in mediating behavioural and biochemical aspects of this sensitisation is emphasised. The sensitisation models provide a conceptual approach to previously inexplicable clinical phenomena in the longitudinal course of affective illness and may provide a bridge between psychoanalytic/psychosocial and neurobiological formulations of manic-depressive illness.

Many of the current biological theories of manic-depressive illness have focused on the acute changes in affective states and on their possible underlying biological determinants. There has been less attention paid to the mechanisms underlying the longitudinal course of affective illness. We examined two different sensitisation models, behavioural and electrophysiological, which might help to conceptualise the progression of symptoms in recurrent affective illness. However, we do not propose that these models fulfil all the usual requirements for an animal model of mania or depression *per se* (McKinney *et al*, 1984).

Several aspects of the course of affective illness deserve further emphasis. First, both bipolar and unipolar affective illness tend to be recurrent in the majority of patients (Perris, 1966; Angst, 1978; Kraepelin, 1921; Grof *et al*, 1974; Zis & Goodwin, 1979). Secondly, the frequency of recurrence and rapid cycling increases not only with age, but as a function of the number of prior episodes (Kraepelin, 1921, Grof *et al*, 1974; Zis & Goodwin, 1979; Cutler & Post, 1982). Thirdly, similar symptoms tend to be reproduced in each episode with new ones added in sequential or stepwise fashion. Affective episodes later in the course of the illness may be more severe and have more precipitous onsets (Post *et al*, 1981a) than earlier epsidoes.

We hypothesise that a subgroup of patients becomes more vulnerable, or 'sensitized', to recurrences of affective episodes. We suggest that these patients show characteristics of a sensitisation or kindling-like process in which the biochemical and physiological processes involved in the illness become progressively more easily triggered by the same circumstances or precipitants. Eventually, the episodes may occur spontaneously. Conditioned behavioural and biochemical changes might also occur, as demonstrated in laboratory studies. The models account for several phenomena observed in the course of affective illness; they suggest new avenues of research and stress the importance of preventing episodes with prophylactic treatment to inhibit sensitisation.

While there is still debate about the aetiological role of psychosocial stress in the onset of affective episodes, there is substantial evidence that for some patients environmental precipitants are associated with the onset of illness (Paykel, 1979a, b; Dunner & Hall, 1980; Brown *et al*, 1975; Amelas, 1979; Lloyd, 1980). Behavioural sensitisation could provide a model for the large subgroup of patients who develop more severe and rapid recurrences, in apparent response to repeated stresses of equal or reduced magnitude. Moreover, as patients develop increasing rapidity of cycling, the illness appears to evolve with its own rhythmicity and spontaneity, independent of ongoing life events. The mechanisms underlying such recurrent illness may be similar to kindling and behavioural sensitisation, as described below. Some patients have only a single affective episode. Genetic and environmental influences may be important in determining this pattern of non-recurrent illness; we will not address this subgroup further.

Kindling

Electrical kindling, as originally described by

Goddard *et al* (1969), refers to the development of major motor seizures in response to repeated intermittent electrical stimulation of the brain with insufficient current to produce overt behavioural effects (Racine, 1978). Recent data suggest that repeated application of some pharmacological agents, either parenterally or directly into the brain, may also produce a progressive increase in neural excitability, similar to kindling, eventually producing major motor seizures in response to a previously subthreshold dose of drug (Post & Kopanda, 1976; Post *et al*, 1982).

The intermittency of the stimulation appears to be critical for the development of amygdala-kindled seizures (Goddard *et al*, 1969; Racine, 1978; Post, 1980). Continuous amygdala stimulation or stimulation every 2–5 min is not associated with kindling; rather, the animal habituates and does not show major motor seizures. In contrast, intermitten stimulation at intervals longer than once every 2 hours (optimally, once every 24 hours or even once a week) is associated with the relatively rapid development of a convulsive response to the original subthreshold kindling stimulation. This temporal pattern of intermittent stimulation in the development of either tolerance or sensitisation may have parallel implications for the development of pathological behaviour in response to other intermittent stimuli, including stress (Post, 1980).

Kindling is a long-lasting, possibly permanent, change in neural excitability. Animals kindled in youth retain convulsive susceptibility in adulthood. As one ascends the phylogenetic scale, particularly in rhesus and human primates, kindling to a convulsive end-point appears to be increasingly difficult to achieve. Therefore, kindled seizures are only one marker of the development of the sensitisation process; many of the important characteristics of the kindling paradigm, including change in threshold and associated changes in behaviour (Adamec, 1975; Post, 1981; Post *et al*, 1984), can be observed in the absence of seizures.

After many repetitions of kindled seizures an animal may exhibit 'spontaneity', i.e. develop seizures in the absence of external stimulation (Pinel, 1981; Wada *et al*, 1974). The phenomenon of spontaneity has obvious importance for establishing kindling as a model of epilepsy. We suggest that kindling may help us understand how stress-induced mood alterations may become so sensitized that they also occur spontaneously; i.e. the rapidly or continuously cycling pattern of manic-depressive illness. It is pertinent that approximately one-third of kindled animals show cycling in their seizure patterns (Post, 1981).

Behavioural sensitisation

Repeated, intermittent application of psychomotor stimulants and dopaminergic agonists produces an increasing behavioural responsivity to selected end-points, such as motor hyperactivity or stereotypes. When sensitisation occurs, the behavioural changes develop with faster onset, increased magnitude and longer duration (Martres *et al*, 1977; Shuster *et al*, 1977; Segal & Mandell, 1974; Kilbey & Ellinwood, 1977). While behavioural sensitisation and electrophysiological kindling show similar progressive time courses, the mechanisms underlying these two phenomena appear to involve different neurotransmitter pathways (Post *et al*, 1982, 1985). The similarities and differences between kindling and behavioural sensitisation may help us understand the mechanisms underlying the progressive phenomenology of affective illness.

Conditioning appears to play a role in the development of behavioural sensitisation. For example, environmental cues associated with repeated cocaine exposure are important determinants of the degree of response to cocaine (Post *et al*, 1981b; 1985). Hinson and Poulos (1981) also found that the increased behavioural response to cocaine could be desensitized with saline injections. Behavioural sensitisation is modulated by peptide hormones, is more robust in females compared to males, shows cross-sensitisation to stress, and may involve a dopaminergic substrate (Post *et al*, 1984). A dopaminergic mechanism in behavioural sensitisation and its potential cross-sensitisation to stress (Antelman *et al*, 1980; Antelman & Eichler, 1979) suggest a link to the dopaminergic mechanisms in affective illness (Post *et al*, 1978; Jimerson & Post, 1984). The findings of Pickar *et al* (1984) also suggest that our model of drug-induced behavioural sensitisation may be extended to include the development of manic syndromes in man. Depressed patients who became manic during their first course of treatment with a monoamine oxidase inhibitor (MAOI) consistently became manic earlier in the course of a second treatment with an MAOI than on the first occasion. We postulate that a similar sensitisation may occur in non-drug-induced episodes.

Stresses of particular type, intensity, and intermittency may produce sensitisation in a fashion similar to the behavioural sensitisation described above. Sklar & Harris (1985) reported that intermittent or temporary loss, rather than continuous loss of a parent, was associated with greater depressive and other types of psychopathology in subjects who came from large families. Repeated exposure to

inescapable shock has been discussed as a model of stress-induced analgesia, 'learned helplessness', or depression (Anisman, 1984; Seligman, 1975; Drugan *et al*, 1981). The quality, intensity, periodicity, and degree of control, as well as environmental context and conditioning, which are important variables for behavioural sensitisation, also appear important to the behavioural and biochemical consequences of this stress model.

Conditioned biochemical changes

There is a growing belief in the literature that drug-induced and environmental stress-induced changes in brain biochemistry may be conditioned (Deutch *et al*, 1985; Post *et al*, 1984; Schiff *et al*, 1981; Cassens *et al*, 1981; Perez-Cruet, 1976; Anisman & Sklar, 1979; Herman *et al*, 1982). For example, Schiff *et al* (1981) have demonstrated that amphetamine-induced alterations in homovanillic acid (HVA) could be conditioned. They observed that the significant increases in mesolimbic HVA areas following amphetamine could be conditioned to a loud tone that was originally paired with amphetamine administration.

Herman *et al* (1982) have observed conditioned biochemical effects on re-exposure to stimuli previously associated with inescapable shock. Rats given inescapable shock showed increases in plasma corticosterone and brain dihydroxyphenylacetic acid (DOPAC) in frontal cortex, olfactory tubercle, nucleus accumbens, and amygdala. Re-exposure of rats to the environment where they had been previously shocked 24 hours earlier induced elevations in plasma corticosterone and brain DOPAC in the frontal cortex only. Deutch *et al* (1985) reported parallel conditioned changes in DOPAC in prefrontal cortex and in the ventral tegmental (A 10) cell body area. Cassens *et al* (1981) also demonstrated conditioned biochemical responses in a model of learned helplessness. They demonstrated that the 3-methoxy-4-hydroxyphenylglycol (MHPG) increases, which were ordinarily elicited during the learned helplessness induction procedure, could be associated merely with the placement of the animal in that apparatus. In this regard, the selective changes in brain MHPG in animals with and without control of the environmental stress deserve particular comment.

Control over shock and environmental contingencies determines whether 'helplessness' behaviour emerges (Jackson *et al*, 1979) and the direction of the biochemical changes involved. Miller & Weiss (1969) have demonstrated increases in MHPG in the brainstem of animals subject to shock which they could terminate themselves; however, decreases in MHPG, the opposite effect, occurred in the brainstem of yoked-control animals that received, but were unable to terminate, the same shock. Vogel (1983) has recently replicated these findings measuring plasma norepinephrine, rather than brain MHPG. The behavioural effects of undemonstrable shock have also been linked to alpha$_2$ mechanisms in the locus coeruleus (Weiss & Simson, 1984) and to beta-receptor increases in the hippocampus (Henn, 1984).

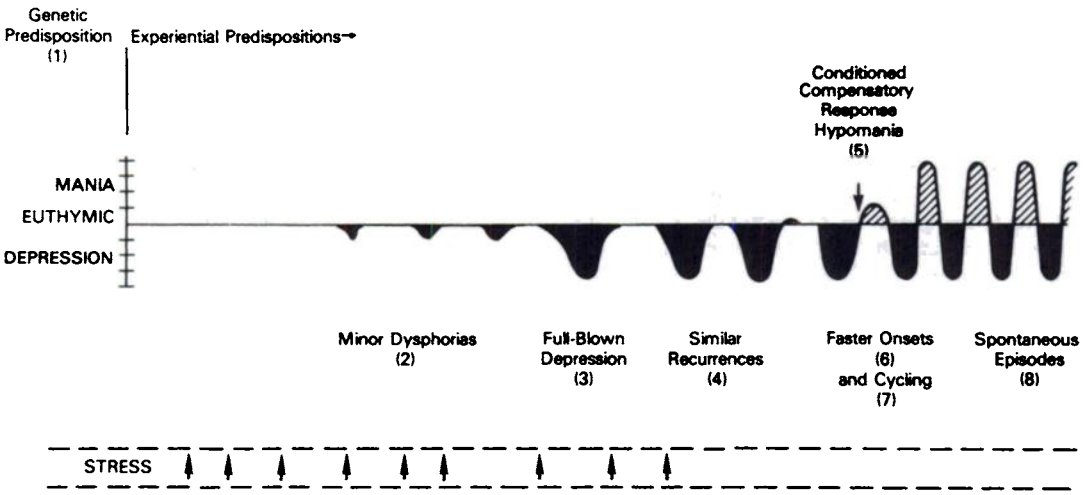


FIG. 1. Schematic illustration of the longitudinal and progressive development of recurrent affective illness.

TABLE I
Parallels in the phenomenology of affective illness to kindling and sensitisation

*Characteristic of affective illness**	*Characteristic of*	
	Kindling	*Sensitisation*
1. Genetic component	+	+
2. Early experience predisposes	+	+
3. Mild alterations emerge as full blown episodes (threshold effects)	+	+
4. Episodes reach plateau and are similar in content and behaviour over repeated recurrences	+	+
5. Repeated episodes of mania or depression may lead to emergence of opposite phase (conditioned compensatory reactions)	±	+
6. Onset of maximum disturbance occurs earlier in episode with repetitions	+	+
7. Vulnerability to recurrences and faster cycling	+	+
8. Early episodes may be precipitated, later appear "spontaneously"	+	
9. Lithium carbonate effective prophylaxis	−	+
10. Carbamazepine effective prophylaxis	±	−

+ = Observed; ± = Equivocal; − = Not observed.
*Numbers 1–8 also refer to those in Fig 1.

Conditioned emotional responses: possible clinical relevance

The possible contributing role of environmental events, psychosocial stress and loss in the precipitation of affective illness has been discussed extensively elsewhere (Paykel, 1979a,b; Dunner & Hall, 1980; Brown *et al*, 1975; Amelas, 1979; Lloyd, 1980). The sensitisation-conditioning suggests that symbolic components of previous triggers of a depressive response might be learned, or conditioned, such that they become capable of eliciting depression in the absence of the unconditioned stimulus; i.e. a 'real' stress or loss.

We are postulating that anticipated stresses or imagined losses, if sufficiently conditioned, may eventually be capable of producing the behavioural, physiological and biochemical alterations usually associated with an affective episode. Should this concept prove to be valid, it might provide a transitional bridge between psychoanalytical concepts of the aetiological role for real or symbolic losses, and biological-endogenous views of depression.

The kindling and sensitisation models for the way in which repetition of early loss experiences might produce overt psychopathology are schematised in Figure 1 and described in Table I. Both biological and social components could occur separately, but our framework also considers how stress- or loss-induced reactions could evolve over time, become increasingly facilitated and autonomous, and eventually show a pattern of spontaneity. Both 'reactive' and 'endogenous' (spontaneous) episodes could occur at different times in the same patient. The model might also be relevant when repeated endogenous or exogenous events, such as repeated episodes of premenstrual dysphoria or drug-induced mania, could lead to a sensitized substrate that might then be triggered more easily by subsequent biological or psychosocial stressors. Thus, the biological and psychosocial approaches might not be mutually exclusive, but potentially interactive. This model is consistent with the data of Paykel (1979a), which show that a clear separation of reactive and endogenous depression is often not possible, even after a careful history of stress and life events.

A testable derivative of our schema would be that more clear identification of psychosocial precipitants would be possible earlier, rather than later, in the course of recurrent affective illness. Support for this concept is found in the observations of Amelas (1979), who noted that a high percentage of first manic episodes were preceded by stress. A corollary proposition would be that symbolic losses might be sufficient to trigger affective episodes later in the course of illness.

Mechanisms inherent in conditioning may also offer a conceptual approach to the emergence of apparently opposite behavioural states of depression and mania following similiar precipitants (Dunner & Hall, 1980; Amelas, 1979; Cohen *et al*, 1954; Aleksandrowicz, 1980). Siegel (1979) has reviewed the evidence that behavioural, physiological and biochemical responses opposite to those initially induced might at times appear during conditioning; i.e. conditioned compensatory responses. For example, he suggested that "subjects with a history of morphine administration display morphine compensatory conditioned responses when confronted with the usual administration procedure, but without the drug". We suggest that opposite mood responses could also develop as conditioned compensatory responses following repeated episodes of affective illness. Analogous to Siegel's formulation, we suggest that subjects with a history of depressive responses may display depression-compensatory responses (i.e. mania) when confronted with cues that would ordinarily elicit a depressive reaction, but when the timing, context, or biological substrate is altered.

Within the psychoanalytic framework, theorists have postulated that manic responses may emerge as a defence against depression (Cohen *et al*, 1954; Aleksandrowicz, 1980; Freud, 1917). Our formulation extends this analytic framework to include the possibility that psychologically- and biologically-triggered compensatory mechanisms may also be involved in this process. Thus, we suggest that the repeated experience of depressive episodes might progressively bring into play biological compensatory mechanisms that not only help terminate the episode, but result in a compensatory manic episode. This process could provide a framework for considering a mechanism by which a large group of apparent unipolar depressed patients experience multiple recurrent depressive episodes prior to the emergence of their first manic episode (Angst & Grof, 1976). In patients with manias at the onset of their illness, compensatory processes might similarly lead to the development of depressive episodes.

One of the primary characteristics of the conditioned response is that, with time, the behavioural response begins to occur earlier in the interval and may even anticipate the conditioned stimulus (Siegel, 1979; Dollard & Miller, 1950). These findings are consistent with the more rapid onset of motor hyperactivity in behavioural sensitisation (Martres *et al*, 1977; Shuster *et al*, 1977; Segal & Mandell, 1974; Kilbey & Ellinwood, 1977) and the observation of the more rapid onset of manic episodes in patients with increased numbers of prior episodes (Post *et al*, 1981a). With sufficient repetition, compensatory responses might move progressively earlier, so that they occurred within, rather than following, an episode. Such a formulation could provide a mechanism for the evolution of dysphoric manias and activated depressions in bipolar patients. If this explanation is well founded, one predicts that these mixed states would tend to occur later in the course of a patient's affective illness after many recurrences.

Bunney (personal communication) has noted an increased incidence of mania in recovered patients in the period immediately before discharge from the hospital. It is interesting to consider that this occurs during a phase of anticipated psychosocial loss, but occurs in the absence of the unconditioned biochemical stimuli (i.e. the associated depressive substrate has been treated) and thus may be sufficient to trigger the compensatory behavioural response of mania rather than depression, just as Siegel (1979) has postulated the triggering of compensatory responses in the absence of the unconditioned stimuli during the opiate response.

The environmental context-dependency of behavioural sensitisation to cocaine and related drugs may provide another explanation for opposite behavioural effects to the same stimulus. Collins *et al* (1979) have shown that cocaine may increase or decrease the response, depending on the associative cues. Similarly, Kopa *et al* (1968) and Belenkov & Shalkovskaya (1980) have shown opposing behavioural responses to the same electrical stimulation of the same brain area (in the thalamus, hypothalamus or amygdala) depending on whether the animal received the stimulation when placed where it had, or had not, previously received a foot shock. Thus, it is possible that similar biochemical changes may be associated with opposing behavioural responses, depending on prior associative contexts and conditional cues.

Similarly, responsivity might be differentially affected by changes in behavioural state following pharmacological manipulations, or the endogenous changes in biochemistry that accompany affective states. Internal biological states can acquire discriminative, or cue, value and become associated with various pathological behaviours. For example, it is possible that an associative link could be established between high levels of circulating glucocorticoids and depressive affect, offering a potential explanation for early morning exacerbation of depression in conjunction with increases in glucocorticoids. The specific relationship between a pathological mood state and a given set of biological variables could thus vary depending on the

association developed through conditioning. Additionally, utilizing the concept of compensatory conditioned responses, one might suggest a mechanism for 48-h cycling. A given phase of a circadian rhythm (e.g. in glucocorticoids, classical or peptide neurotransmitters) might be associated with the switch into depression, while the occurrence of a similar change the next day might evoke the opposing manic response.

These 'theoretical vignettes' are highly condensed and are presented to stimulate discussion about possible biochemical and conditioning mechanisms underlying some clinical phenomana in affective illness. Schou (1982), Dunner and Hall (1980), and Dunner *et al* (1976) have noted that adequate lithium prophylaxis may develop gradually over a period of months in some patients. Schou does not believe this delay in onset is related to pharmacokinetic considerations or the very late onset of biochemical changes, but to psychological processes in the patient and his family. Based on the conditioning principles discussed above, an alternative formulation could be offered. Time may be required to decondition recurrent or cyclic affective disturbances. Only after repeated experiences of psychological or biological changes, which would previously have been associated with an affective episode, but which now occur in the new substrate of lithium-induced biochemical alterations (i.e. in the absence of the unconditioned stimulus), do affective recurrences begin to subside.

Potential implications for pharmacological and psychotherapeutic treatments

The conditioning and sensitisation models described above would appear to have implications not only for possible mechanisms of action of psychotropic

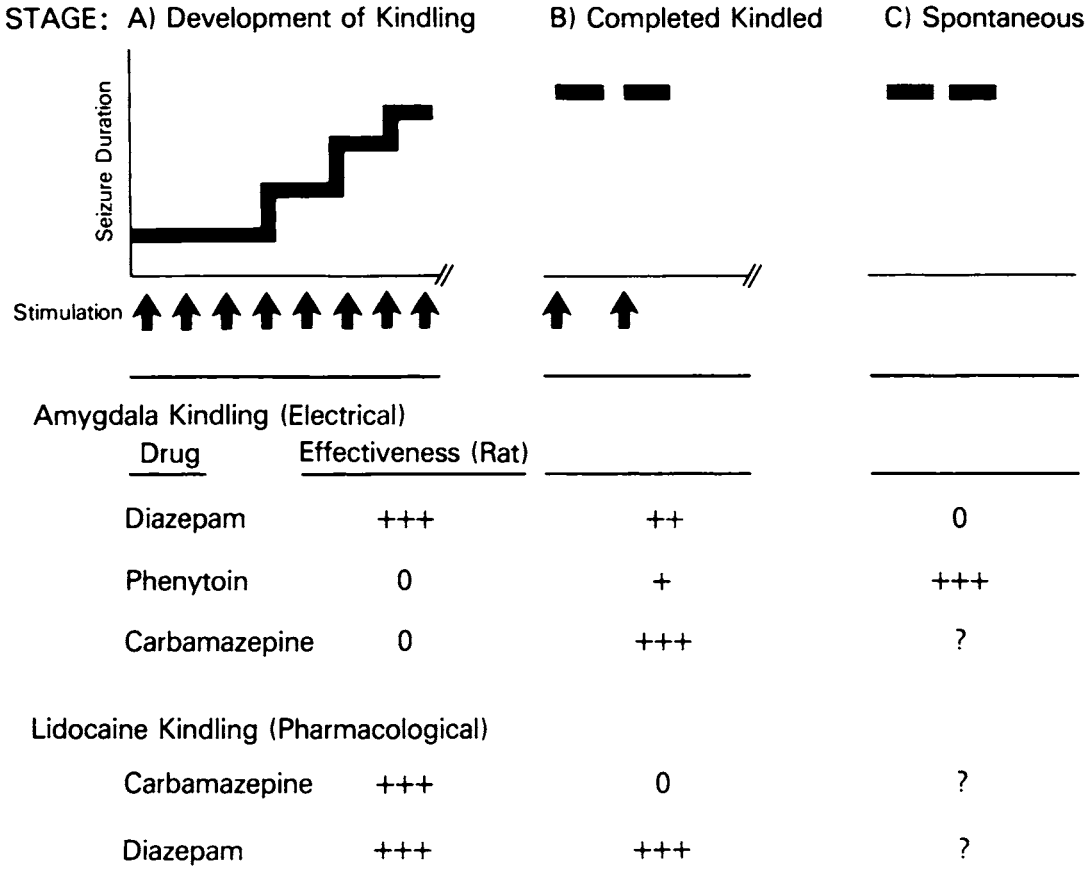
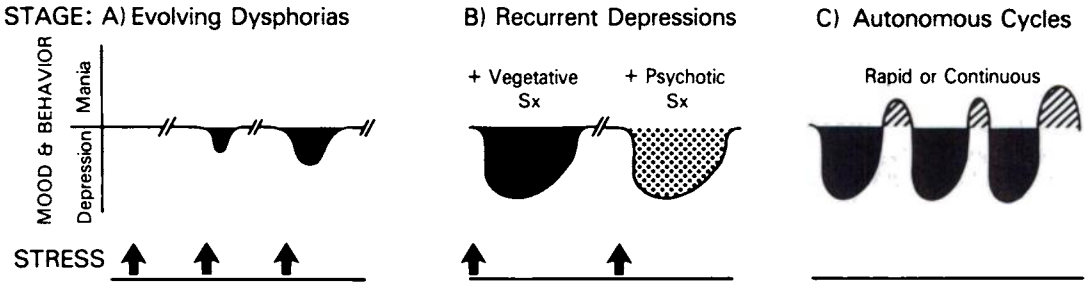


FIG. 2. Pharmacology of kindling as a function of stimulus type and stage of development.



TREATMENT				
Psychotherapy	+++	++		(+)
Benzodiazepines	++	(++)	(+)	
Tricyclics	±	+++	+	– –
MAOI's	±	+++	(+)	– –
ECT		+++	+++	(+)
Tricyclics plus Neuroleptics			+++	
Lithium	±	+	+	(++)
Carbamazepine		(+)	(+)	+++
Lithium plus Carbamazepine				+++

FIG. 3. Hypothetical psychopharmacotherapy of affective illness as a function of type and stage of development.

drugs and psychotherapeutic techniques, but also for suggesting alternative interventions. As reviewed in detail elsewhere (Bunney & Garland, 1984), lithium appears to inhibit a variety of acute and compensatory biochemical and behavioural changes observed following perturbations, particularly of the catecholamine system.

It is possible that other agents, such as carbamazepine, may affect other mechanisms and thus be associated with a different spectrum of clinical efficacy. Carbamazepine appears to be an effective treatment for many lithium-non-responsive, rapidly-cycling patients, both acutely and prophylactically (Post *et al*, 1984, 1985). The kindling and sensitisation models were influential in our initiating clinical trials of this anticonvulsant in affective illness. Carbamazepine inhibits amygdala-kindled seizures (Albright & Burnham, 1980; Wada *et al*, 1976; Babington, 1977), but not cocaine-induced behavioural sensitisation phenomena (Post *et al*, 1984). In contrast, lithium appears to inhibit behavioural sensitisation, but not amygdala kindling.

As summarised in Figure 2, different stages of kindling and different types of kindling are differentially responsive to anticonvulsant treatment. For example, diazepam blocks the development of kindling, is effective in blocking completed seizures, but is ineffective for spontaneous seizures that develop very late in the kindling process (Pinel, 1983). In contrast, phenytoin is largely ineffective in the first phases, but blocks spontaneous seizures. Carbamazepine does not block the development of electrical kindling, but blocks completed amygdala-kindled seizures (Weiss *et al*, 1986a). In contrast, carbamazepine blocks the development of lidocaine-kindled seizures, but fails to inhibit completed lidocaine seizures (Weiss *et al*, 1986b). Thus, different developmental stages of an apparently unitary phenomenon such as kindling are differentially responsive to treatment.

We suggest that a parallel phenomenon might occur in affective illness, where treatment efficacy may vary as a function of course of illness. As depicted in Figure 3, psychotherapy and benzodiazepine may be effective in early stress-related dysphorias, while traditional antidepressants are effective in recurrent depression, but may exacerbate cycling in some bipolar patients. Lithium appears to be less effective in the treatment of rapidly or continuously cycling patients (Kukopulos *et al*, 1980; Prien, 1984), while these factors may be associated with better response to carbamazepine (Post *et al*, 1985, 1986; Kishimoto & Okuma, 1985). While investigators and clinicians would no doubt argue about the precise categorisations in Figure 3, and the validity of their current supporting evidence, we present the figure in order to raise the question of a differential pharmacology based on the course of illness and to stimulate further research. If valid, this concept might also suggest that underlying neurobiological mechanisms differ as a function of course of illness. Finally, the sensitisation and kindling models would predict that sufficiently early and adequate prophylactic treatment of affective illness should retard the development of later stages of the illness, such as more rapid recurrence and continuous cycling.

Dollard and Miller (1950), in their classic work, 'translated' a variety of psychotherapeutic techniques into the language of learning and conditioning. We have tried to emphasise how the sensitisation and conditioning perspectives might provide additional alternative conceptions of the impact of psychosocial stresses and psychotherapy, not only on psychological conditioning, but on biochemistry and physiology as well. Many current psychotherapeutic techniques could be viewed in relationship to providing effective cognitive restructuring (Beck, 1970: 1976), social support (Weissman, 1979), and potential desensitisation (Wolpe, 1973) or extinction of core conflicts and stress-loss precipitated reactions.

In addition, one might conceive of therapeutic strategies more systematically directed at desensitisation of critical cognitive structures, and symbolic representations of loss or stress, which have acquired cue or precipitant potential in relation to affective illness. We have found that longitudinal charting of affective episodes (Squillace *et al*, 1984; Roy-Byrne *et al*, 1985) is useful, not only in accurately describing the course of affective illness, but also in helping to more systematically identify critical psychosocial stresses and areas of sensitivity in a given patient, which appear to be temporally related to repeated episodes of affective illness. Work in psychotherapy might also include the construction of a hierarchy of events and ideas that are particularly prone to evoke dysphoric feelings, affects, and the depressive syndrome. These might provide the focus for psychotherapeutic working through and systematic desensitisation. Particularly in patients who have achieved a relatively high state of conditioned emotional reactivity or stress sensitisation, more formal deconditioning techniques might be explored as adjunctive procedures to psychotherapy and pharmacotherapy.

A further utility of the sensitisation-conditioning model might be in the better understanding by the patient of the possible role of both psychological and biological processes in the evolution and/or treatment of his or her illness. With the increasing potential for polarisation of theory and therapy into either biological or psychosocial schools, the patient may be at a loss to understand how psychotherapy and psychosocial influences may be related to the growing evidence for biochemical abnormalities and responses to drug treatment in affective illness. The current exposition highlights the possibility that both psychological and biochemical responses can be associated with conditioning processes, which are themselves amenable to both psychological and pharmacological intervention. This frame of reference adds the longitudinal perspective to the multifactorial considerations of Akiskal and McKinney (1975) and others (Meyersburg & Post, 1979) who have emphasised biological and psychosocial interplay in the development of affective symptomatology.

The kinding and sensitisation paradigms may help focus theoretical and practical clinical attention on the longitudinal course of behavioural and biological change in affective illness, in contrast to the more frequently considered acute characteristics and treatment. We suggest these models not as accurate homologies for the depressive and manic-depressive illness, but as potentially useful constructs in the consideration of a variety of normal and pathological adaptive processes (both tolerance and sensitisation) which may occur upon the repeated presentation of physiological, biochemical or psychosocial stresses.

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