THE PSYCHOPHYSIOLOGICAL ASPECTS OF ANXIETY

AND DEPRESSION

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This thesis describes six experiments which were designed to investigate the nature of the problems of anxiety and depression using psychophysiological measures.

The first three experiments (Chapters 5, 6 and 7) are concerned with abnormal skin conductance in depression. Indices of electrodermal activity and thyroid function were both assessed in 72 untreated patients with primary depression and 53 normal controls in order to identify clinical picture present in abnormal skin conductance. Sixty-eight percent of the subjects were identified as having abnormal skin conductance. Forty-seven percent of those patients classified as neurotic on the Newcastle scale were also found to be neurotic in terms of their electrodermal activity. Consistent correlations were found between the skin conductance and thyroid function suggesting that abnormalities of thyroid activity may be responsible for skin conductance abnormalities observed in depressed patients.

Mood changes of anxious, depressed and non-psychiatric subjects were measured over a period of 4 weeks (Chapter 8). By this means it was hoped to ascertain whether anxiety and depression were separate psychological processes or part of the same psychological process. It was found that overall mood did not differ significantly between groups. Patterns of mood change over time were investigated and strikingly similar patterns emerged for anxious and depressed moods.
A group of chronic anxious patients recently withdrawn from benzodiazepines were given test doses of diazepam (5mg) and placebo (Chapter 9). They were compared with a control group who had never been chronic benzodiazepine users, using a battery of physiological and psychological tests sensitive to benzodiazepine effects in order to establish the dependence-inducing properties of these drugs. The persistence of withdrawal symptoms to diazepam's effects on self-rated symptom scales was demonstrated unequivocally.

The final results presented (Chapter 10) are from the psychophysiological responses in the patients whose results were presented in Chapter 9 in comparison with hysterical and anxious patients, and normal subjects. In this way, it was hoped to ascertain whether the symptoms which have resulted from benzodiazepine withdrawal in the patients withdrawn following long-term benzodiazepines treatment were a form of conversion reaction or anxiety. Although these patients showed little anxiety and physiological arousal in comparison with anxious patients, the results of psychological questionnaires largely supported the view that these patients have a very similar pattern of reactions to other patients with conversion symptoms.
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THE VALUE OF PSYCHOPHYSIOLOGICAL TECHNIQUES:

General considerations and some psychophysiological concepts

INTRODUCTION

Darrow (1964) defined psychophysiology as 'the science which concerns those physiological activities which underlie or relate to psychic function' (p.4). This is undoubtedly a very wide definition as it could be construed to refer to an extremely comprehensive range of central nervous system functions. Others, for example Sternbach (1966), have been more concerned with the type of experimental approach which the psychophysiological favours - the use of a polygraph, simultaneous recordings of several physiological functions, the concentration on autonomic measures, etc. There seems general agreement that psychophysiology concerns itself with experiments in humans.

Psychophysiology deals with the measurement of physiological responses attendant on psychological changes and conditions, that is, the subject's feelings, beliefs, expectations, knowledge, and prior
experience, and the effects these have on the response to manipulations of the external environment. The emphasis is generally on non-invasive monitoring techniques, and hence on peripheral response systems. Response systems monitored have included cardiovascular, electrodermal, respiratory, gastrointestinal, the skeletal musculature, ocular, and electroencephalographic (both rhythmic and evoked responses), among others.

Phasic changes and tonic levels in these systems may be indicative of reflexive, attentional, or adaptive responses, transient emotional responses, individual personality characteristics, and persistent effects such as physiological or psychophysiological disorders. The methods of psychophysiology thus find current application in diverse areas. The affects (emotions, feelings) have been a favourite topic for psychophysiological research because of the marked, widespread physiological changes which occur. Anxiety, in particular, has been extensively studied for a variety of reasons. The relationship between the physiological changes and the perceived feelings has been a source of controversy but has acted as a spur to much fruitful research. Many psychiatric conditions are either primary disorders of affect, for example depression and anxiety, or disturbances of affect are very obvious, for example in schizophrenia. It is therefore not surprising that psychophysiological techniques have been applied to these problems.

This first chapter introduces the basic measures used in monitoring electrically recordable aspects of psychophysiological response systems and some conceptual concerns underlying their
application. I address myself principally to the settings and procedures under which the responses of interest are commonly monitored and the general theoretical considerations relating to those procedures. Individual differences affecting reactivity in these response measures will also be discussed. More specific measures relating to anxiety and depression are discussed in Chapter 3.

Fundamental Response Variables

Measures of "State" and Arousal

In general, autonomic activity reflects the state of the organism. "State" generally refers to the level of arousal or alertness of the organism. Such levels range from sleep to wakefulness to being hypervigilant or excited. Psychophysiologists concerned with level of "alertness" during sleep have identified different levels of sleep depth, based on electroencephalographic as well as behavioural measures. Higher levels of arousal or emotion generally correspond to higher tonic levels and more frequent phasic responses in psychophysiological systems. Tonic level shifts refer to relatively slow changes in baseline level of a response system. In most systems, these are changes which persist for 15-30 seconds or more. Phasic responses are changes of shorter duration. They commonly last from a fraction of a second to 15 seconds and are followed by a return to the prior basal level. The direction, duration, and nature of the changes seen depend on both the nature of the state change and the particular response system under examination.
The effects of arousal on psychophysiological measures are best illustrated by its inverse, that is relaxation. When a normal subject is first brought to the laboratory in order to monitor his/her response, arousal levels are relatively high. If the patient is asked merely to sit still in a comfortable chair and relax, the arousal level will decrease. This relaxation is accompanied by appropriate autonomic changes.

In the electrodermal system, reduced arousal is indicated by decreased conductance (increased resistance) level and a reduced incidence of phasic responses triggered by either environmental stimuli or internal responses such as thoughts and sensations. Electroencephalographic (EEG) measures show changes in the pattern of activity as a function of arousal changes. Higher arousal levels are accompanied by predominantly higher frequency, low voltage EEG activity. As individual's level of arousal is lowered, this pattern is replaced by slower, higher amplitude-patterned activity (Martin and Venables, 1980). In a relaxed, awake individual this pattern shows a dominant frequency in the range from 8-13 Hz (the alpha frequency band). The incidence of alpha activity varies greatly across individuals. Within individuals, however, the incidence usually increases as relaxation progresses. Alpha is commonly facilitated if subjects are requested to relax with their eyes closed, rather than open (Lader, 1975).
Emotion

Changes occur in a variety of physiological functions during the experiencing of emotional states. Such states are, however, neither necessary nor sufficient for either the subjective experience of emotion or the behavioural concomitants of emotion. In animals, surgical elimination of autonomic responses failed to impair appropriate emotional behaviours (Cannon, 1927). Similarly, clinical observation of a human patient (Dana, 1921) indicates no disruption of reports of subjective emotional experience following (accidental) transection of the spinal cord at the neck. However, in a classical study, Schacter and Singer (1962) failed to show emotional responses following adrenaline injections in the absence of environmental stimuli appropriate for the elicitation of emotion, or when subjects were informed of the physiological effects of the drug. Together, these two lines of evidence indicate that emotional behaviour and experience (1) can occur in the absence of autonomic or visceral activity and feedback, and (2) may fail to occur even when autonomic activity appropriate to emotional response is present.

The argument presented above should not be taken to imply that autonomic activity does not provide feedback to temper the experience of emotion nor that emotional response is not accompanied by psychophysiological changes. Indeed, it is the interaction of autonomic with behavioural and cognitive events which provises the full flavour of emotional experience. Schacter and Singer (1962), for example, found that if eliciting situational and social contexts were provided, subjects who had received injections of adrenaline displayed
emotional behaviour. Subjects who had not been injected did not show the emotional response in the same settings. The nature of the emotional response (anger or euphoria) was appropriate to the staged context and dependent on ignorance concerning the physiological effects of the injection. Only the blending of social-cognitive factors produced emotional behaviour and experience. It is particularly important to note that the same injection of an adrenergic substance, which produced the same pattern of autonomic and visceral activity, contributed to two very different emotional experiences. This suggests that a single pattern of psychophysiological activity is common across the spectrum of emotional behaviours. This pattern is essentially one of arousal (see above).

Although the pattern of activity is similar across a variety of emotions, this does not preclude the possibility of specific activity unique to a particular emotion or set of emotions. Cannon (1927) suggested the possibility of two distinct patterns of autonomic discharge present in different emotional states. One pattern corresponds to somewhat greater activity in the sympathetic than in the parasympathetic portion of the autonomic system. The other pattern corresponds to the reverse situation. Subsequent investigators (Arnold, 1950; Ax, 1960) have explored the patterns of psychophysiological response accompanying emotional response to particular situations. Arnold (1950) reports patterns of activity which suggest that parasympathetic system reacts more strongly during the experiencing of anger as compared to fear. Ax (1960) reports patterns indicative of an adrenaline-like reaction to situations
designed to provoke fear. The pattern subsequent to situations provoking anger indicated a combined adrenaline, noradrenaline-like reaction.

Research into the patterning of autonomic activity is problematical because of large differences between subjects and between measures both between and within subjects. In Ax's study, for example, each of the seven physiological measures that best discriminated between fear and anger was more highly correlated with that same measure in the other condition than with any of the other measures in same condition. In other words, the measure (skin conductance, heart rate, blood pressure, etc.) which showed the greatest change for anger in a particular subject, also showed the greatest change for fear. The patterns of activity were more specific to the individual than to the emotion. Even a sophisticated composite of such measures is likely to be useful indicator of emotional state only if there is considerable prior knowledge of the individual's typical manner of response (Lader, 1983; Meyer et al., 1988).

The importance of autonomic outflow and afferent return on subjective experience of the intensity and perceived "reality" of emotion has been examined by Hohmann (1966). Structured interviews were conducted with 25 adult males with more-or-less complete spinal cord lesion. These patients reported decreases in sexual feelings, fear, and anger from their experienced pre-trauma feelings. Many reported that they often behaved emotionally either because the situation called for such behaviour or because it was expected of them. Their corresponding experiences, however, were primarily
cognitive and seemed to them lacking in subjective reality as emotional experiences. The generality (across emotions) and severity of the deficit corresponded to the level of the lesion; the higher the lesion, the greater the effect. One emotion, sentiment, increased in frequency and intensity among these subjects. Although the physiological components of particular emotions cannot be specified, the Hohmann data indicate that autonomic afferents are essential contributors to the totality of emotional experience.

Lacey and Lacey (1970) have presented a somewhat different conceptualisation of autonomic activity in emotion. According to their interpretations, the pattern of activity varies depending on whether the attention of the individual is internally or externally focused. On task requiring reception of external events, heart rate slows. In situations where a noxious stimulus is presented and in situations involving a cognitive task requiring internal elaboration, heart rate increases. Tasks involving both the perception of external events and cognitive manipulation of those events produce intermediate results. During the preparatory period of a reaction time task, while the subject is awaiting the cue to respond, the heart rate decelerates. The response to the cue, however, is normally acceleratory. EEG recordings made in the same situation show concordant changes in the negativity of the vertex-to-mastoid DC potential. The heart rate deceleration during the preparatory period is accompanied by an increasing negativity of the EEG recording. In the same reaction time task, electrodermal activity is indicative of generalized arousal. This work shows promise for the use of central and autonomic measures in the study of emotion when emotion can be categorized on a
dimension of internal-external focus of attention (Coles et al., 1988; Coles, 1989).

Drug Effects

Drug used in medical practice as well as drugs ingested without prescription (such as tobacco and alcohol) exert significant effects on both basal and reactive measures (Knotts and Venables, 1977; Petursson and Lader, 1984; Higgitt et al., 1985). Some drugs have specific effects on a large group of physiological response systems. Atropine, for example, produced pupillary dilation, in low doses cardiac deceleration, in large doses cardiac acceleration, inhibition of sweat gland activity, and an increase in body temperature (Goodman and Gilman, 1941 in Walrath and Stern, 1980). Other drugs, such as vitamins, have more restricted or not measurable effects. The effects of drugs are generally complex. The effects of acute versus chronic intake of some drugs markedly different effects. As will be discussed later (Chapter 4), tolerance effects to some drugs have been described as well as antagonistic effects associated with ingesting more than one drug.

Since psychoactive drugs are helpful to some but not all patients with a specific psychiatric diagnosis, considerable effort has been expended in using psychophysiological responses to the acute effects of such drugs to predict clinical effectiveness of the drug with that patient. For example, in the area of EEG research, many studies have conducted attempting to evaluate the effectiveness of drugs in the
treatment of specific psychiatric disturbances (e.g. Saletu et al., 1971; Bond et al., 1984; Vansweden, 1984). Others have used a wider armamentarium of psychophysiological measures to make similar predictions. Setterfield et al. (1973) do so in studies of drug effectiveness in the treatment of the hyperactive child. The results of such studies have been, at best, provocative. They certainly do not generate optimism about their immediate applicability.

Response to Stimulation

The psychophysiological response to stimulation consists of an integrated pattern of primarily phasic responding. The exact nature of the response depends on the nature and intensity of the stimulus, how the stimulus is perceived, and prior experience that the subject may have had with that particular stimulus. Specific components of the total response vary widely among individuals, but the overall pattern is relatively consistent.

Orienting Response

When a novel or unexpected stimulus occurs, we orient toward that stimulus. The orienting response is a kind of "what is it" response which may include spatial orientation such as head movements and a shift in direction of gaze, seemingly directed toward the source of stimulation. The orienting responses can be readily observed in most physiological response systems regardless of whether or not the overt motor components of the response are present. The form of the phasic
response within each system is highly consistent: 1) electrodermal activity - increases in skin conductance initiated 1 to 5 sec following stimulus onset, 2) heart rate - cardiac deceleration during the first few beats following stimulus presentation, 3) cardiovasculature - peripheral vasoconstriction and central vasodilation, 4) ocular - pupil dilation and large lateral saccadic eye movements, 5) ENG - bursts of muscle activity, and 6) EEG - event-related potentials (the evoked response) and a desynchronization of alpha activity, if it was present (this is sometimes referred to as "alpha blocking"). The orienting response is tightly time-locked to stimulus change. For example, the electrodermal component of the orienting response is generally defined as a phasic increase in conductance occurring between 1 and 5 sec following the stimulus. Dimberg et al. (1986) pointed out that "true" orienting responses occur within an interval from 0.25 sec before to 0.50 sec following that subject's median orienting response latency for stimuli of a given type. The orienting response is most readily observed at stimulus onset. Under appropriate conditions, however, it is also observed at stimulus termination (Stern and Walrath, 1977).

One characteristic of an orienting response, then, is that it is a generalized response in the sense that it is a whole-body response involving the total organism in patterned activity. A second is that it is not specific to the nature of the eliciting stimulus. A third attribute is that it demonstrates habituation. That is, the various components of the orienting response decrease in amplitude or in likelihood of occurrence on successive presentations of the same stimulus.
Habituation

We would be in a continual state of arousal, unable to maintain attention if we could not inhibit our responses to the thousands of stimuli which perpetually impinge upon us. The capacity of the organism to block response to unimportant stimulation is essential to its survival. Fortunately, we are equipped with a central nervous system processor which provides for elimination of responses to irrelevant and repeated stimulation. The response to a repeated stimulus decreases across successive presentations. The generalized response, elicited by the initial presentation, becomes more circumscribed with respect to the specific nature and location of the stimulus within the first few trials. With continuing presentations, physiologically measurable responses to many kinds of stimulation disappear completely. The reduction, and eventual cessation, of response to repeated stimuli is called habituation.

The importance of habituation for survival is beginning to be recognized by medical practitioners. In the construction of a clinically useful scale of infant development, for example, Brazelton (1983) includes several habituation series, as well as orienting response evaluation. The ability of the infant to habituate to auditory, visual, and tactual stimuli is thought to reflect its ability to protect itself from excess stimulation. The rate of habituation is a measure of cortical control and responsiveness and of the capacity to manage the demands of postnatal adjustment. Scores on the habituation items in the scale are used as predictors of central nervous system organization. The efficacy of these predictors, at
least for the initial months of life, appears to be well demonstrated (Brazelton et al., 1985).

Habituation, as the most basic form of behavioural plasticity, plays an important role in the adaptation of an organism to its environment. In addition, the process is important in relationship with other mechanisms of response modification. Habituation is thought to illustrate, along with sensitization, the most elementary form of learning (Razran, 1971). It has been postulated that habituation, together with classical conditioning, provides the motivational and associational basis for all learned behaviour (Mowrer, 1960). It has been suggested that habituation is intimately implicated in the mechanics and abilities involved in attending to the environment (Konorski, 1967; Lader, 1980, 1983). At the very least, habituation is an illustrative prototype of the learning process, and perhaps a basic building block for all response plasticity. A thorough understanding of habituation is therefore doubly important both in its own right and for the understanding of more complex phenomena.

**Individual Variation in Psychophysiological Responses**

Even within a relatively homogeneous population there may be large variations in patterns of psychophysiological activity. Within a sample of young, male, college students, for example, some will show marked electrodermal responses to a loud tone, while others show no electrodermal responses. Among those who do respond, the number of trials required for the habituation of the response varies from 2 to
over 20 (Martin and Venables, 1980). Some of those subjects who give no electrodermal response (as well as some of those who do) make distinct vasoconstrictive responses to the tone. Others do not.

The sources of much of this individual variation are yet to be documented (although they must be, at least potentially, available for discovery). Other sources have been explored in greater or lesser detail. Characteristics which have been shown to influence, or be reflected by, psychophysiological response include sex, age, race, cognitive style, personality structure, laterality effects, and of most important for this thesis — psychopathology. A major point which must be made is that known sources of response variation must be taken into consideration in the evaluation or treatment of individual case.
INTRODUCTION

Anxiety and depression are terms used to describe negative affect ranging from normal to morbid. That is, anxiety and depression can both be conceptualised as normal mood states, as symptoms of morbidity, as syndromes and as diagnostic entities (Lipman, 1982). The distinction between normal and morbid is made on the basis of intensity and duration of the affect and on the number of symptoms clustered together.

While there has been a longstanding distinction drawn between the concepts of anxiety and depression, it is the intent of this chapter to explore whether these two constructs can be meaningfully separated. Both conceptual and empirical arguments will be advanced. Conceptual distinctions that have been drawn between the constructs of anxiety and depression will also be reviewed. Finally, the evidence from emotional models of affect, psychophysiological evidence related to the separation of anxiety and depression, and data on the clinical diagnosis of anxiety and depressive states will be reviewed.
ANXIETY

Anxiety has been variously defined, but in general it seems to be considered an affective, physiological, cognitive, and behavioural state (Beck et al., 1974; Spielberger, 1975). Tyrer (1982) defines clinical anxiety as a group of psychiatric disorders in which the primary symptoms are twofold:

"Psychic symptoms of dread and awareness of threat in the absence of a known danger and independent of external situation and bodily symptoms (somatic and autonomic) occasioned by increased sympathetic arousal and including muscular, cardio-respiratory and gastrointestinal components" (p.59). He points out that although psychic and somatic symptoms are always present, their relative emphasis may vary greatly from patient to patient.

Characteristically, the anxious patient builds up anticipatory fear, that he/she will not be able to cope with or control his/her racing autonomic sensations. This anticipatory fear helps to create an upward spiral of anxiety, which increases the likelihood of actually having an anxiety attack and frequently leads to a "fear of anxiety" which acts independently of the initial anxiety (Stampler, 1982). Typically, the anxious patient copes with his/her feelings by avoiding the anxiety-provoking stimulus.

Feighner et al.'s (1972) diagnostic criteria take account of recurrent anxiety attacks, somatic and autonomic symptoms, and
feelings of apprehension, fearfulness, or sense of impending doom. Hamilton (1983) pointed out that in clinical practice it is not only anxious mood (e.g. feelings of tension, autonomic symptoms such as sweating, flushing, dryness of mouth) but also the presence of features of depressed mood (e.g. difficulty in concentrating, inability to relax, insomnia) that lead to a diagnosis of anxiety neurosis.

These diagnostic criteria indicate that somatic symptoms form an integral part of the anxiety syndrome. In fact, anxiety is one of the few psychiatric conditions in which there are consistent physiological changes. Many of the somatic symptoms expressed by anxious patients are a consequence of heightened sympathetic arousal, such as increased forearm bloodflow, increased pulse rate, sweating, muscle tension and tremor.

The literature on anxiety has made a notable distinction between the trait of anxiety (i.e. the tendency to become anxious, although not necessarily to be anxious at any particular moment), and state anxiety (i.e. to be experiencing anxiety) (Spielberger, 1972; Endler and Magnusson, 1976). Evidence for the empirical integrity of the state-trait model of anxiety is widely available (see Spielberger, 1975 for a review), and there have been a number of attempts to define more situationally-specific predispositions for anxiety. This latter person-situation interaction model for anxiety (Magnusson and Endler, 1977) has led to the development of situationally-related measures of trait anxiety and an increase in the ability to make differential predictions of anxiety in different situations (Magnusson
Epidemiological evidence suggests wide cross-cultural variability in the prevalence of anxiety neuroses. Carey et al. (1980) provided estimated prevalence rates that ranged from 0.6 per 1000 (Bille and Juel-Nielsen, 1968) to 39.2 per 1000 (Brunetti, 1976). Based on the work of Carey et al. (1980), there appear to be consistent sex differences in the prevalence of anxiety neuroses, with the average prevalence rate for women being 2.17 times that for men.

DEPRESSION

In contrast to anxiety, unipolar depression has been defined as a multifaceted state (Craighead, 1980) that eventuate from a perception of an important loss or threat of such a loss (Beck, 1976; Costello, 1980). For example, depression can be triggered by the loss of a spouse through divorce, or the perception that such a loss is imminent. The state itself has emotional, cognitive, and physiological components as does anxiety, but the general nature of the components of depression involves avoidance, withdrawal, and diminished activity. With regard to the distinction between trait and state depression, some conceptual and empirical work has been accomplished (Zuckerman and Lubin, 1965; Costello and Comrey, 1967), but the thrust of research has been on the nature and effect of the experience of the state depression (Dobson, 1985). This work has been spurred by the question of the distinction between "normal" state depression (in
which the individual shows elevated signs of a depressive type) and "clinical" state depression, which consists of a diagnosable syndrome of symptoms (Snaith, 1987).

Clinical depression has been widely researched, and a comprehensive review of the literature is not possible here (see Doefler, 1981; Snaith, 1987). It is important, however, to note that there are a number of categories of affective disorders according to the DSM-III-R (American Psychiatric Association, 1987). Included in DSM-III-R's diagnostic scheme are major affective disorders (manic episode and major depressive episode), bipolar disorder, major depression, specific affective disorders (cyclothymic disorder, depressive neuroses) and atypical depression. Feighner et al.'s (1972) criteria are based on the presence of dysphoric mood and certain accessory symptoms (e.g. anorexia, insomnia, retardation and guilt). The Research Diagnostic Criteria (Spitzer et al., 1978) adopted the same rules. Generally, research in clinical depression is aimed at the major depressive episode (also the major depressive disorder) group. Estimates of the prevalence of depression (Carey et al., 1980) range from 0.43 per 1000 (Lemkau et al., 1942) to 117.6 per 1000 (Brown et al., 1977). The average female: male prevalence rate is 2.28:1 based on the data of Carey et al. (1980).

Only recently have some trait predictors of clinical depression begun to be developed (e.g. Dobson and Breiter, 1983; Dobson and Shaw, 1985), and some of the most promising appear to be physiological in nature (Carroll et al., 1981).
ANXIETY AND DEPRESSION

Conceptually, there are both similarities and differences between the constructs of anxiety and depression (Costello, 1976). In this section, the evidence from emotional models of affect, psychophysiological evidence related to the separation of anxiety and depression, and the data on clinical diagnosis of anxiety and depressive states will be reviewed. The section will encompass increasingly narrow definitions of anxiety and depression, from emotions to traits to clinical syndromes.

Anxiety and Depression as Combinations of Fundamental Emotions

Theories of emotion vary in their description of anxiety and depression, but generally suggest that anxiety and depression are general emotions comprised of combinations of more fundamental emotions (Izard, 1977; Klerman, 1977; Plutchik, 1980; Dobson, 1985). Izard (1977) suggests that anxiety and depression are higher order emotional states in the sense that they represent complex combinations of primary emotions. Simply stated, the major component of clinical anxiety is the fundamental emotion of fear, whereas the major component of depression is the fundamental emotion of sadness. However, anxiety is more than just fear, since according to Izard it includes degrees of interest (alertness) and distress (sadness). Conversely, depression is more than just sadness, according to Izard, it includes degrees of anger and disgust. To test this basic theory,
Izard developed the Differential Emotion Scale, a self-report adjective checklist containing items presumably reflecting fundamental emotions. For example, words loading high on Izard's distress dimension were "sad", "lonely", "upset", "distressed" and "emotional"; while words loading high on the fear dimension were "afraid", "scared", "fearful", "jittery", and "anxious". This instrument was administered to a number of normal and patient subject groups and support for Izard's hypotheses about anxiety and depression was obtained. However, thus far these conclusions rely primarily on evidence of self-report from subjects of their perception of inner mood.

The concept stresses the importance of considering mood, psychophysiological and behavioural component systems not simply as correlates, but as functionally interactive. Thus, the specification of fundamental emotions stimulates clustering observational, self-report and physiological data. In combination, patterns of fundamental emotions do not necessarily occur one at a time; on the contrary, they can and do occur in various combinations depending on both situational and biological factors.

In contrast to Izard's perspective that emotions can be uniquely defined and then examined for their inter-relationship, other theorists and researchers have attempted to determine high-order emotional dimensions that might order or pattern more basic affective experiences. For example, Russell (1980) presented evidence that 28 emotion adjectives could be ordered in circular array that was defined by the two dimensions of pleasure-displeasure and degree-of-arousal.
Within his model of affect, the adjectives "depressed", "sad", "tense", "distressed", and "afraid" were located on the extreme displeasure side of the pleasure-displeasure dimension. The adjectives "depressed" and "sad" were different from the other adjectives, however, in that they were placed towards the "sleepy" end of the degree-of-arousal dimension, while the anxiety-related adjectives were placed towards the "aroused" end of the degree-of-arousal dimension. Russell's work, therefore suggests that while the emotions of anxiety and depression are comparable in terms of their degree of unpleasantness, anxiety states reflect a more aroused condition than depression.

Individuals vary in the extent to which they present all of the symptoms indicative of a given fundamental emotion. Intensity of the affective state may be such a variable. For example, in mild depression the primary symptoms may be cognitive and possibly motor, whereas in severe depression all the symptoms might be present, including marked attenuation of the visceral components associated with pleasure. Similarly, mild anxiety may be evident in cognitive and motor signs, whereas in extreme anxiety all the symptoms could be present, including marked increases in sympathetic arousal. Other factors such as frequency and duration of the affective state, individual stereotype (Lacey and Lacey, 1958), different modes of coping, and even response set (for example, depressed patients may see themselves as extremely anxious, whereas in fact they are autonomically and somatically only mildly fearful; Kelly and Walter, 1969) can influence the final pattern of symptoms that are expressed for an individual.
Psychophysiological Differentiation of Emotions

It has long been a commonsense observation that emotional states are paralleled by changes in organs which are innervated by the autonomic nervous system. Thus, we speak, for example, of our hearts pounding with fear or our faces being red with anger. The belief that there are underlying physiological changes which accompany subjective states and which can be measured has generated a large body of research attempting to assess this relationship.

Until the middle of this century, however, there was little compelling experimental evidence for differential physiological activity during specific emotional states, although several theories had been developed based on this view (James, 1884; Schacter and Singer, 1962; Valins, 1970; Mandler, 1975). This lack of evidence stems, in large part, from Cannon's (1927) influential criticism of the James-Lange theory of emotion and from Selye's (1956) work. From the writings of Cannon and of Selye it was an easy progression to the more inclusive view that these physiological measures are indicators of the general "activation" or "arousal level" of the individual (Lindsley, 1950; Malmo, 1957, 1966). Much of the recent research done has been based on the work of these early activation theorists.

The concept of physiological arousal has played an important role in many theories of emotion. Broadly speaking, peripheral physiological arousal is taken to be the effect of autonomic nervous system activity; its non-specific and diffuse nature has been inferred from the fact that stimulus material with different emotional effects
tends to produce similar peripheral changes (Levi, 1975). The concept of a diffuse arousal state continues to be useful despite definite constraints on its validity. These are, for example, the demonstration of individual differences in characteristic patterns of arousal (Lacey and Lacey, 1958) and stimulus-response specificity.

The attention given to arousal probably stems from the way that the James-Lange hypothesis, which concerns the source of emotional experience, has been understood. James (1884) and Lange (1885) reversed the traditional assumption that ideas cause feelings and suggested the opposite view that emotional feeling is the result of perceiving one's own bodily reactions. The self-perception of bodily activity has remained an important element in later developments of the James-Lange position, but the idea that reports of emotions are correlated with distinct patterns of physiological arousal has not been supported empirically. In the theories of Schacter and Singer (1962) and Mandler (1975), physiological arousal is treated as a necessary but not sufficient condition for emotion to be reported. These theorists conceive of arousal as being a diffuse generalised state varying only in intensity.

The clue that factors in addition to arousal are necessary came from early investigations of the effects of injecting adrenaline into human subjects (e.g. Maranon, 1924). After receiving the injection, subjects variously reported palpitations, motor tremor and feeling hot, flushed and sweaty. The experience was not usually described as an emotional one, but some subjects reported that they felt as if they were in a state of emotion. However, some subjects who were
engaged in conversation about unresolved problems at the time of the injection, did not report real emotions.

Diagnostic Symptoms

Clinical research on the relationship between anxiety and depressive syndromes has long been controversial, with research perspectives varying from those aimed at documenting separate anxiety and depression syndromes (Downing and Rickels, 1974; Prussof and Klerman, 1974), a unitary model of anxiety and depression (Johnstone et al., 1980), secondary depression in anxiety disorders (Clancy et al., 1978; Cloninger et al., 1981; Dealy et al., 1981) and anxiety disorders secondary to depressive disorders (Fawcett and Kravitz, 1983; Leckman et al., 1983).

A common combination is that of anxiety with non-psychotic depressive symptoms, and there has been much controversy over its diagnostic validity. Under present rules of classification mixed anxiety-depressive states cannot occur and are all subsumed under depressive disorders. Although the symptoms of anxiety and depression can successfully be separated by appropriate statistical tests (Roth and Mountjoy, 1982), patients themselves cannot be separated quite so easily. Prusoff and Klerman (1974) found that patients with anxiety and depressive neuroses could be separated but although those defined as anxiety had typical anxiety symptoms, the depressive group included many with mixed anxiety and depressive symptoms and 35% could not be allocated satisfactorily. Further support for the existence of mixed
anxiety-depressive states has come from studying life events in anxious and depressive disorders. When life events are separated into those of danger and loss anxiety states are more often preceded by an excess of danger, patients with depressive neurosis experience events of loss, and a mixed anxiety-depressive group experience both severe danger and loss (Finlay-Jones and Brown, 1981).

Response to treatment might appear to be a suitable way of either validating the existence of mixed anxiety-depressive states, or supporting their separation into anxiety and depressive disorders. The data from studies do not permit any definite conclusion but in general they suggest that there are more similarities than differences between the two disorders (e.g. Hollister et al., 1967; Henry et al., 1970). Johnstone et al. (1980) found no significant drug effect which could differentiate patients on the basis of either clinical or self-rating of anxiety and depression: amitriptyline proved to be superior to diazepam in the treatment of both anxious and depressed patients.

The usefulness of the concept of mixed anxiety-depression has been investigated for those neurotic outpatients who receive treatment for some mixture of anxious and depressive symptomatology. Paykel (1972) provided evidence that anxious depressives needed to be distinguished from other subtypes of neurotic depressives. He showed that they did not respond to antidepressant medication as did other groups of depressives. However, the concept of mixed anxiety-depression as a working diagnosis has not proved to be useful (Downing and Rickels, 1974). It increased the heterogeneity of the diagnostic concept not only in terms of severity and chronicity of
the condition, but also in terms of the configuration of symptoms they display. The DSM-III ignores the uncertain areas of overlap between anxiety neurosis and neurotic depression, and it is therefore of little use to the clinician when it comes to differential diagnoses between these two conditions (Tyrer, 1984).

In a series of studies (the so called Newcastle Studies), Roth et al. (1972), Gurney et al. (1972) and Kerr et al. (1972) found that in spite of the considerable overlap between the conditions of anxiety and depression, there were striking differences in presenting symptoms, personality characteristics and course and outcome for the disorders. For instance, symptoms typical of depression but which also occurred in anxiety states but significantly more so in the former were: mood worse in the morning; early morning wakening; suicidal acts; and psychomotor retardation. Symptoms typical of anxiety states, which were also found in depression, but less so, were: panic attacks; increased vasomotor responses; emotional lability; perceptual distortions and marked depersonalisation and derealisation. Personality characteristics differed in the two groups. Anxious patients proved significantly more introverted than depressives. This result was shown to be independent of illness, having also been elicited during or after recovery. It was of interest that the highest introversion scores as well as the lowest neuroticism scores were recorded for endogenously depressed patients whose scores proved higher than the adult norms reported by Eysenck (quoted from Roth and Mountjoy, 1982). Traits of immaturity, emotional dependence, instability of mood and neuroticism were associated with anxiety more than with depression.
The conclusion from the Newcastle Studies was that the two syndromes were distinct, despite the overlap. Persistent depression was found among the majority of patients diagnosed as depressed. Episodic depression was characteristic of anxiety patients. Only a minority of the latter showed persistent depression. Episodic tension was found in both groups, but more persistently so in the anxiety group. This means that time dimension plays an important role in characteristic patterns of anxiety and depression, and that anxiety and depressive complaints needs to be supported by longitudinal studies which show that problems can be predicted from prior psychological characteristics. There is little evidence of this kind available.

Foa and Foa (1982) obtained similar results when trying to work out the relationship between anxiety and depression. They found that highly depressed patients were almost always highly anxious whilst most highly anxious patients were only moderately depressed. Mild depression was associated with either moderate or low anxiety. The moderately depressed patients were either very or moderately anxious. These studies suggested that anxiety and depression are two distinct phenomena.

There is physiological evidence in support of the separate entity hypothesis (Kelly and Walter, 1969): when subjected to experimentally induced stress, anxious patients had a mean basal forearm blood flow significantly greater than that of depressed patients. Mountjoy and Roth (1982b) also found a tendency for anxiety states to show increased physiological response, while depressive states were
frequently associated with psychological response to stress.

In contrast, Goldberg (1982) concluded from his study that there was substantial overlap, not only between the symptoms of anxiety and depression, but between the syndromes. This finding was supported by the study by Russell and De Silva (1983). They tried to answer the question whether there was a clear demarcation between anxiety states and minor depressive illnesses or whether it was better to consider them as lying along a continuum of disturbed mood. They concluded, that anxiety and depression were possibly different syndromes but the symptoms were yoked to each other. That is, depressive and anxious moods fluctuate in a similar fashion.

The overall conclusion from these studies is that anxiety and depression are different at syndrome level but have overlapping symptomatology. That is in their extreme forms they can be categorised whereas in milder forms a dimensional approach would seem more appropriate. For further investigations on the relationship between anxiety and depression it should therefore be remembered that one is dealing with multiple component constructs which have patterns of relationship. That is some symptoms of the conditions will fluctuate together, others fluctuate independently, and some may be causally related (Dobson, 1985). One cannot expect unidimensional solutions (Lipman, 1982; Foa and Foa, 1983). But the evidence on which this conclusion is based is methodologically weak. Whilst all the previous studies have tended to be cross-sectional, it is the dynamic interplay of anxiety and depressive symptomatology across time that might offer a solution in studying the relationship between anxiety and depression.
longitudinally. Thus, the need for replication of the crucial studies is obvious, if the ambiguity in the present findings is to be resolved.

In summary, the clinical literature on anxiety and depression consistently documents a relationship between anxious and depressive neuroses, although the patterning and severity of the symptoms is at times such that statistical separation of diagnostic groups is possible. While estimates of the overlap between anxiety and depressive disorder vary, the commonly cited 25% to 40% overlap (Klerman, 1977) is sufficient to necessitate careful consideration of the psychological mechanisms by which patients develop concomitant anxiety and depressive symptomatology (Derogatis et al., 1972). Also, it has been pointed out that the failure to perfectly separate anxiety and depressive disorders has very serious implications for the consideration and application of therapies (and particularly psychotropic medications) for anxiety and depressive disorders (Downing and Rickels, 1974; Hamilton, 1983; Coryell et al., 1988).

The frequent coexistence of anxiety and depressive symptomatology has raised an important and long-debated question. Are anxiety and depression different psychological processes or are they different aspects of the same psychological process? More practical questions apply as well. Do individuals experiencing both anxiety and depressive syndromes have different prognoses from those who display one or the other syndrome in purer form? Moreover, if these individuals indeed suffer from only one or the other primary illness, how might the clinician identify the correct one? These practical questions call for
further data. And only methodologically precise and analysis taking time lag into account will provide answer to these questions.
CHAPTER 3

MEASUREMENT OF ANXIETY AND DEPRESSION

INTRODUCTION

Both anxiety and depression are affective disorders which have physiological, behavioural and cognitive components. Measures developed to assess the two conditions have concentrated on the different components of the disorders. The fact that different subtypes of the two conditions have been differentiated has complicated the issue of measurement. The overlap of symptoms used to describe the two conditions has been an additional source of confusion when attempting to distinguish between the conditions of anxiety and depression on a categorical basis.

This chapter therefore discusses the issue of measurement in anxiety and depression. Of most importance for this discussion are the psychophysiological measurements used in each study, although some aetiological argument concerning physiological mechanisms will also be presented where necessary.
MEASUREMENT OF ANXIETY

The physiological correlates of psychiatric diagnosis have been extensively investigated. Early in this century it had been demonstrated that neurasthenics could be distinguished from normals by their responses to physiological tests (Altschule, 1953). For example, neurasthenics' pulse rates rose markedly during stressful interviews, physical exercise, or voluntary overbreathing. During strenuous exercise, systolic blood pressure was observed to rise to higher levels, and concentrations of sodium lactate in the blood were elevated. Resting levels of physiological activity were not on the whole found to differ.

Malmo (1957, 1966) conducted further studies of patients given a psychiatric diagnosis of anxiety neurosis and showed that they were more reactive to a variety of laboratory stressors, motor tasks and other psychological tests. Again, differences in activation were not noticeable under resting conditions, but following stimulation, sustained after-reactions were observed in muscle tension, blood pressure and heart-rate. Malmo explained his results by postulating that his subjects had a defective inhibitory system, probably inherited, although he thought that the inhibitory mechanism could also be weakened by overuse (Malmo, 1957). The physiological correlates of psychiatric diagnosis are still being vigorously investigated (see below).
Electrodermal Activity

Correlations between anxiety and psychophysiological measures have been sought in patients with anxiety states and in patients with other conditions in which anxiety is prominent. In general, the relationships are strongest when anxiety states are studied. For example, a heterogeneous group of anxious and depressed patients was rated for anxiety, depression and hostility on the basis of an interview (Zukerman et al., 1968). The presence of anxiety correlated with the frequency of spontaneous skin conductance fluctuations but this variable did not distinguish between the patients and a group of normal control subjects. Similarly, anxious patients had higher skin conductance levels than depressed patients (Gilberstadt and Maley, 1965; Frith et al., 1982). Lader and Wing (1966) were able to distinguish patients with chronically high levels of anxiety from other patient and non-patient groups in terms of their spontaneous electrodermal responsivity and the rate of habituation of their skin conductance response to orienting stimuli. Lader (1980) reviewed evidence suggesting an association between skin conductance level and manifest anxiety. Lader concluded that anxiety is accompanied by impairment of adaptation and slowing of habituation.

Psychophysiological studies of patients complaining of anxiety have suggested causal mechanisms which, even if they do not explain how the problem of anxiety begins, may account for its continued maintenance. Lader and Mathews (1968) based their physiological model of anxiety on studies which compared the physiological characteristics of subjects given different anxiety diagnoses. Compared with specific
phobics or normal subjects, patients given the diagnoses of anxiety states or agoraphobia showed more spontaneous fluctuations in skin conductance and lower rate of habituation of the orienting response to tones, the rate being inversely related to the level of spontaneous fluctuations. They therefore proposed that certain individuals are in a vulnerable state of high tonic arousal in which habituation to innately arousing stimuli is minimal or non-existent. In fact, such individuals may be pushed beyond a critical level of arousal, above which a positive feedback process occurs. That is, the phasic arousal associated with novel stimuli adds to tonic arousal with the consequence that habituation fails to occur and arousal increases in increments to the point that a panic attack is precipitated.

This model has been influential in stimulating research, especially in the area of therapeutic process, but it has been difficult to prove or disprove. Although physiological measures usually show greater variability when anxiety is reported (Lader, 1975; Kelly, 1980), a consensus on the meaning of an arousal system has not yet been achieved.

Bond et al. (1974) examined sweat gland activity in a group of patients with anxiety states and compared them with thirty normal subjects matched for age and sex. Skin conductance was recorded while the subjects sat listening passively to a series of auditory clicks and again while the subjects performed a reaction-time task in response to clicks. In the normal subjects the skin conductance level were higher during the active task than the passive situation, whereas in the patients the levels were the same; also, the mean level in the
patients was almost twice that of the normal subjects. Fluctuation rate rose in both groups to the same level during the active task but was lower in the normal subjects during the passive task. It was concluded that pathological anxiety involves an increase in arousal irrelevant to the task and has a disorganising rather than a facilitating effect on performance.

Horvath and Meares (1979) found that number of spontaneous fluctuations but not basal skin resistance discriminated anxiety patients from paranoid and non-paranoid schizophrenics and hysterics. Normals were significantly lower on both measures.

Electrodermal activity has proved particularly useful in evaluating fear responses in phobic subjects and in monitoring the response of these patients to behavioural treatments (Hare, 1973; Hare and Blevings, 1975; Klorman et al., 1977; Fredrikson and Ohman, 1979; Fredrikson et al., 1985). Fredrikson et al. (1985) ascertained two groups of subjects with specific phobias, those with a high rating for fear of spiders and low for fear of snakes, and those with low ratings for both phobias. Skin conductance was recorded before and during slide presentation. Compared to neutral exposures, phobic slides elicited greater skin conductance responses with slow recovery. Ohman et al. (1978) showed that skin conductance habituation was quicker for neutral visual stimuli such as slides of houses than for potentially phobic stimuli such as slides of snakes or spiders.

It may be seen that three different approaches to the problem of psychiatric classification have been used: anxiety states as a
syndrome have been studied, 'neuroticism' as a concept in its own
right has been studied, and anxiety as a symptom in any psychiatric
illness has been used as the criterion. In the first category, the
results are fairly clear-cut; skin conductance levels and fluctuations
are raised. Habituation of the electrodermal responses is certainly
not rapid, but no evidence as to whether it is abnormal was found. In
the two latter approaches with neuroticism and with anxiety as a
symptom in other mental illnesses, the confusion to be expected when
using heterogenous populations of patients was very much in evidence.

However, one very consistent finding is the lack of habituation
in anxious individuals. While a normal subject soon ceases to respond
to a monotonously repeated stimulus, such as a tone, an anxious
patient shows persistent responses. Indeed, in states of severe
anxiety, responses may even increase with repetition rather than
decrease, a form of "recruitment" (Lader, 1983). These data provide
yet another distinction that must be addressed in theories of anxiety.
That is, mechanisms inducing anxiety must be distinguished from
mechanisms maintaining anxiety.

Central Measures

The electroencephalogram (EEG) is the only true central measure
available for psychophysiological study (Lader, 1980). The EEG
findings in anxiety states have been fairly consistent and
predictable. In clinically anxious and anxiety-prone patients there is
a reduction in the amount of alpha activity and an increase in the
amount of beta activity (Lindsley, 1950; Roubicek, 1969; Bond et al., 1974; Petursson and Lader, 1984). In an early study comparing 100 neurotics with 100 normals, alpha activity was less abundant in the patients, especially those suffering from chronic anxiety states (Strauss, 1945). This was confirmed by Tucker (1984) in an extensive study of a heterogenous group of patients with the common symptoms of anxiety. In normal subjects, the dominant alpha frequency followed a single normal distribution with a mean of 10 Hz; in neurotics, the distribution was bimodal with peaks at 9 and 10.5 Hz. In anxiety states the distribution was normal with the dominant frequency at 11.2 Hz. Automatic quantification using a wave analyser has confirmed the association of anxiety and fast wave activity (Ray and Cole, 1985).

Thus, the EEGs of anxious patients consistently show less alpha and more beta activity than normals. Ellingson (1954) dismissed this as insignificant, attributing it to the patients' inability to relax. However, this itself is a distinguishing characteristic of anxious patients, of which the EEG provides objective evidence (Gaebel and Ulrich, 1988). The use of the EEG might therefore throw some light on the neurophysiological correlates of morbid anxiety.

Almost all psychoactive drugs have marked effects on the EEG. Those which are relevant in the context of anxiety include the barbiturates, benzodiazepines and phenothiazines, and all of these produce changes in the EEG (Fink, 1969, Kales et al., 1979; Petursson and Lader, 1984; Schopf et al., 1984; Higgitt et al., 1986; Higgitt et al., 1987). Central nervous system abnormalities are indicated by marked EEG changes following benzodiazepine withdrawal such as changes
in fast wave and diffuse slow wave activity (Lader et al., 1980; Bond et al., 1983; Petursson and Lader, 1984; Higgitt et al., 1986). As autonomic arousal is rarely observed in the absence of cortical arousal (Christie et al., 1983) and EEG studies of anxiety states tend to show greater cortical arousal in patients with anxiety (Bond et al., 1974; Lader, 1980), these findings with EEG measures also raise questions about the nature of the physiological mechanisms that may be responsible for the abnormalities.

The electroencephalographic evoked response to a variety of stimuli has received a great deal of attention in the past twenty years. Wilkinson (1967) proposed that only four components of the evoked response had definite psychological significance, a peak at 60-70 msec (after an auditory click), P1, a trough at 100-120 msec, N1, another peak at 170-200 msec, P2, and another trough at 240-300 msec, N2. Three amplitudes of evoked response are derived from these, the P1N1 difference, the P2N1 difference and the P2N2 difference.

The auditory evoked response (AER) components have been shown to be an index of activation (Wilkinson and Morlock, 1967; Bostock and Jarvis, 1970; Bond et al., 1974; Tyrer, 1976). Bond et al. (1974) found that N1 and P2 latencies were shorter under condition of high activation. Increase in these components are said to be responsive to stimuli that are relevant (Wilkinson and Lee, 1972) or are thought to require selective attention (Donald, 1983; Hansen and Hillyard, 1984). There is evidence that the first of the AER amplitudes is dependent on selective attention (Satterfield, 1965; Naatanen, 1982) and the last of these (P2N2) is related to vigilance (Wilkinson et al., 1966;
Hillyard and Kutas, 1983). Known sedative drugs and anaesthetics tend to reduce all three of these amplitudes (Jarvis and Lader, 1971; Schopf et al., 1984; Petursson and Lader, 1984; Higgitt et al., 1986) and so study of the amplitudes in particular is relevant to the investigation of central effects of anxiolytics.

Since the above measures may reflect levels of attention and arousal and, as will be seen in Chapter 4, since the benzodiazepines are essentially sedative drugs and known to cause perceptual impairment and lowering in the overall state of arousal (e.g. Bond and Lader, 1981; Wesson and Smith, 1982; Tyrer and Seivewright, 1984), studying the AER components could explain the perceptual hypersensitivity reported by the patients treated with benzodiazepine medication.

MEASUREMENT OF DEPRESSION

There has been a lot of research to identify physiological correlates of depression. The impetus for this was the effective treatment of some depressive states since the 1950s, made possible by the pharmacological advances of the monoamine oxidase inhibitors and tricyclic drugs. Recently the lithium salts and biogenic amine precursors have contributed therapeutically, but increasing knowledge of the pharmacological difference between these drugs has yet to produce a clear picture of their diverse action.
Similarly, attempts to classify depressive states have yet to yield clear evidence of their possibly diverse aetiology. While classification helps to provide the practicing clinician with a basis for treatment, however empirical, it also forms a hypothetical substrate for researchers to establish, refute, or refine the validity of clinical observation. The definition of descriptive data which classification can provide is a prerequisite for meaningful comparison between scientific studies, and forms the basis of a clinical and research language which facilitates communication.

The symptom cluster of the depressive states has ill-defined boundaries, merging with the syndromes of schizophrenia, anxiety, and personality disorder. Attempts to contain this broad spectrum of symptoms by descriptive subclassification has provided a series of schemata. The refining of research techniques has not resolved the problems of subclassification, but attention to patient sampling, improved statistical analysis, and standardized interview procedure has placed the investigation of the classificatory dilemma on a more valid scientific basis. Most subclassifications recognize the emergence of two main clinical presentations in depression; a severe, unmitigated mood change and a milder, less sustained and more variable illness. Terms such as psychotic-neurotic and severe-mild have been applied to these different syndromes. Explanatory hypotheses of this observed division include the concept of two distinct illnesses, the concept of a continuum of illness in one or two dimensions with the two syndromes represented at the poles of the spectrum, and the concept of a central single depressive illness with two main variants.
Acceptance of any diagnostic classification finally depends on the identification of disturbances in recognized biological function. Despite the advances in physiological measurement and their research application in depressive illness, no classificatory system including physiological measures has emerged, although it can be argued that psychophysiology has a potentially valuable role in this context. Measurement of peripheral indices may provide information which characterises depressive states, whether such characteristics result from the disease process or the process of pharmacological intervention.

**Electrodermal Activity**

Abnormalities of electrodermal activity have been demonstrated in depressed patients (Christie et al., 1980). With one exception (Toone et al., 1981) most recent investigations have found reduced baseline and tonic skin conductance levels, lowered frequencies of spontaneous skin conductance activity, reduced responses following orienting stimuli and faster habituation rates when compared with controls (Heimann and Straube, 1979; Giedke et al., 1980; Lapierre and Butter, 1980; Mirkin and Coppen, 1980; Storrie et al., 1981; Thorrell, 1987). The reduction in electrodermal activity has frequently been found to persist following symptomatic improvement (Dawson et al., 1977; Iacono et al., 1983) and to be independent of medication (Stern et al., 1960; Noble and Lader, 1971; Janes and Strock, 1982; Iacono et al., 1982).
Diagnostic subgroups of depressed patients have been differentiated by skin conductance measures. Low skin conductance responses of lower amplitude coupled with impaired or non-existent habituation to stimuli are associated with psychotic or endogenous depression (Noble and Lader, 1972; Byrne, 1975; Lapierre and Butter, 1980; Mirkin and Coppen, 1980). Significantly higher skin conductance level and more frequent skin conductance responses of higher amplitude are associated with agitated depression, the presence of anxiety or the non-endogenous syndrome (Gilgerstadt and Maley, 1965; Lader and Wing, 1969; Byrne, 1975; Toone et al., 1981; Thorell et al., 1987).

Although abnormal electrodermal activity is more firmly established for depression than for other psychiatric disorders (Spohn and Patterson, 1979), the nature of this abnormality is not well understood. Only a proportion of such patients show reduced electrodermal activity and in particular patients subtyped as reactive, neurotic or agitated, have been shown not to differ from normal subjects or to have higher levels of electrodermal activity than controls (Lader and Wing, 1969; Noble and Lader, 1972; Byrne, 1975; Lapierre and Butter, 1980; Mirkin and Coppen, 1980). Whilst abnormal electrodermal activity may be regarded as a consequence of other symptoms of the depressed state such as decreased energy levels, fatiguability and psychomotor retardation, this explanation is inconsistent with the observed persistence of the abnormality following recovery, as well as the lack of correlation between various clinical states and electrodermal activity measures (Iacono et al., 1983). The absence of consistent relationships between skin conductance variables and other measures of arousal such as heart rate
and EEG (see Christie et al., 1980; Iacono et al., 1983) also raises questions about the nature of the physiological mechanisms that may be responsible for the abnormality.

There have been several interesting studies of depression in non-patient subjects. McCarron (1973) looked at those who had an abnormal profile on the MMPI in terms of depression ratings and compared them with those with normal profiles, finding reduced skin conductance responsivity in the abnormally depressed group. Gatchel and Proctor (1976), again with normal subjects, took "learned helplessness" as a model of depression and investigated the possibility that there were physiological differences between subjects who were able or unable to escape from aversive stimuli. They found that those who were unable to escape had lower skin conductance levels, small skin conductance responses, and more spontaneous skin conductance activity.

It would appear that there is considerable evidence of reduced skin conductance responsivity in retarded and endogenous depression, but the evidence is far from unanimous: this probably reflects difficulties in adequate subcategorisation of depression, and argues the need for further investigation with what would appear to be the potentially useful peripheral indices of electrodermal activity. Many of the above studies compared depressed patients with normal subjects. Greater deviations from normal in electrodermal activity have generally found in patients with endogenous depression than in those with neurotic depression. Where different types of depression have been compared, the changes have similarly been more pronounced in patients with endogenous depression, but it is not always clear
whether these changes reflect severity or type of depression. Thus, studying the clinical features associated with abnormal skin conductance may provide some explanations for the electrodermal abnormalities observed in depressive patients.

**Endocrine Measures**

It is known that changes in physiological responses are associated with fluctuations in levels of plasma and urinary catecholamines (McCubbin et al., 1983) and plasma and urinary cortisol (Fredrikson et al., 1985). With the advent of radioimmunassay (RIA) and related techniques, reliable measurements of hormones in small samples have become practicable, and endocrine research on the mechanisms of stress response has, in turn, been stimulated (Selye, 1980).

Catecholamine excretion rates of healthy subjects are generally low during rest. Severe emotional stress elicits a pronounced increase in adrenaline secretion in healthy subjects, whereas depressives tend to have low adrenaline secretion during stress. However, there is evidence that the cortisol secretion rate of patients suffering from depression is elevated. Production runs as high as 30mg/day whereas it rarely exceeds 20mg/day in normals (Depue and Kleiman, 1979). There is, in fact, a strong relationship between cortisol production rate and a patient's level of anxiety and psychotic disorganisation. It is therefore thought that the cortisol production rate is not simply a stress response but a dysfunction. Plasma free cortisol levels are
higher in depression than in control psychiatric inpatients (Carrol et al., 1976; Traskman et al., 1980; Joyce et al., 1986; Ball et al., 1987).

Numerous reports have documented the presence of abnormalities of the hypothalamo-pituitary-thyroid axis in a proportion of depressed patients (e.g. Loosen and Prange, 1982; Joyce et al., 1986; Peselow et al., 1987; Rubin et al., 1987). Both elevated and reduced levels of thyroid hormone have been found. Depressed patients have been shown to have blunted responses of thyroid-stimulating hormone to thyrotropin-releasing hormone in comparison with patients with other psychiatric illnesses and normal controls (Kirkegaard et al., 1978; Extein et al., 1981). The proportion of depressed patients with a blunted thyroid-stimulating hormone response to thyrotropin-releasing hormone has been found to vary from 25% to 70% across different studies (Loosen and Prange, 1982). Some patients were found to have augmented thyroid-stimulating hormone response to thyrotropin-releasing hormone (Targum et al., 1981). Gold et al. (1980) found that patients with unipolar illnesses had blunted responses, whereas those with bipolar illness had augmented responses; other studies have been unable to confirm this finding (Kirkegaard et al., 1978; Linkowski et al., 1981).

The significance of the blunting and augmentation is as yet unclear, but in some patients they may reflect increases and decreases in thyroid hormone output (Peselow et al., 1987). Hatotani et al. (1977) suggested that blunting may be due to reduced thyroid function. On the other hand, Loosen and Prange (1982) suggested that during
depression there is hypersecretion of thyrotropin-releasing hormone with a transient increase in thyroid activity, producing blunting by negative feedback. Studies measuring levels of thyroid hormones in depressed patients have produced conflicting results (Yamaguchi et al., 1977; Rieneris et al., 1978). However, longitudinal studies, and those assessing thyroid function during depressive episodes and again after recovery, suggest that thyroid levels are high during depression and fall on recovery (Board et al., 1957; Kirkegaard and Faber, 1981). However, free thyroxine index levels have not been shown to be related to the blunted thyrotropin-releasing hormone test (Kirkegaard and Faber, 1981).

Raised cortisol levels may cause blunting of the thyroid-stimulating hormone response (Rubin and Poland, 1984; Poland et al., 1985; Rubin et al., 1987). Loosen et al. (1978) found, in a small group of depressed patients, that blunting was associated with elevated cortisol levels. A study by Agren and Wide (1982) also reported an inverse relationship between thyroid-stimulating hormone response and cortisol levels, but this association was not confirmed by Davis et al. (1981) and Rubin et al. (1987a). Moreover, there appears to be no association between a positive dexamethasone suppression test and blunting of the thyrotropin-releasing hormone test (Rubin et al., 1987a; Meller et al., 1988).

Inconsistency across the studies in this area of research may be related to a number of factors: lack of strict diagnostic criteria, poor definition of patient groups, possible effects of drugs (Beery et al., 1983), physical illness in the patient groups (Brown et al.,
and failure to account for the relationship between non-suppression and certain clinical variables such as anxiety. Early studies reported that anxiety symptoms were particularly associated with cortisol hypersecretion (Sachar et al., 1970). This relationship may have been obscured in some recent studies by inclusion of patients who were on drugs (e.g. Aggernaes et al., 1983; Joyce et al., 1986; Peselow et al., 1987). Psychotropic drugs not only affect endocrine function but also mental states (see Chapter 4 for discussion), thus obscuring possible relationships between endocrine status and symptom profiles. Therefore, in order to study endocrine abnormality in depression, the issues of concurrent illness and medication usage by patients should adequately be covered and patients should carefully be screened for physical illness in any future research.
CHAPTER 4

BENZODIAZEPINE DEPENDENCE

INTRODUCTION

Patients with anxiety states can present a difficult clinical problem from the point of view of treatment. Because of this, practically every psychotropic drug introduced into clinical practice has been used to treat patients with anxiety states. Benzodiazepines are among the most widely prescribed of all drugs (Blackwell, 1973; Williams, 1978) and there are many case reports of their abuse and of physical dependence on them in high doses (Marks, 1978). Most patients on normal therapeutic doses are presumed to continue their medication in order to prevent their symptoms returning. However, it has been suggested (Hallstrom and Lader, 1981) that chronic users of benzodiazepines might experience difficulty in stopping medication because of the emergence of a withdrawal syndrome even after modest dosage (Rickels et al., 1988). Thus, they continue their medications to prevent this. Despite the growing awareness of the potential of the benzodiazepines to cause dependence, it is uncertain how many long-term users become dependent.
The chief purpose of this review is to establish a rationale for the experimental work that is reported in Chapter 10. Some evidence concerning dependence-inducing properties of the benzodiazepines will now be presented. First, however, I will briefly review the present knowledge concerning the mode of action of these drugs. Benzodiazepines are rapidly absorbed after oral administration and are extensively bound to plasma proteins. They are highly lipid-soluble and are rapidly distributed to various body tissues. There are two main kinetic properties which define their clinical profile: firstly, the possession by some compounds of pharmacologically active metabolites, and secondly, the duration of elimination half-lives of both parent compounds and any active metabolites (Fulton et al., 1981).

Mode of Action and Withdrawal Effects

The benzodiazepines are assumed to act primarily on subcortical structures, such as the amygdala and hippocampus of the limbic system. Specialized binding sites with a high affinity for benzodiazepines have been identified throughout the brain (Braestrup et al., 1977; Braestrup and Squires, 1978; Braestrup and Nielson, 1982; Haefely, 1983; Morre et al., 1985; Costa, 1985) and the existence of an endogenous benzodiazepine-like substance has even been postulated (Skolinck et al., 1983; Costa et al., 1983; Costa, 1985; Petersen et al., 1986). Biochemical data indicate that the benzodiazepines indirectly potentiate and prolong the synaptic actions of GABA, an inhibitory neurotransmitter (Costa, 1980).
Although the acute effects of benzodiazepines on amine metabolism in the Central Nervous System have been extensively investigated, relatively little is known about their chronic effects, nor is the putative neurochemical basis of the withdrawal symptoms elucidated. The benzodiazepines lower the turnover of both brain noradrenaline and 5-HT probably through a primary action of GABA inhibitory mechanisms (Corrodi et al., 1971). The initial sedative effects of the benzodiazepines tend to wear off as tolerance supervenes, and probably result from an effect on noradrenaline mechanisms (Agarwal et al., 1977; Braestrup and Nielsen, 1982; Haefely, 1983). The rebound phase, seen when animals are withdrawn from long-term benzodiazepine administration, is associated with enhanced release and decreased uptake of noradrenaline, dopamine and 5-HT (Rastogi et al., 1978).

Although some evidence supports a neurochemical basis for benzodiazepine withdrawal effects, the neurophysiological mechanisms underlying benzodiazepine withdrawal symptoms in man are unknown. The effects on monoaminergic neurones may be nonspecific and indirect, that is, resulting from the benzodiazepines' primary action of facilitating GABA transmission. Furthermore, preliminary studies suggest that changes in benzodiazepine receptors are insufficient to explain the development of tolerance and dependence following chronic treatment (Braestrup et al., 1979; Braestrup and Nielsen, 1980; Tallman, 1981).
Pharmacodynamic Actions

Effects on respiration and the cardiovascular system are slight (Tyrer et al., 1983; Ashton, 1984; Petursson and Lader, 1984). Unlike the barbiturates, alcohol, and most other sedative drugs, benzodiazepines are not general neuronal depressant. Thus, with increasing dosage, sedation merges into sleep, but no true general anaesthesia occurs. It is not clear whether the anxiolytic effects of benzodiazepines are separate from their sedative and hypnotic effects or an intrinsic part of this action (Lader, 1979; Petursson and Lader, 1984; Higgitt et al., 1985).

The pharmacodynamic profiles of action of benzodiazepines differ somewhat. Diazepam is more anticonvulsant than chlordiazepoxide. Clobazam has less effect on muscle relaxation than diazepam given in clinically equal antianxiety doses, and also produces less psychomotor impairment. Lorazepam seems particularly sedative and is potent in producing amnesia after intravenous use or after large oral doses.

In sufficient dosage, all the benzodiazepines impair psychomotor performance and cognition (Seppäla et al., 1980; Bond et al., 1983; Petursson et al., 1983; Pørt and Foulhouse, 1985; Brosan et al., 1986). Most data stem from investigations of the residual effects of benzodiazepines when used as hypnotics. Although impaired performance is well known during the initiation of treatment, such decrements have generally disappeared by the end of a week or two of repeated dosage (Rickels et al., 1988). In contrast, comparatively little is known about potentially adverse psychomotor effects after long-term
The Benzodiazepine Withdrawal Syndrome

The first reported incidences of benzodiazepine dependence were in schizophrenic patients who were given high doses of diazepam for periods of 6 weeks to 6 months (Hollister et al., 1961). On withdrawal they manifested intense symptoms of fits, worsened psychosis, sweating, twitching, insomnia and loss of appetite.

No attempt has been made to define withdrawal syndromes with respect to the duration of treatment, but clinically two syndromes have been distinguished on the basis of the dosage involved (Woody et al., 1975; Wesson and Smith, 1982). High-dose (normally 2-5 times the normal antianxiety dose) withdrawal has been best characterised by Hollister et al. (1961, 1963), but the literature is peppered with single case reports (Marks, 1978; 1982). Withdrawal after therapeutic dosage has now been confirmed in both laboratory and clinical studies (Howe, 1980; Tyrer et al., 1981; Petursson and Lader, 1984; Ashton, 1984; Higgitt et al., 1985; Rickels et al., 1988). Even with therapeutic doses there is some evidence that a withdrawal syndrome is found more frequently the longer the treatment, for example 6 compared with 22 weeks (Rickels et al., 1983, 1984).

Withdrawal symptoms, summarised by Ladewig (1984), fall into three categories: 1) psychological symptoms of anxiety such as apprehension, irritability, insomnia and dysphoria; 2) bodily symptoms
of anxiety, particularly tremor, palpitations, sweating and severe muscle spasms; 3) perceptual disturbances such hypersensitivity to light, sound and touch; pains; feeling of emotion; metallic taste. The first two categories may resemble the original anxiety, but the withdrawal symptoms are more severe (Ladewig, 1984). Most commonly these symptoms subside in 5-15 days, which is not consistent with a re-emergence of the original anxiety (Owen and Tyrer, 1983).

Studies have been performed which provide support for the existence of benzodiazepine dependence and associated withdrawal symptoms and control for the possibility of re-emergence of the original complaint. Patients suffering from anxiety received benzodiazepines or placebo for 4-6 weeks. Treatment was then either terminated abruptly or gradually. The group abruptly withdrawn from benzodiazepines suffered anxiety that was worse than that in patients who had been on placebo throughout (Fontaine et al., 1984; Power et al., 1985; Rickels et al., 1988). In addition, in the former group new symptoms also emerged. This was interpreted as indicating a withdrawal

Gradual withdrawal may be followed by a milder, yet specific syndrome which is the same whether the dosage was high or low (Hallstrom and Lader, 1981). However, even with gradual withdrawal from low doses, prolonged and bizarre responses have been described (Ashton, 1984). Ashton emphasizes how physically ill the patients felt and also describes agoraphobic, panic and depressive symptoms. At times a clinical depression may follow benzodiazepine withdrawal (Olajide and Lader, 1985) and in some cases the psychotic reactions
are noted to have a depressive content.

A large-scale survey, attempting to establish the prevalence of symptoms in the general population comparable to those presented by patients withdrawn from benzodiazepines, suggested that these symptoms occur relatively frequently as a constellation and their prevalence is particularly high in an anxious and depressed group (7.5%) (Merz and Ballmer, 1983). An even higher incidence of such symptoms was reported by Rodrigo and Williams (1986) who found that symptoms related to perceptual hypersensitivity were reported by an anxious group of students (before exams) at a frequency similar to patients in withdrawal studies. They suggested that such symptoms are non-specific and anxiety-related.

In some cases then re-emergence must form part of the explanation of benzodiazepine withdrawal symptoms. The exact timing of onset of symptoms may, however, clarify the picture (Fontaine et al., 1984). Withdrawal symptoms are expected to arise from one to seven days after stopping intake (depending on the half-life) while the re-emergence of pre-existing anxiety would be expected in the second and third week (Rickels et al., 1983). Further points of differentiation are that new symptoms could be expected in the withdrawal syndrome and it would eventually settle without further treatment (Higgit, 1987).
Tolerance to the Benzodiazepines

The benzodiazepines are undoubtedly effective anxiolytics in the short-term (Rickels et al., 1988), but in spite of the extensive and chronic usage of these drugs, their long-term anxiolytic efficacy is still not well established. On other hand considerable circumstantial and clinical evidence supports the view that some degree of tolerance probably occurs to the sedative/hypnotic, anticonvulsant, muscle-relaxant and ataxic effects of the benzodiazepines (Greenblatt and Shader, 1978; Bond et al., 1983; Rickels et al., 1983,1984,1985; Tedeschi et al., 1985).

In patients who had been taking normal doses of benzodiazepines for 6 months or more, tolerance was assessed by giving test doses of diazepam (Petursson and Lader, 1984). The responses of patients were compared with the effects of the test dose of diazepam in normal subjects. Subjective feelings of sedation to the diazepam were reduced, indicating marked tolerance; and there was no tolerance in the EEG fast wave response. In patients taking high doses of benzodiazepines for at least one year there was marked tolerance to the psychomotor effects of a test dose of lorazepam; little tolerance was shown in patients taking low doses for one to eleven months (Aranko et al., 1985). In long-term benzodiazepine users, the anxiolytic effect, reduction of critical flicker fusion threshold and the short-term memory impairments induced by benzodiazepines were found to persist, whereas there was no longer any psychomotor impairment or sedation (Lucki et al., 1986). This suggests that tolerance had developed to the latter effects, but not to the former.
The experiments with patients did not permit evaluation of the onset of tolerance, but at least in normal volunteers tolerance to some of the effects of benzodiazepines seems to develop very rapidly. Tolerance developed after three doses to the impairments of driving performance seen in some tests the morning after night time administration of nitrazepam (Laurell and Tornros, 1986). However, it is important to note that in well controlled studies tolerance is not invariably demonstrated across almost all performance measures. For example, Aranko et al. (1983) found no tolerance to reaction time errors and Petursson et al. (1983) and Bond et al. (1983) found no tolerance developing to performance decrements on the symbol copying test. Brosan et al. (1986) found no tolerance to the psychomotor or cognitive impairments after 3 weeks of diazepam administration to normal volunteers.

Some workers have claimed that doses of benzodiazepines producing a given effect initially do become ineffective and that higher doses need to be given in order to maintain anxiolysis (Haefely, 1983). Gross (1977), for example, reported that he needed to increase the dose of lorazepam after one month of administration in order to maintain a therapeutic effect. A number of reports have been published indicating the re-appearance of symptoms, primarily of anxiety, whilst patients are still taking benzodiazepines, suggesting tolerance development (Greenblatt and Shader, 1978; Browne, 1983; Ashton, 1984; Allen et al., 1985). Thus the clinical evidence for tolerance developing to the anti-anxiety effects of benzodiazepines following long-term treatment is not unequivocal. The generally accepted conclusion, however, is that evidence of long-term efficacy
is sparse (Lader and Petursson, 1983a; Rickels et al., 1984), an opinion which has been accepted by the Committee on the Review of Medicines (1980) as applying to the hypnotic as well as anxiolytic use of benzodiazepines.

The long-term effectiveness of the benzodiazepines as anxiolytics or hypnotics is a matter for debate. Most trials of new anxiolytics involve the prescribing of the drug to patients for a period of two to four weeks only (Greenblatt and Shader, 1978) and thus do not address the issue.

The contradiction expressed in the literature suggest that the problem of benzodiazepine dependence is either rare, or is rarely recognized by doctors. One reason why signs of benzodiazepine dependence may be missed or misdiagnosed is the fact that unlike withdrawal from opiates or alcohol, anxiety is the cardinal symptoms of the benzodiazepine withdrawal syndrome (Petursson and Lader, 1984). Moreover, the temporal relationships of the respective syndromes are quite different because of pharmacokinetic differences. Most of the recent studies and reviews seem to agree that withdrawal symptoms may occur from therapeutic doses of benzodiazepines, especially if the treatment has been prolonged. Although the extent of such normal dosage dependence is unknown, and even if it supervened only to a minor degree, the extensive and chronic usage of these drugs could mean that thousands of patients are at risk. Most reports concern less severe, but unexpected and unusual symptoms supervening on cessation of treatment. An important question, therefore, is whether abnormalities can be shown in these patients following withdrawal from
benzodiazepines independent of their anxiety in terms of tolerance to benzodiazepines.
ABNORMAL SKIN CONDUCTANCE IN DEPRESSION

INTRODUCTION

As the review in Chapter 3 indicated, a number of studies (Lader and Wing, 1969; Byrne, 1975; Dawson et al., 1977; Lapierre and Butter, 1980; Mirkin and Coppen, 1980; Giedke et al., 1980; Storrie et al., 1981; Ward et al., 1983; Thorrell, 1987; Thorell et al., 1987) have offered evidence of abnormal electrodermal activity in depressive patients. An important question to which there remains no clear answer is whether the electrodermal activity varies in different subgroups of depressive patients.

Comparison between depressives and normal controls has shown that the former generally have reduced skin conductance levels, lowered frequencies of spontaneous skin conductance activity, reduced response following orienting stimuli and faster habituation rates than the latter. Thus, Lader and Wing (1969) reported significantly lower skin conductance levels in depressive patients with psychomotor retardation than matched normal controls. Similar findings have been reported later in endogenous depressive patients (Byrne, 1975; Mirkin and
defined according to the Newcastle scale (Carney et al., 1965), in patients with primary depression (Dawson et al., 1977; Giedke et al., 1980) according to the Criteria of Feighner et al. (1972), in depressive patients with psychomotor retardation (Lapierre and Butter, 1980), and in unipolar affective disorders (Ward et al., 1983) according to the Research Diagnostic Criteria (RDC) (Spitzer et al., 1978). However, some exceptions exist. Unipolar depressive patients and matched normal controls did not show any significant difference in skin conductance levels, number of spontaneous fluctuations, or habituation rate, in an experiment on habituation to a series of flashes (Toone et al., 1981). In agitated (Lader and Wing, 1969; Noble and Lader, 1972) and neurotic (Byrne, 1975) depressive patients, the electrodermal activity was higher than in normal subjects.

Contradictory findings may be explained by drug effects. Anticholinergic, anxiolytic, or other pharmacological effects of antidepressive drugs may be responsible for the low electrodermal activity in some of the studies above. In other studies only some of the patients were drug-free (Dawson et al., 1977; Giedke et al., 1980; Ward et al., 1983; Thorell et al., 1987).

In conclusion, the indices of lower electrodermal activity in depressive patients as compared to normal controls are quite consistent in spite of the diverse criteria for selection of the depressive patients, the variant control groups, the various experimental settings, the different techniques of measurement, and the selection and derivation of electrodermal variables. This strongly
indicates the existence of abnormality of electrodermal activity in groups of patients suffering from depressive disorders. However, The precise nature of the abnormality remains controversial. Not even is it bedevilled by problems of diagnosis, drug treatment and the current status of the patients being investigated. The relative importance of skin conductance variables has not yet been examined. Furthermore, the relationship of particular diagnostic subgroups to particular aspects of skin conductance abnormality is not known. As the review in Chapter 3 indicated, the previous studies which approached this question had insufficient data at their disposal in terms of sample size, diagnostic information and the use of univariate statistical models to permit the derivation of reliable conclusions.

The purpose of the present study was to re-examine the significance of skin conductance abnormality in a relatively large sample of comprehensively assessed drug-free patients with primary depressive illnesses, using statistical methodologies different from those that have been used in prior research. The use of a standardised assessment procedure will permit the examinations of the relationship between individual symptoms of depression and skin conductance abnormalities as well as the relationship between skin conductance variables and classifications of the depressed group assessing to the reliably elicited symptoms. In the present study discriminant function analysis was performed on a sample of 114 drug-free subjects. This analysis not only permitted a more thorough evaluation of multiple psychophysiological response (pattern), but also permitted to find unique contribution of each of the skin conductance variables to particular diagnostic subgrouping.
The specific aims of the present study were: 1) to examine the degree of skin conductance abnormality in depressive patients in comparison with normal controls matched for age and sex; 2) to try to answer the question that it is severity or diagnosis of depressive symptoms that predicts abnormal skin conductance in depression; 3) in particular to try to replicate findings of lower electrodermal activity in endogenous depressive patients diagnosed according to the Newcastle scale; 4) and to try to replicate findings of lower electrodermal activity in depressive patients with predominant psychomotor retardation.

METHOD

Patients

The patients were admitted to the study from several sources: a psychiatric hospital, a district general/teaching hospital (in-patients, out-patients, Accident/Emergency), a psychiatric day hospital, and directly from general practice. One hundred and thirty patients were interviewed over a 2-year period; those with physical illnesses, secondary depression, or in whom it was considered unethical to interrupt or delay treatment were excluded from the study. Patients over the age of 70 were also excluded from the study. The remaining 80 patients all met the Research Diagnostic Criteria (RDC) for depression (Spitzer et al., 1978) and were drug free for a minimum period of one week before the investigations were carried out.
In some patients placebo medication was given at night, and 13 patients received 10-20 mg of temazepam at night. These 13 patients showed a very slight, non-significant trend towards lower electrodermal activity but their exclusion from the sample did not change the pattern of results and patients therefore were included in the investigation.

Of the 80 patients investigated, 8 were excluded from the study. Five of these 8 received alternative psychiatric diagnoses on follow-up (one schizophrenia, two schizo-affective, one anorexia nervosa and one Pick's disease). Of the remaining 3 patients, one was found to have a brain tumour following CT scan, one developed pneumonia, and one failed to complete the investigations. Only patients with primary depression were included in the sample. These 72 patients were classified by means of The RDC as Major Depressive Disorder (54), Probable Major Depressive Disorder (9) and Minor Depressive Disorder (9). There were 64 unipolar and 8 bipolar cases. The mean age of the sample was 41.6 years (SD=13.7). 60% of the sample were female and 39% were inpatients. Clinical characteristics of the patients are shown in Table 5.1. Using the Present State Examination Index of Definition (ID) (Wing et al., 1978), 70 of the 72 patients met the criteria of 'caseness' (an ID of 5 or more) and the remaining 2 patients had an ID of 4. These 2 patients were excluded from the analysis. The distribution by CATEGO classes is also shown in Table 5.1.
Table 5.1. Clinical features of patients (N = 70)

<table>
<thead>
<tr>
<th>Previous history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous episodes (mean ± S.D.)</td>
<td>3.7±2.8</td>
</tr>
<tr>
<td>Presenting with first episode</td>
<td>20 (27.8)</td>
</tr>
<tr>
<td>Age of onset of first episode (mean ± S.D.)</td>
<td>32.9 ± 15.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressant</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>MAOIs</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>27 (37.5)</td>
</tr>
<tr>
<td>ECT</td>
<td>6 (8.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CATEGO classes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive psychosis</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Retarded depression</td>
<td>33 (45.8)</td>
</tr>
<tr>
<td>Neurotic depression</td>
<td>29 (40.3)</td>
</tr>
<tr>
<td>Paranoia</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Obsessional neurosis</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

The table shows the number of patients, with the percentages in parentheses.
Normal Controls

Fifty-three normal controls were matched with the patients for age and sex. The age range was 19 to 66 years with a mean age of 42 years (SD=11.5). They were 30 female and 23 male volunteers who were hospital employees consisting mainly of clerical workers and some doctors and nurses.

CLINICAL ASSESSMENT

Present State Examination (PSE)

The PSE (Wing et al., 1974) is an interview technique which allows psychiatric symptoms to be elicited in a standard form and reliably rated. Once rated the symptoms may be grouped into syndromes giving profile of the mental state. A clinical classification consistent with ICD-9 (WHO, 1978) may be derived from symptom ratings using an objective computerised scoring system.

Hamilton Depression Scale

The Hamilton Depression Scale (Hamilton, 1967) is the most widely used clinician-rated scale for estimating the severity of clinical depression. It consists of 21 items covering mood states, sleep disturbances, somatic symptoms, weight loss, reality disturbance, agitation and diurnal variation.
Newcastle Diagnostic Index

This scale subdivides depression into endogenous and neurotic (Carney et al., 1965). There are two items on the diagnostic scale which score negatively, "blames others" and "anxiety" and eight positive items. The items and weights used in scale were derived from the study of 148 subjects admitted to hospital for treatment with ECT. All patients were interviewed in a standard way and their response to questions previously found relevant in differentiating endogenous and neurotic depression were recorded. Criterion diagnoses were established within a few days of admission and patients were allocated either to a diagnosis of definite endogenous or definite neurotic depression. When patients' scores were plotted on the basis of the diagnostic index a non-unimodal distribution was found. The cut off score for endogenous depression is set at +6 or greater and for neurotic depression 5 or less.

Procedure

Subjects were tested after the initial interview. In patients with extreme retardation the full interview was delayed until some clinical improvement had taken place. Upon arrival, each subject was informed about the details of the experiment. After verbal consent to participate, skin conductance electrodes were applied to the left thumb. The testing conditions were kept as standard as possible and recordings were carried out in a sound-attenuated room.
Skin Conductance

Skin conductance was measured whilst patients were seated comfortably in a reclining chair. This test represents an indirect measure of palmar sweat gland activity. Skin resistance was measured from the left thumb. A self-adhesive foam ring maintained a constant area. Electrode jelly (0.05M sodium chloride) was applied to the skin in the ring. A constant current of 14 amp/cm was passed through this electrode to an earth electrode strapped on the forearm (see photographs in Appendix 5.1 for equipment layout and electrode placements). Skin conductance responses were amplified using an Electronic Development skin conductance meter and recorded on a Devices 10 channel polygraph. Skin conductance orienting responses to 14 one second 90 decible, 1000 Hz tones generated by an Amplivox audiometer and presented through loudspeaker at pseudo-random intervals ranging from 15-30 seconds were measured. Skin conductance level (SCL) was measured at the onset of each response or, if no response occurred, at the onset of the tone. Skin conductance responses were defined as occurring between 1 and 5 seconds after stimulus onset. Spontaneous responses (SPONT) were those that occurred before or at least 5 seconds after the tone. To be counted as such, all skin conductance responses had to have a minimum amplitude of 0.05 microsiemens. Habituation (HABIT) was defined as no measurable response to 3 successive tones. Response latencies (LAT), rise times (RISET) and half-recovery times (RECT) were also calculated. 9 out of the 70 subjects failed to have their skin conductance measures taken because of equipment failure.
RESULTS

Skin conductance in patients and matched normal controls

As Table 5.2 illustrates, rise time, recovery time, and the number of spontaneous fluctuations turned out to differentiate significantly between the total depressive sample and the normal controls. Both the latency and rise time of responses were significantly greater for the total sample of depressive patients (t=2.19, df=112, P<0.05 and t=3.69, df=112, P<0.001 respectively) than normal controls. The recovery time following a response in the total depressive sample was significantly longer than that of the normal controls (t=2.14, df=112, P<0.05). The number of spontaneous fluctuations in the total depressive sample was significantly above that of the normal controls (t=2.37, df=112, P<0.02). There was no significant differences between the total depressive sample and the normal controls on the number of trials to habituation and the basal skin conductance levels.

On the basis of the Newcastle Diagnostic Index 32 patients (53%) were classified as endogenous and 29 (40%) were neurotic. The mean Newcastle score for the endogenous subgroup was 6.54 (SD=3.29) and for the neurotic subgroup it was 3.9 (SD=1.49). The patients diagnosed as endogenous according to the Newcastle scale had significantly lower skin conductance levels (t=2.53, df=59, P<0.01) and fewer number of spontaneous fluctuations (t=2.18, df=59, P<0.02) in their skin conductance.
When these subgroups were compared with the normal controls, the rise time of responses and the number of spontaneous fluctuations in skin conductance were the only measures to show significant differences ($F=4.75$, $df=2,112$; $P<0.05$ and $F=7.31$, $df=2,112$; $P<0.001$ respectively) (see Table 5.3). Subsequent paired comparisons were made by Scheffe method which is the most conservative available. The neurotic subgroup showed significantly higher rise time ($P<0.05$) and increased frequencies of spontaneous skin conductance fluctuation ($P<0.01$) as compared with normal controls. There was, however, no significant difference between the endogenous depressives and the normal control group on any of these measures.

Relationship between skin conductance variables

Table 5.2 shows the mean levels of the skin conductance variables for depressive patients and normal controls. Pooled within-group correlations among the skin conductance variables are shown in Table 5.4.

Of the fifteen correlations, nine showed statistical significance at $\alpha=0.01$ when tested individually. Latency was positively correlated with rise time ($r=0.52$, $df=112$, $P<0.01$) and recovery time ($r=0.34$, $df=112$, $P<0.01$) and negatively with the number of spontaneous fluctuations ($r=-0.38$, $df=112$, $P<0.01$). Rise time was positively correlated with recovery time ($r=0.49$, $df=112$, $P<0.01$) and negatively correlated with number of spontaneous fluctuations ($r=-0.41$, $df=112$, $P<0.01$). There was a negative correlation between recovery time and
Number of spontaneous fluctuations ($r = -0.36$, df = 112, $P < 0.01$). Number of trials to habituation was positively correlated with both skin conductance levels and number of spontaneous fluctuations ($r = 0.39$, df = 112, $P < 0.01$ and $r = 0.58$, df = 112, $P < 0.01$ respectively); and skin conductance levels was positively correlated with number of spontaneous fluctuations ($r = 0.39$, df = 112, $P < 0.01$).

**Classification of Depression and Skin Conductance**

A direct discriminant function analysis was performed using the six skin conductance variables as predictors of membership in three groups. Predictor variables were response latencies (LAT), rise times (RISET), recovery times (RECT), habituation rate (HABIT), skin conductance levels (SCL), and spontaneous fluctuations (SPCNT). Two discriminant functions were calculated, with a combined Chi-squared ($12$) = 28.72, $P < 0.01$. After removal of the first function, there was still significant discriminating power, Chi-squared ($5$) = 12.20, $P < 0.05$. The two discriminant functions accounted for 67% and 32%, respectively, of the between-group variability. As shown in Figure 5.1, the first discriminant function maximally separates neurotic depressives from normal controls, with endogenous group falling between these two groups.

A loading matrix of correlations between predictor variables and discriminant functions, as seen in Table 5.4, suggests that the primary variable in distinguishing between neurotic and control groups (first function) is the number of spontaneous fluctuations. Neurotic
depressives have more spontaneous fluctuations in their responses (mean SPONT = 9.42) than both endogenous depressives (mean SPONT = 4.91) and normal controls (mean SPONT = 3.87). Also contributing to discrimination between these groups are rise times and recovery times following a response. Neurotic depressives have greater rise time in their responses (mean RISE T = 2.25) than both endogenous depressives (mean RISE T = 1.80) and normal controls (mean RISE T = 1.66). Similarly, neurotic depressives have longer recovery rate following a response (mean RECT = 3.57) than both endogenous depressives (mean RECT = 2.92) and normal controls (mean RECT = 2.79).

After adjustment for all other variables, and keeping overall alpha<0.05 for the six variables, only the number of spontaneous fluctuations significantly separated neurotic depressives from the other two groups (F=4.14, df=1, 108). The squared semipartial correlation between the grouping of neurotic depressives versus the other two groups and the number of spontaneous fluctuations was 0.05. Endogenous depressives showed no variable that significantly could distinguish them from the remaining groups after adjusting for all other variables, with strongest variable, latency of responses, producing F=3.89, df=1, 108, P<0.05.

One predictor variable had loading in excess of 0.45 in the second discriminant function, which distinguished between the control subjects and the other two groups. This contribution came from recovery time following a response. Normal subjects had shorter recovery time following a response than either of the two patient groups, means for which have previously been cited.
After adjustment for Type I error rate and adjustment of variables for overlap with each other, only recovery time significantly discriminated normal subjects from patient groups (F=4.89, df=1, 108). The squared semipartial correlation between the grouping of normal subjects versus the other two groups and recovery time was 0.03.

With the use of a jackknifed classification procedure, the discriminant function was able to classify 78 (68.4%) correctly of the total sample of 114. This classification rate was achieved by classifying a disproportionate number of cases as neurotic depressives. Although 33% of the subjects were neurotic, the classification scheme, using sample proportions as prior probabilities, classified 84 (73.7%) of the subjects as neurotic. This means that the neurotic depressives were more likely to be correctly classified (86.1% correct classifications) than either the endogenous depressives (18.4% correct classifications) or the normal subjects (7.9% correct classifications) (see Table 5.5).

The stability of the classification procedure was checked by a cross-validation run. Approximately 25% of the cases were withheld from calculation of the classification functions in this run. For the 75% of the cases from whom the functions were derived, there was a 60.5% correct classification rate. For the cross-validation cases, 58.3% were correctly classified. This indicates a high degree of consistency in the classification scheme.
Figure 5.1. Plot of three group centroids on two discriminant functions derived from six skin conductance variables.
Table 5.2. Skin conductance measures of all the depressives compared with normal controls. (Means, with standard deviations in parenthesis)

<table>
<thead>
<tr>
<th>Skin conductance Measures</th>
<th>All depressives (N=61)</th>
<th>Controls (N=53)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responders (as %)</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Latency (sec.)</td>
<td>2.24 (0.96)</td>
<td>1.80 (0.86)</td>
<td>t=2.19, p&lt;0.05</td>
</tr>
<tr>
<td>Rise time (secs.)</td>
<td>2.64 (1.25)</td>
<td>1.36 (0.67)</td>
<td>t=3.69, p&lt;0.001</td>
</tr>
<tr>
<td>Half recovery time</td>
<td>3.13 (1.70)</td>
<td>2.79 (1.18)</td>
<td>t=2.14, p&lt;0.05</td>
</tr>
<tr>
<td>Habituation rate</td>
<td>7.05 (5.12)</td>
<td>7.17 (4.39)</td>
<td>t=-0.81, NS</td>
</tr>
<tr>
<td>Skin conductance levels (log microsiemens)</td>
<td>0.79 (0.30)</td>
<td>0.70 (0.22)</td>
<td>t=1.51, NS</td>
</tr>
<tr>
<td>Spontaneous fluctuations (no/min.)</td>
<td>8.26 (11.10)</td>
<td>3.87 (4.85)</td>
<td>t=2.37, p&lt;0.02</td>
</tr>
<tr>
<td>p</td>
<td>Spontaneous fluctuations (no/min)</td>
<td>Skin conductance levels (106 microsiemens)</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recovery time</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latency (sec.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (sec.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-responders (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.112=7.31)</td>
<td>7.40 (4.97)</td>
<td>8.06 (5.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.112=0.28)</td>
<td>0.60 (0.27)</td>
<td>0.81 (0.31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.112=0.25)</td>
<td>1.05 (0.85)</td>
<td>1.26 (1.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.112=1.35)</td>
<td>1.40 (1.16)</td>
<td>1.40 (1.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1.2 Skin conductance measures of adrenergous and hypnotic depressives compared with normal controls. (X + S.D.)

*Note: *Means with standard deviations in parentheses.
<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled within-group correlations among predictors</td>
<td>Univariate</td>
<td>Univariate</td>
</tr>
</tbody>
</table>

Table 5.4: Results of discriminant function analyses of skin conductance variables.
Table 5.5. Classification rate of the cases in the discriminant function.

<table>
<thead>
<tr>
<th>Group</th>
<th>Actual</th>
<th>Number of cases predicted into group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Neurotic</td>
</tr>
<tr>
<td>Neurotic</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Endogenous</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Controls</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>84</td>
</tr>
</tbody>
</table>
DISCUSSION

The results of this investigation support the hypothesis of abnormal electrodermal activity in depressive patients. Over sixty percent of the patients were found to have abnormalities in their skin conductance in comparison with the normal controls. Significantly higher number of spontaneous fluctuations, longer recovery rates, and faster rise times were found in the patients responses following orienting stimuli than normal controls. The endogenous depressive patients defined according to the Newcastle scale were less electrodermally active than the neurotic subgroup. The high proportion of patients were found to be non-responders as compared to the normal controls.

Generally speaking, these findings are in accordance with previous studies (Lader and Wing, 1969; Byrne, 1975; Mirkin and Coppen, 1980; Lapierre and Butter, 1980; Ward et al., 1983), with one exception (Toone et al., 1981). Toone and his co-workers suggested their depressive patients may have lacked severity of symptoms described in earlier studies. In another study (Geidke et al., 1980), the differences in electrodermal activity between the patients and the normal subjects were observable only during a pre-checking period but not during the experimental period.

The present results also support previous findings (Lader and Wing, 1969; Noble and Lader, 1971; Dawson et al., 1977; Lapierre and Butter, 1980; Williams et al., 1985) of an association between
abnormally low skin conductance levels and high psychomotor retardation. In contrast to previous studies (Lader and Wing, 1969; Noble and Lader, 1971; Williams et al., 1985), the phasic electrodermal activity was not significantly associated with psychomotor retardation. One explanation for the divergent results may be that the patients in the present study were less retarded than in other studies. This suggests that abnormally low electrodermal activity in depressive patients may only be observable at high levels of psychomotor retardation. Noble and Lader (1972) have also reported that peripheral autonomic arousal may vary considerably according to degree of retardation present.

In terms of individual skin conductance variables, there were no significant differences between patients groups and normal controls in terms of skin conductance levels and habituation rate. Mirkin and Coppen (1980) also found no significant differences in skin conductance levels and habituation rate of depressive patients in comparison with normal controls. In the present study, however, a large proportion of neurotic patients showed significantly increased frequencies of spontaneous fluctuations rather than faster habituation rate and lower skin conductance levels, which a number of workers previously found to differentiate diagnostic subgroups of depressed patients (e.g. Gieldke et al., 1980; Lapierre and Butter, 1980; Storrie et al., 1981; Thorell, 1987), as the variable primarily associated with abnormal skin conductance in these patients. In fact, using discriminant function analysis, only the number of spontaneous fluctuations in skin conductance significantly identified neurotic patients from normal controls. An increase in frequency of
spontaneous fluctuations have been considered typical of anxiety, whether viewed as a distinct syndrome (Lader and Wing, 1966; Frith et al., 1979) or as a morbid characteristic in a mixed psychiatric population (Spohn and Patterson, 1979). Thus, the presence of a higher number of spontaneous fluctuations in the present study also suggests that levels of anxiety might have separated neurotic depressives from endogenous depressive and normal subjects, although Thorell et al. (1987) reported that patients with reactive depression were more likely to have abnormally lower spontaneous electrodermal activity than normal controls. This issue, however, could be settled by looking at the relationship of individual clinical features to skin conductance abnormality and will be dealt with comprehensively in the next chapter.

The index of skin conductance non-responding has been higher in groups of depressive patients than in normal subjects in the present as well as in other studies (Lader and Wing, 1969; Mirkin and Coppen, 1980). In the study by Lader and Wing (1969), the proportions of non-responders were 31% in the group with psychomotor retardation, 13% in the total depressive sample including agitated depressives, and 0% among the normal subjects. Similar proportions were found in the present study (15% of the patients and 2% of the normal group) and by others (Thorell et al., 1987) (17% of 22 bipolar patients in the depressive phase). This indicates that these patients were singularly unaffected by external stimulation, thus reflecting a trait more than a state of abnormality. All of the ten non-responding endogenous patients remained non-responders throughout the experimental period. Similar results were also reported for a group of endogenous patients
by Noble and Lader (1971), who found no significant differences in skin conductance levels after recovery from ECT.

Mirkin and Coppen (1980) defined non-responding differently: a maximum of three responses to 20 stimuli. The responses did not need to be consecutive, for which reason their proportions, 67% of the depressive patients and 13% of the normal subjects, are not comparable to the present study or most others (Levinson and Edelberg, 1985).

According to a review by Ohman (1981) the proportion of non-responders among normal subjects has consistently been reported to be small (0-12%). The results of the present study thus confirm previous findings of both the greater proportion of non-responders among depressive patients and the small proportion among normal subjects.

In conclusion, these findings are congruent with the observations in previous relevant studies. Taken together, available data strongly indicate the existence of abnormal functioning in the electrodermal system in groups of depressive patients. Nonetheless, since only some of these patients showed the abnormality, it is important to further examine the clinical features of these patients and compare them with those patients who did not show abnormalities in their skin conductance on a number of psychiatric rating scales.
CHAPTER 6

ABNORMAL SKIN CONDUCTANCE IN DEPRESSION:

PSYCHIATRIC CORRELATES

INTRODUCTION

In the previous chapter the results presented that strongly support the hypothesis of abnormal electrodermal activity in depressive patients. However, the observation that only some depressed patients show the abnormality needs further clarification. In view of diagnostic and predictive difficulties of classification systems and their relationship to skin conductance abnormalities in depression, it is important to further investigate the relationship of individual clinical features to skin conductance abnormality. Thus, in order to examine the relationship of individual clinical features to skin conductance abnormality we need to compare those patients who showed abnormalities in their skin conductance in the previous study with those who did not on a number of psychiatric rating scales.

Current practice relies heavily on nosologies developed by the analysis of clinical data. Although there is a disagreement as to
whether depression is an unique entity varying along a continuum of severity or whether discrete subgroups exist, the preponderance of evidence favours the existence of at least one well-defined syndrome, endogenous depression (Kendell, 1976). Although the analysis of clinical data has been fruitful in helping to produce typologies, the usefulness of this approach is limited and has produced mixed results. For example, endogenous depressive patients, according to the Newcastle scale (Carney et al., 1965), showed lower electrodermal activity than neurotic depressive patients (Byrne, 1975; Noble and Lader, 1972; Mirkin and Coppen, 1980; Chapter 5). On the other hand, differences in electrodermal activity between endogenous and non-endogenous depressive patients according to the Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), were not confirmed (Ward et al., 1983). However, the electrodermal activity has repeatedly been reported to be lower in the presence of psychomotor retardation in depressive patients (Lader and Wing, 1969; Noble and Lader, 1971; Dawson et al., 1977; Lapierre and Butter, 1980; Williams et al., 1985). Associations found between agitation and high electrodermal activity (Lader and Wing, 1969) were not confirmed in a later study (Dawson et al., 1977).

Family history of psychiatric illness, and course of illness, do not seem to bear any relationship to electrodermal activity (Lader and Wing, 1969; Ward et al., 1983; Thorrell et al., 1987). Patients with recurrent depression have shown lower tonic electrodermal activity than non-recurrent (Ward et al., 1983). Age at the first depression and duration of the present one, up to the time of investigation, were negatively related to low skin conductance response magnitude
while the number of previous depressions was not correlated with any of the electrodermal variables (Ward et al., 1983; Thorrell et al., 1987). However, very little is known about the significance of these factors for the electrodermal activity in depressive patients.

On the whole, the relationship of abnormal electrodermal activity to diagnostic symptoms of depressive patients is insufficiently known. What none of the previous studies taken into consideration is the extent to which the diagnostic symptoms are likely to explain the relationship of skin conductance to the classification systems. No study has so far investigated the clinical profiles of patients with abnormal skin conductance in depression. The present study therefore aimed to identify the clinical picture present in patients with abnormal skin conductance in depression.

METHOD

Details of the selection of patients and the procedure of the study are fully described in the preceding chapter (Chapter 5). Of the 61 patients studied in Chapter 5, 41 (68%) were identified as showing abnormal electrodermal activity were compared with those patients who did not show any abnormality in their electrodermal activity on a number of psychiatric scales. In differentiating patients into "abnormal" and "non-abnormal" groups, according to the results of skin conductance, the "abnormal" group was defined either as having a response higher or lower than the mean skin conductance
responses for the normal controls. The clinical features of the abnormal and non-abnormal groups are shown in Table 6.2.

Clinical Assessment

Clinical data included the Hamilton Rating Scale (Hamilton, 1967), the Newcastle Diagnostic Index (Carney et al., 1965), and the PSE (Wing et al., 1974). All of these scale are described fully in Chapter 5.

Family History and Course of Illness

Information was collected on family history of depressive episodes and other psychiatric illness, number of prior depressions, age at first depression, type of onset of current depression, and duration of current depression before the investigation. Close attention was paid to the course of illness, past history and family history.

Statistical Analysis

The patients were grouped according to the results of the skin conductance, and the mean levels of a number of psychiatric rating scales were compared in these groups using one-way analysis of variance. The associations between skin conductance variables,
clinical features, and psychiatric rating scales were examined using Pearson product-moment correlations. The associations between patients grouped according to the results of the skin conductance and the common diagnostic classifications were examined using chi-squared tests. The clinical features and scores on psychiatric rating scales of patients were compared, using one-way analysis of variance for continuous variables and chi-squared tests for categorical variables. A step-wise discriminant function analysis was carried out in an attempt to identify the clinical features which in combination could best identify patients with skin conductance abnormality.

RESULTS

Relationship between skin conductance and diagnostic categories

Patients were classified using a number of commonly used classificatory systems for depression. The proportion of patients with abnormal electrodermal activity in each category is shown in Table 6.1. When the patients were classified into major and minor depressive disorder by means of The RDC there was no difference in the incidence of abnormal and non-abnormal electrodermal activity. The proportion of patients with abnormal responses was similar in patients classified as endogenous and those classified as neurotic by the Newcastle Diagnostic Index. The PSE classes did not distinguished between patients with abnormal and non-abnormal responses, although in the
Table 6.1. Patients with abnormal skin conductance in various diagnostic sub-divisions of depression.

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>Patients with abnormal response</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>(%)</td>
</tr>
<tr>
<td>Research Diagnostic Criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>50</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Minor depressive disorder</td>
<td>13</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>Newcastle Diagnostic Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous</td>
<td>29</td>
<td>22 (53.6)</td>
</tr>
<tr>
<td>Neurotic</td>
<td>32</td>
<td>19 (51.2)</td>
</tr>
<tr>
<td>PSE classes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive psychosis</td>
<td>6</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Retarded depression</td>
<td>30</td>
<td>23 (56.1)</td>
</tr>
<tr>
<td>Neurotic depression</td>
<td>25</td>
<td>13 (52)</td>
</tr>
</tbody>
</table>
Table 6.2. Clinical features and scores on psychiatric rating scales of patients with abnormal and non-abnormal skin conductance. (Means, with standard deviations in parenthesis)

<table>
<thead>
<tr>
<th></th>
<th>Abnormal (N = 41)</th>
<th>Non-abnormal (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.3 (14.1)</td>
<td>39.6 (13.4)</td>
</tr>
<tr>
<td>Family history of depression (%)</td>
<td>43.1</td>
<td>32.5</td>
</tr>
<tr>
<td>Age at onset of first episode</td>
<td>33.5 (16.5)</td>
<td>32.4 (14.6)</td>
</tr>
<tr>
<td>Number of previous depressions</td>
<td>1.2 (1.7)</td>
<td>0.5 (0.9)</td>
</tr>
<tr>
<td>Duration of current depression (months)</td>
<td>8.4 (5.1)</td>
<td>7.4 (6.4)</td>
</tr>
<tr>
<td>Newcastle score</td>
<td>5.8 (2.6)</td>
<td>5.3 (2.4)</td>
</tr>
<tr>
<td>Hamilton score</td>
<td>21.8 (8.5)</td>
<td>19.2 (5.6)</td>
</tr>
<tr>
<td>PSE score (total)</td>
<td>29.3 (11.8)</td>
<td>24.4 (8.4)</td>
</tr>
<tr>
<td>PSE syndrome score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slowness (SL)</td>
<td>1.72 (2.1)</td>
<td>0.55 (1.1)</td>
</tr>
<tr>
<td>General Anxiety (GA)</td>
<td>1.97 (1.46)</td>
<td>1.25 (1.24)</td>
</tr>
<tr>
<td>ED</td>
<td>1.24 (1.2)</td>
<td>1.05 (0.95)</td>
</tr>
</tbody>
</table>
small group of patients classed as depressive psychosis 5 out of 6 patients had abnormal electrodermal activity.

Clinical features associated with abnormal skin conductance

The clinical features associated with patients with abnormal and non-abnormal skin conductance were examined. The clinical features and the mean scores of a number of psychiatric rating scales for abnormal and non-abnormal groups are shown in Table 6.2. There was no significant age difference between the two groups, although the patients with abnormal responses tended to be older.

The PSE syndrome score which significantly differentiated between abnormal and non-abnormal groups was slowness (SL) (F=8.24; df=1,59; P<0.01), the PSE measure of retardation. The difference in score for General Anxiety (GA), which combines free-floating anxiety, panic attacks and observed anxiety, approached significance (F=5.16; df=1,59; P<0.05). The scores on other PSE syndromes, including special features of depression (ED), consisting of guilt, loss of affect, dulled perception, did not differ between the groups (F=0.28; df=1,59; NS). The Hamilton score was not significantly different between the two groups either.

In order to determine which of the above features were most important in identifying a patient as abnormal in terms of skin conductance, a step-wise discriminant function analysis was performed. In addition to the PSE syndrome scores, the total PSE score, Hamilton
<table>
<thead>
<tr>
<th>Feature</th>
<th>CD10</th>
<th>CD05</th>
<th>CD02</th>
<th>CD01</th>
<th>CD00</th>
<th>CD09</th>
<th>CD08</th>
<th>CD07</th>
<th>CD06</th>
<th>CD05</th>
<th>CD04</th>
<th>CD03</th>
<th>CD02</th>
<th>CD01</th>
<th>CD00</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Anxiety</td>
<td>0.13</td>
<td>0.12</td>
<td>0.11</td>
<td>0.10</td>
<td>0.09</td>
<td>0.08</td>
<td>0.07</td>
<td>0.06</td>
<td>0.05</td>
<td>0.04</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.07</td>
<td>0.07</td>
<td>0.08</td>
<td>0.09</td>
<td>0.10</td>
<td>0.11</td>
<td>0.12</td>
<td>0.13</td>
<td>0.14</td>
<td>0.15</td>
<td>0.16</td>
<td>0.17</td>
<td>0.18</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>PSD (total score)</td>
<td>0.40</td>
<td>0.41</td>
<td>0.42</td>
<td>0.43</td>
<td>0.44</td>
<td>0.45</td>
<td>0.46</td>
<td>0.47</td>
<td>0.48</td>
<td>0.49</td>
<td>0.50</td>
<td>0.51</td>
<td>0.52</td>
<td>0.53</td>
<td>0.54</td>
</tr>
<tr>
<td>Hamilton score</td>
<td>0.60</td>
<td>0.61</td>
<td>0.62</td>
<td>0.63</td>
<td>0.64</td>
<td>0.65</td>
<td>0.66</td>
<td>0.67</td>
<td>0.68</td>
<td>0.69</td>
<td>0.70</td>
<td>0.71</td>
<td>0.72</td>
<td>0.73</td>
<td>0.74</td>
</tr>
<tr>
<td>Duration of current depression</td>
<td>0.80</td>
<td>0.81</td>
<td>0.82</td>
<td>0.83</td>
<td>0.84</td>
<td>0.85</td>
<td>0.86</td>
<td>0.87</td>
<td>0.88</td>
<td>0.89</td>
<td>0.90</td>
<td>0.91</td>
<td>0.92</td>
<td>0.93</td>
<td>0.94</td>
</tr>
<tr>
<td>Number of previous depressions</td>
<td>0.95</td>
<td>0.96</td>
<td>0.97</td>
<td>0.98</td>
<td>0.99</td>
<td>1.00</td>
<td>1.01</td>
<td>1.02</td>
<td>1.03</td>
<td>1.04</td>
<td>1.05</td>
<td>1.06</td>
<td>1.07</td>
<td>1.08</td>
<td>1.09</td>
</tr>
<tr>
<td>Age at onset of first episode</td>
<td>1.10</td>
<td>1.11</td>
<td>1.12</td>
<td>1.13</td>
<td>1.14</td>
<td>1.15</td>
<td>1.16</td>
<td>1.17</td>
<td>1.18</td>
<td>1.19</td>
<td>1.20</td>
<td>1.21</td>
<td>1.22</td>
<td>1.23</td>
<td>1.24</td>
</tr>
<tr>
<td>Family history of depression</td>
<td>1.25</td>
<td>1.26</td>
<td>1.27</td>
<td>1.28</td>
<td>1.29</td>
<td>1.30</td>
<td>1.31</td>
<td>1.32</td>
<td>1.33</td>
<td>1.34</td>
<td>1.35</td>
<td>1.36</td>
<td>1.37</td>
<td>1.38</td>
<td>1.39</td>
</tr>
<tr>
<td>Age</td>
<td>1.40</td>
<td>1.41</td>
<td>1.42</td>
<td>1.43</td>
<td>1.44</td>
<td>1.45</td>
<td>1.46</td>
<td>1.47</td>
<td>1.48</td>
<td>1.49</td>
<td>1.50</td>
<td>1.51</td>
<td>1.52</td>
<td>1.53</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Table 6.3: Correlations of clinical features and psychiatric rating scales with skin conductance
score, Newcastle score, and age were included in this analysis. Only the PSE syndromes of general anxiety and slowness were selected by the procedure to be entered into the discriminant function. A jackknifed classification was performed. Slowness was entered first and correctly classified 69% of the patients. The entry of GA into the discriminant function improved the number of patients by 6. The function based on values of slowness and General Anxiety was able to classify 71% of patients with abnormal skin conductance (see Table 6.4).

Differences in family history of depression were not reflected in abnormal skin conductance. Age at onset of the first depression (r=-0.27, P<0.05) and duration of the present one (r=-0.29, P<0.02) were significantly negatively related to low skin conductance levels while the number of previous depressions was not correlated with any of the skin conductance variables (Table 6.3). Recurrence of depression and type of onset of depression showed no significant relationship to electrodermal activity. There was no significant relationship between PSE and Hamilton scores with any skin conductance variables (Table 6.3). However, a significant negative correlation emerged between the PSE measure of retardation (slowness) and skin conductance levels (r=-0.28, P<0.05).

Table 6.4. Classification rate of patients with abnormal skin conductance. (N=41)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cases correctly classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowness</td>
<td>28</td>
</tr>
<tr>
<td>General Anxiety</td>
<td>34</td>
</tr>
<tr>
<td>GA + SL</td>
<td>29</td>
</tr>
</tbody>
</table>
D I S C U S S I O N

Differences in the clinical profiles of depressed patients with abnormal and non-abnormal skin conductance were examined on a number of psychiatric rating scales in order to identify the clinical picture present in patients with abnormal skin conductance. There was no significant difference between the patients with abnormal responses in various diagnostic sub-divisions of depression. In spite of this, some interesting results emerge which suggest that the study merits replication. Of this population of 41 patients with abnormal skin conductance, 56% were classified into major and 84% into minor depressive disorders according to the RDC. Over 50% of patients with endogenous features of depression tended to show abnormalities in their skin conductance. The retarded group on the PSE classification contained a similar proportion. However, 52% of patients classed as neurotic depression by the PSE and 51% of patients classified as neurotic by the Newcastle scale were also found to show abnormalities in their skin conductance.

Since the present study is the first available one investigating electrodermal activity in various diagnostic sub-groups of depression, no comparison can be made to other results. However, attempts to classify patients as endogenous or neurotic have produced conflicting results especially with regard to the presence or absence of skin conductance abnormality. Some studies have found that skin conductance was effective in distinguishing endogenous from non-endogenous depression (e.g. Lader and Wing, 1969; Noble and Lader, 1972; Mirkin
and Coppen, 1980; Williams et al., 1985); however, this finding was not confirm in other studies (e.g. Dawson et al., 1977; Lapierre and Butter, 1980; Ward et al., 1983).

Patients selection may be an exlanation for the discrepancies found in different studies. In the present study it emerged that 5 out of 6 patients with psychotic symptomatology were abnormal in terms of electrodermal activity, a similar proportion to that reported by Williams et al. (1985). The presence of a large number of psychotic patients in a population under investigation could result in a greater association between endogenous depression and skin conductance abnormality than would occur in studies such as those of Lader and Wing (1969) which was performed on an out-patient population.

The effects of medication on patients' symptomatology must also be taken into account in view of the fact that many studies include patient on tricyclic antidepressants or tranquillizers. Depressed patients treated with psychotropic drugs may experience relief from anxiety before other symptoms of depression are alleviated. Such patients would then be more likely to be classified as having endogenous depression on the Newcastle Scale (because of the negative loading for anxiety) than if they had remained drug-free. Because some of these patients would show skin conductance abnormalities (as shown in the present study), this could produce a bias towards an association between abnormal skin conductance and endogenous depression. It is possible that the present study would have demonstrated a stronger association between anxiety and skin conductance abnormality in depression if the 13 patients taking
benzodiazepines at night had received placebos instead.

Other clinical data confirm previous (Lader and Wing, 1969; Ward et al., 1983; Thorell et al., 1987) negative findings in depressive patients with respect to family history of affective and other psychiatric disorders and skin conductance.

Ward et al. (1983) found significantly lower skin conductance levels in patients with recurrent than in non-recurrent depressive patients. An obvious difficulty in classifying patients as recurrent or not, is that it is impossible to know if a patient who experiences his first or second depression will relapse in the future. Applying the criterion of three or more prior depression, 18 patients were judged to be recurrent, and, consequently, the rest, 23 patients, could not be definitely classified. Thus, the present study was not able to offer new evidence in this matter. The number of previous depressions were also unrelated to abnormal skin conductance.

These results, taken in conjunction with those of previous studies, suggest that skin conductance abnormality is not restricted to any particular depressive syndrome. This suggests that the abnormality may be due to non-specific processes occurring in depressed patients, more commonly in those patients with endogenous symptomatology. Such processes may also occur in other conditions, as skin conductance abnormality has been reported in some patients with schizophrenia (Toone et al., 1981; Frith et al., 1982) and anorexia nervosa (Calloway et al., 1983).
However, as retardation and anxiety appeared to be independent factors discriminating abnormals from non-abnormals (as demonstrated in the present study), it is possible to speculate that there were two separate sub-groups of patients with skin conductance abnormality: a predominantly anxious group, somewhat younger in age, with earlier age of onset; and a predominantly retarded group, with later age of onset. It is possible that these differences between the two groups merely reflect a tendency for younger depressed patients to present with anxiety, while older patients present with retardation. However, the fact that later age of onset of first episode rather than older present age was associated with retardation (as reflected in low skin conductance level) is consistent with this, and suggests that there may be two sub-groups of patients with skin conductance abnormalities or, more likely two processes accounting for the abnormality within any group of patients.

The two processes might represent quite different patterns of autonomic nervous system dysfunction producing retardation and agitation of autonomic activity. The possibility that depressed patients who show abnormalities in their skin conductance have different underlying autonomic abnormalities has important implications for future research into aetiology and treatment.

The results of this study call into question the use of electrodermal activity to identify any particular depressive syndrome as the abnormality occurred across the currently used diagnostic categories. These results suggest that there might be at least two different mechanisms, not necessarily mutually exclusive, accounting
for abnormal electrodermal activity in depressed patients.
ABNORMAL SKIN CONDUCTANCE IN DEPRESSION:

ENDOCRINE CORRELATES

INTRODUCTION

As the review in Chapter 3 indicated, changes in physiological responses are associated with fluctuations in levels of plasma cortisol (Fredrikson et al., 1985). With the advent of radioimmunassay (RIA) and related techniques, reliable measurements of hormones in small samples have become practical, and endocrine research on the mechanisms of stress response has, in turn, been stimulated (Mason, 1975). Although many physiological variables are known to respond to psychological stimuli, the principles that organise these responses have remained elusive. One view is that subjective, behavioural and physiological arousal are tightly linked. The electrodermal abnormalities reported in previous chapters associated with depression are however unlikely to be the direct consequence of psychological changes. A more probable explanation would involve endocrine changes, which are known to be sensitive to psychosocial events, may account for the electrodermal abnormalities associated with depression. An
alternative view may however be that endocrine changes related to
depression occur independently from other autonomic markers of the
disorder. The present study was designed to clarify this issue.

There are good reasons for supposing that electrodermal and
endocrine correlates of depression represent manifestations of the
same underlying pathophysiological process. Hyperactivity of the
hypothalamo-pituitary-adrenal cortical (HPA) axis, as reflected by
increased circulating cortisol concentrations, increased urine free
cortisol excretion, and cortisol resistance to dexamethasone
suppression, has been noted in a few as 25% to as many as 75% of
patients with major depressive disorders (Carroll et al., 1981; Joyce
et al., 1986; Rubin et al., 1987; Meller et al., 1988). In many of
these investigations, post-dexamethasone cortisol levels may represent
the only indication of HPA axis abnormality. Even in investigations of
single specific biologic markers, the dexamethasone suppression test
status of experimental subjects is often included as an indicator of
HPA axis function (Meller et al., 1987; Lopez et al., 1987).

The occurrence of adrenocortical hyperactivity as determined by
increased plasma cortisol concentrations and urinary cortisol
excretion has been linked to autonomic activation indexed by slowly
recovering electrodermal responses (Klorman et al., 1977; Fredrikson
et al., 1985) as well as slow rate of electrodermal habituation
(Wyatt et al., 1971; Fredrikson et al., 1985; Dimberg et al., 1986).
HPA abnormalities in depression therefore could be an explanation for
electrodermal abnormalities observed in patients with major depressive
disorders.
Furthermore, numerous reports have documented the presence of abnormalities of the hypothalamo-pituitary-thyroid axis in a proportion of depressed patients (e.g. Loosen and Prange, 1982; Joyce et al., 1986; Peselow et al., 1987). Both elevated and reduced levels of thyroid hormone have been found. Across several studies (Kierkegaard et al., 1978; Rieneris et al., 1978) between 25 and 70% of depressed patients have been shown to have blunted thyroid stimulating hormone (TSH) response to thyrotropin releasing hormone (TRH) (Loosen and Prange, 1982). Some patients were found to have augmented TSH responses to TRH (Targum et al., 1981). The significance of the blunting and augmentation is as yet unclear, but in some patients they may reflect increases and decreases in thyroid hormone output (Peselow et al., 1987; Rubin et al., 1987).

Sweating occurs in hyperthyroidism (Hoffenberg, 1983) and conversely reduction in electrodermal activity may be associated with reduced thyroxine release. Abnormalities of the hypothalamo-pituitary-thyroid axis observed in depression may therefore be an explanation for skin conductance abnormalities observed in some of these patients. The present study aimed to examine possible explanations for skin conductance abnormalities observed in depression by assessing both thyroid function and post-dexamethasone plasma cortisol concentration in a group of drug-free patients with major depressive disorder. Both univariate and multivariate statistical procedures were employed to examine the degree of relationship between the skin conductance variables and thyroid and adreno-cortical hormones.
Patients

Details concerning patient selection are described in detail in Chapter 5. Sixty-one patients with primary depression studied in the experiment presented in the previous chapter were used. They were 37 women and 24 men with an age range of 19 to 68 years and a mean age of 41.6 years (SD=13.7). All patients were drug-free for 7 days or more (apart from night sedation with benzodiazepines).

Procedure

A three-day acclimatization period was allowed for in-patients before endocrine tests were performed, during which time the clinical interviews took place. In patients with extreme retardation the full interview was delayed until some clinical improvement had taken place. On day 1 a 24-hour urine collection was taken from 11 p.m. to 11 p.m. the next day (day 2), when 1 mg of dexamethasone was given orally at 11 p.m., and a second 24-hour urine collection started. Blood was taken for plasma cortisols at 4 p.m. on day 3. The first 24-hour urine was used to give the baseline cortisol production. The second 24-hour urine provided information on post-dexamethasone urinary-free cortisol output which has been shown to be a good discriminator of depressed from non-depressed patients (Carroll et al., 1981). A TRH-
test was performed on day 4 or 5. Skin conductance was measured whilst patients were seated comfortably in a reclining in a sound-attenuated room at least 3 days after the initial interview.

**Skin Conductance**

Skin conductance was monitored as described fully in Chapter 5. Skin conductance orienting responses to a series of auditory stimuli were recorded. Skin conductance levels (SCL), habituation rate (HABIT), number of spontaneous fluctuations (SPONT), response latencies (LAT), rise times (RISET) and recovery times (RECT) were calculated.

**Hormone Assays**

The TRH test was performed 4 or 5 days following patients' initial interview. An intravenous butterfly needle was inserted at around 8.15 a.m. following an overnight fast and an initial blood sample was taken 15 minutes after insertion. A baseline blood sample was taken half an hour later and 400 mg TRH (Roche) was infused over a one-minute period. Further blood samples were taken at 20 and 60 minutes after TRH administration. The test failed on 4 patients because of problems with the intravenous line. Serum thyroxine (T4) and triiodothyronine (T3) were measured in the baseline sample by Radioimmunoassay using the RIA-UK kit. The free thyroxine index (FTI) was calculated by multiplying T4 and T3 and dividing by 100. TSH was
measured in duplicate by double-antibody RIA technique using Amerlex TSH RIA kit. The inter-assay coefficient of variation was 3.2%.

Cortisol in plasma and urine were measured in duplicate using a double-antibody RIA method (Amerlex Cortisol RIA kit). The coefficient of variation for repeated assays was 4.4%. The normal range for 24-hour urinary-free cortisols using this method is 35-120 ug/24 hours, although the upper range for this laboratory is taken as 130 ug/24 hours.

Statistical Analysis

Univariate and multivariate correlational analyses were conducted on the combined set of skin conductance and thyroid hormones. Univariate Pearson product-moment correlation coefficients were obtained. Canonical correlational analysis was then conducted to determine the maximum correlations between the set of skin conductance variables and the set of thyroid and adreno-cortical hormone indicators.

In presenting the findings of this analysis I have chosen to focus on two aspects of the canonical analysis. First, the structure coefficients were examined to gain an appreciation of the dimensions. Under circumstances in which a simple causal ordering is inappropriate, the structure coefficients provide a means of coping with the multicollinearity problem. That is, the focus of the analysis is removed from the necessarily unstable (in the sense of "bouncing
beats") canonical weights which reflect the unique or partial relationships. Instead, the analysis proceeds by describing the dimensions in terms of those variables which best describe them. Thus the variables, instead of competing with each other for a share of the "accounted for" variance, are employed descriptively by the magnitude of their association with the major predictive dimensions. A step-wise discriminant function analysis was carried out in an attempt to identify the patients with abnormalities on the TRH and dexamethasone tests.

RESULTS

Results of endocrine variables

Baseline T4, T3 uptake, FTI and results from the TRH-test were obtained from all 61 patients. The mean T4 level of the patients was 11.9 n mol/l (SD=10.9, range 16.0-76.6). Sixteen (26.2%) patients had FTI levels above the upper limit of 45 n mol/l (Kirsten et al., 1981). The mean maximum response of TSH to TRH was 10.0 u U/ml (SD=10.5, range 0.5-71.0).

Plasma cortisols were estimated on all 61 patients. The mean predexamethasone 24-hour urinary-free cortisol was 158.6 ug/24 hours (SD=77.8, range 33-378). Thirty-eight of the patients (62.2%) had a 24-hour secretion above the normal range (25-130 ug/24 hours). The
mean post-dexamethasone 24-hour urinary-free cortisol was 65.4 ug/24 hours (SD=56.3, range 6-232). The mean 4 p.m. plasma cortisol was 6.2 ug/dl (SD=7.0, range 0.5-35.0).

Seventeen patients had both an abnormal dexamethasone suppression test response and blunting of the TSH response; 14 had a blunted TSH response with a normal dexamethasone suppression test; 12 had an abnormal dexamethasone suppression test with normal TSH response; and 18 patients (29.5%) had normal responses on both tests. Thus, 70.5% of patients had one or both abnormalities. There was no association between the two abnormalities, and the presence of either abnormality was not associated with any particular diagnostic group. However, 5 of 6 patients with psychotic depression had both abnormalities.

Relationship between skin conductance and thyroid activity

The results of the skin conductance and thyroid hormones are both shown in Table 7.1. Product-moment correlation coefficients were computed between all thyroid and all skin conductance variables shown in Table 7.1 and the coefficients obtained are presented in Table 7.2. As this table illustrates, there were modest but significant correlations between measures of thyroid functioning and electrodermal activity.

There was a significant correlation between basal levels of thyroid hormone and skin conductance levels. Indices of TSH response to TRH (max TSH and log area under the response curve) did not correlate with basal skin conductance level but did correlate with
recovery time following a response. Increased basal TSH levels were negatively correlated with the number of spontaneous fluctuations. Other indices yielded insignificant correlations although there was a trend for TSH responses also to correlate with rise time. Examination of scatter plots revealed that the significant associations represented genuine linear relationships rather than associations attributable largely to the presence of outliers.

A canonical correlation analysis was performed between the skin conductance and endocrine sets of variables. With all five canonical correlations included, Chi-squared = 44.45, df = 30, P < 0.05. With the first canonical variate pair removed, Chi-squared was not significant: Chi-squared = 18.02, df = 20, NS. Therefore, the first canonical correlation accounts for the significant linkage between the two sets of variables.

The canonical correlation was 0.49, representing 24% overlapping variance between the pair of canonical variates. Analyses of the pair of canonical variates that accompany the canonical correlations appear in Table 7.3. Shown in the table are correlations between the variables and the canonical variates, standardized canonical variate coefficients, within-set variance accounted for by the canonical variates (percent of variance), redundancies, and canonical correlation and eigenvalue. The percent of variance and redundancy indicate the canonical analysis is more efficient for the second set of variables.
Table 7.1. Skin conductance and thyroid hormone measurements of depressed patients (N=61, there were 4 skin conductance non-responders in this group).

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin conductance</td>
<td></td>
</tr>
<tr>
<td>LAT (secs.)</td>
<td>2.28 (0.62)</td>
</tr>
<tr>
<td>RISET (secs.)</td>
<td>2.41 (1.26)</td>
</tr>
<tr>
<td>RECT (secs.)</td>
<td>3.53 (1.31)</td>
</tr>
<tr>
<td>HABIT</td>
<td>7.05 (5.12)</td>
</tr>
<tr>
<td>SCL (log microsiemens)</td>
<td>0.79 (0.30)</td>
</tr>
<tr>
<td>SPONT (no/min.)</td>
<td>8.40 (12.17)</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td></td>
</tr>
<tr>
<td>T4 levels (nmol/L)</td>
<td>11.92 (3.77)</td>
</tr>
<tr>
<td>FTI (nmol/L)</td>
<td>38.98 (11.25)</td>
</tr>
<tr>
<td>Basal TSH (μU/ml)</td>
<td>2.39 (3.01)</td>
</tr>
<tr>
<td>Max TSH (μU/ml)</td>
<td>10.24 (10.89)</td>
</tr>
<tr>
<td>Log area</td>
<td>1.64 (0.33)</td>
</tr>
</tbody>
</table>
Table 7.2. Product-moment correlation coefficients between skin conductance measures and thyroid function test scores in depressed patients (Number of subjects in parenthesis).

<table>
<thead>
<tr>
<th></th>
<th>T4</th>
<th>FTI</th>
<th>Basal TSH</th>
<th>Max TSH</th>
<th>Log area</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAT</td>
<td>-0.07(46)</td>
<td>-0.16(46)</td>
<td>0.17(47)</td>
<td>0.19(47)</td>
<td>0.23(47)</td>
</tr>
<tr>
<td>RISET</td>
<td>-0.07(46)</td>
<td>-0.17(46)</td>
<td>0.07(47)</td>
<td>0.23(47)</td>
<td>0.28(47)*</td>
</tr>
<tr>
<td>RECT</td>
<td>-0.13(40)</td>
<td>-0.22(41)</td>
<td>0.21(41)</td>
<td>0.40(41)**</td>
<td>0.31(41)*</td>
</tr>
<tr>
<td>HABIT</td>
<td>0.10(60)</td>
<td>0.16(60)</td>
<td>-0.21(61)</td>
<td>-0.09(61)</td>
<td>-0.09(61)</td>
</tr>
<tr>
<td>SCL</td>
<td>0.33(55)**</td>
<td>0.29(55)*</td>
<td>0.24(55)</td>
<td>-0.07(55)</td>
<td>-0.08(55)</td>
</tr>
<tr>
<td>SPONT</td>
<td>0.08(60)</td>
<td>0.15(60)</td>
<td>-0.27(61)*</td>
<td>-0.12(61)</td>
<td>-0.12(61)</td>
</tr>
</tbody>
</table>

* P < 0.05    ** P < 0.01  Two-Tailed
Table 7.3. Canonical correlation between the endocrine and skin conductance sets of variables (N=61).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Canonical variate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>Coefficient</td>
<td></td>
</tr>
<tr>
<td>Endocrine set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max TSH</td>
<td>0.82</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Log area</td>
<td>0.63</td>
<td>-0.93</td>
<td></td>
</tr>
<tr>
<td>FTI</td>
<td>-0.16</td>
<td>-0.22</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>0.11</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Basal TSH</td>
<td>-0.02</td>
<td>-0.03</td>
<td></td>
</tr>
<tr>
<td>% of variance</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redundancy</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin conductance set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECT</td>
<td>0.86</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>RISET</td>
<td>0.58</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>SPONT</td>
<td>-0.41</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>HABIT</td>
<td>-0.39</td>
<td>-0.30</td>
<td></td>
</tr>
<tr>
<td>LAT</td>
<td>0.36</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>SCL</td>
<td>0.35</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>% of variance</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redundancy</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canonical correlation</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eigenvalue</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7.4. Skin conductance of patients with normal (N=33) and abnormal (N=28) post-dexamethasone responses

<table>
<thead>
<tr>
<th>Skin conductance</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAT</td>
<td>1.90 (0.89)</td>
<td>2.28 (0.98)</td>
<td>t=2.15, p &lt; 0.05</td>
</tr>
<tr>
<td>RISET</td>
<td>1.66 (0.66)</td>
<td>2.41 (1.26)</td>
<td>t=3.89, p &lt; 0.001</td>
</tr>
<tr>
<td>HRECT</td>
<td>2.68 (1.20)</td>
<td>3.53 (1.31)</td>
<td>t=2.54, p &lt; 0.02</td>
</tr>
<tr>
<td>HAB</td>
<td>8.07 (4.51)</td>
<td>7.88 (4.47)</td>
<td>t=-0.92, NS</td>
</tr>
<tr>
<td>SCL</td>
<td>0.83 (0.22)</td>
<td>0.79 (0.30)</td>
<td>t=1.80, NS</td>
</tr>
<tr>
<td>SPONT</td>
<td>4.78 (4.18)</td>
<td>8.46 (12.17)</td>
<td>t=2.57, p &lt; 0.02</td>
</tr>
</tbody>
</table>
With a cut-off correlation of 0.4 for interpretation, the variables relevant to the first canonical variate in the endocrine set were, in order of magnitude, max. TSH and log area under response curve. Among the skin conductance variables, RECT, RISET, and SPONT were relevant to the canonical variate. Taken as a pair, the canonical variates indicate that patients with higher levels of TSH response to TRH (Max TSH = 0.82 and log area = 0.63) also tend to have a longer recovery time (0.86) and faster rise time (0.58) following a response, but a relatively lower number of spontaneous fluctuations in their skin conductance (-0.41).

In order to determine whether those patients identified as having abnormal skin conductance in Chapter 5 had thyroid function abnormalities, a step-wise discriminant function analysis was performed. All the thyroid hormones variables included in this analysis. Only two variables, max TSH and FTI, were selected by the procedure to be entered into the discriminant function. A jackknifed classification was performed. TSH was entered first and correctly classified 47.9% of the patients. The entry of FTI into the discriminant function did not improve the number of patients correctly classified. However, there was a highly significant correlation between the TSH response and FTI ($r=-0.33$, $P<0.001$).

Relationship between skin conductance and plasma cortisol

The patients were grouped according to the results of the post-dexamethasone plasma cortisol levels, and the mean levels of a number
of skin conductance variables were compared in these groups using Student's t-test. The mean plasma cortisol was 6.2 ug/dl (SD = 7.0). Using the 50 ng/ml cut-off point for a post-dexamethasone cortisol level (Carroll et al., 1981), 28 (45.7%) were classified as having abnormal responses and 33 (54.3%) had normal responses. Table 7.4 shows the mean values for the two groups.

As Table 7.4 illustrates, latency, rise-time, recovery-time and the number of spontaneous fluctuations in the skin conductance turned out to differentiate significantly between the two groups. Both the average latency and rise-time following a response were significantly greater for the patients with abnormal post-dexamethasone cortisol level (t=2.15, df=59, P<0.05 and t=3.89, df=59, P<0.001 respectively). The average recovery-time following a response in the abnormal group was significantly longer than that in the normal group (t=2.54, df=59, P<0.02). The average number of spontaneous fluctuations in the patients with abnormal post-dexamethasone cortisol responses was significantly above that of the patients with normal responses (t=2.57, df=59, P<0.02). There were no significant differences between the two groups on the average number of trials to habituation and the basal skin conductance levels.

In order to determine which of the skin conductance variables were most important in identifying a patient as either a 'abnormal' or a 'non-abnormal', a step-wise discriminant function analysis was performed. All the variables were included in this analysis. Two variables — recovery time and the number of spontaneous fluctuations were selected by the procedure to be entered into the discriminant
function. Using a jackknifed classification procedure, the discriminant function was able to identify 62.9% of the patients with abnormal responses on the dexamethasone test.

DISCUSSION

The present study produced some evidence in support of the view that abnormalities of thyroid activity may be responsible for previously observed abnormalities in electrodermal activity in depressed patients. The significant correlations between thyroxine level, free thyroxine index and skin conductance level indicate that reduction in thyroid activity is associated with the reduced tonic skin conductance that has been reported in the literature (e.g. Storrie et al., 1981; Iacono et al., 1983). Likewise, in some patients there may be increased tonic skin conductance associated with increased thyroid activity. The association was only slightly reduced for FTI compared with T4 indicating that the relationship holds even when thyroid level is adjusted for differences in thyroid binding proteins. The TRH test results correlated better with measures of the orienting response rather than basal skin conductance levels, patients with greater responses to TRH showing a significantly longer recovery time and somewhat slower rise times. This indicates that subjects with augmented responses (who may be subclinically hypothyroid) show slow recovery whereas subjects with blunted responses (who generally had raised levels of thyroid hormones) manifested faster recovery rates.
These results are consistent with a direct relationship between skin conductance levels and thyroid hormone levels. Although it is unlikely that these hormones directly affect the sympathetic nervous system activity, there may be a number of related mechanisms to explain the association that have been observed in this study. Williams (1981) suggested that thyroid hormones might have effects separate from but similar and additive to those of the catecholamines (Levey, 1976) or might enhance tissue sensitivity to circulating catecholamines (Landsberg, 1977).

It was found that about a quarter of the total group of patients had elevated levels of circulating thyroid hormone; a number of these patients, although not clinically hyperthyroid, had levels which were clearly in the hyperthyroid range. Some studies have suggested that stress, especially if prolonged, leads to increased output of thyroid hormones (Mason, 1975). It is possible that, in some depressed patients, elevated levels of thyroid hormones may be part of a stress response, producing a sub-clinical hyperthyroid state. The present finding that patients with increased TSH response to TRH had longer recovery rates and higher rise time in their responses would support this. Moreover, the finding of an inverse relationship between the number of spontaneous fluctuations and TSH response to TRH suggests that abnormalities of spontaneous electrodermal activity in depression may be due to increased output of thyroid hormones with negative feedback operating at the level of the thyroid gland.

However, not all patients with abnormal electrodermal responses had higher FTI scores. An alternative mechanism such as pituitary
gland dysfunction, with failure of normal TSH stimulation by TRH, may be responsible for the observed abnormality in these patients. The two processes would not necessarily be mutually exclusive. Six of the patients, all women, showed increased spontaneous electrodermal responses. These patients had lower levels of circulating thyroid hormones, with lower FTI values, than patients with normal responses on the TRH test. They did not, however, have elevated basal TSH values. It may be that there is a sub-group of depressed patients, usually women, who are mildly hypothyroid. It is of interest that, whereas most studies find relatively high levels of thyroid hormones during depression, one of the few studies to show that depressed patients had lower mean levels of thyroid hormone was that of Rieneris et al. (1978), in which all the patients were women. It is possible that there may be a sub-clinically hypothyroid group of female patients with low thyroid levels, normal basal TSH levels but increased spontaneous electrodermal activity.

The results of post-dexamethasone cortisol level point to the wide incidence of HPA axis abnormalities among depressive patients at least in terms of some of the skin conductance variables. There were increases in latency, rise time, recovery time and the number of spontaneous fluctuations in patients with abnormal post-dexamethasone responses. Similarly, hyperactivity of HPA axis as reflected in high plasma cortisol levels has been related to slowly recovering rate in skin conductance responses (Klorman et al., 1977; Fredrikson et al., 1985). Furthermore, an association between abnormal post-dexamethasone cortisol responses and the number of spontaneous skin conductance fluctuations found in the present study, may suggest the presence of
anxiety in this group of patients with abnormal post-dexamethasone responses. Longitudinal studies on depressed patients have also found that changes in cortisol levels are related to changes in features, such as anxiety (Sachar, 1967).

The positive relationship between the number of spontaneous fluctuations and the post-dexamethasone cortisol measures in these patients calls to mind the early hypothesis that increased HPA activity occurs in depression is related to the subjective dysphoria and 'felt' anxiety that depressive patients experience (Rubin and Mandell, 1966). However, subsequent findings that increased HPA activity occurs in retarded (Joyce et al., 1986) as well as in agitated (Meller et al., 1987) depressives and that the greatest relative increase in HPA activity in depression occurs during the hours of sleep shifted the focus away from a non-specific, stress-mediated activation of the HPA axis to more specific neurotransmitter hypotheses which could account for both the symptomatology and the hormone disturbance (Rubin et al., 1987).

The present results have implications for previous assessments of the importance of electrodermal abnormality in depression. Although the present research was not able to show that all the measures of electrodermal activity which have in the past been demonstrated to be abnormal in depression significantly correlated with thyroid and adreno-cortical activity (e.g. habituation rate), suggestive evidence was produced that at least some of the previously observed abnormalities may be attributed to thyroid and HPA abnormalities. Abnormalities of thyroid and HPA axis functions are not reliably
correlated with either severity or sub-classification of depression (Targum et al., 1981; Rubin et al., 1987) and subjects with a family history of depression are less likely to manifest thyroid and HPA axis functions deficits. In that abnormalities of electrodermal activity may be a function of thyroid activity, it is unlikely that abnormal electrodermal activity will prove to be either a diagnostic aid or a genetic marker for depression as a number of workers previously hoped (e.g. Iacono et al., 1983; Ward et al., 1983).
CHAPTER 8

LONGITUDINAL STUDY OF THE RELATIONSHIPS BETWEEN ANXIETY AND DEPRESSION

INTRODUCTION

In the three previous chapters abnormalities of electrodermal activity were demonstrated in a group of depressed patients. It was shown that anxiety and depressive symptomatology could be differentiated in terms of physiological activity present in different subtypes of depression. Neurotic depressives were found to have significantly more spontaneous fluctuations, longer recovery rates, and faster rise times in their responses following orienting stimuli than both endogenous depressives and normal subjects. However, as the study reported in Chapter 6 showed the classificatory systems for subtypes of depression did not identify accurately those patients with skin conductance abnormality. These findings raise the question that while psychiatric conditions such as major depression can successfully be discriminated by psychophysiological methods from 'normal' states, patients within such major categories cannot be separated quite so readily on the bases of phenomenological and physical symptoms.
In recent years, there has been an increased emphasis in the psychiatric literature on phenomenology in general and the process of mood disturbance in the various disorders of affect in particular (Roth et al., 1972; Prusoff and Klerman, 1974; Clancy et al., 1978; Roth and Mountjoy, 1982; Hamilton, 1983; Coryell et al., 1988). This has received its impetus from attempts to construct a clinically relevant taxonomy of the affective disorders by identifying defined criteria to separate one disorder from another. For example, anxiety and depressive disorders are defined by the DSM-III-R (American Psychiatric Association, 1987) and ICD-9 (World Health Organization, 1978) in terms of the prevailing symptoms, their intensity and their duration (see Chapter 2). In these systems the diagnostic categories are independent of supposed aetiology. This is difficult because of complex symptom patterns in which there is considerable overlapping of symptomatology between any two disorders. A particular problem arises with distinguishing patients who do or do not have a particular form of affective disorders. In fact there is considerable doubt if a differential diagnosis can be made as anxiety and depression. There are many anxious patients who present with concurrent symptoms of depression, and many depressed patients who present with concurrent symptoms of anxiety (Prusoff and Klerman, 1974; Johnstone et al., 1980; Cloninger et al., 1981; Leckman et al., 1983).

Whilst frequently occurring in the same individuals, it is possible that these two forms of manifestations of mood disturbance represent quite distinct psychological processes. Alternatively, their co-occurrence may reflect the fact that these abnormalities of mood dynamically interact and exacerbate each other. It is the aim of this
chapter therefore to investigate the question whether anxiety and depression are two distinct psychological processes or are part of the same psychological process. It is the present writers view that the distinction between the processes can only be made in a longitudinal investigation where the processes underlying these mood distortions may be seen to interact dynamically.

From community surveys, the impression is gained that states of anxiety and depression are inseparable from one another. However, extrapolations from ordinary emotional experiences to their pathological variants in depressed and anxious disorders are unjustified. Even if normal states of the conditions co-exist, develop in parallel or alternate with one another within short intervals, it does not necessarily follow that the corresponding pathological syndromes must be related in similar ways (Roth and Mountjoy, 1983).

How are anxiety and depression distinguished in diagnostic practice? Patients are diagnosed as either depressed or anxious largely on the basis of the ratio of symptoms of depression and anxiety (Wing et al., 1978). Symptoms mentioned by patients classed as either depressed or anxious are often similar. The diagnostic decision appears to be made primarily on the basis of the patient's behaviour: the clinician makes a judgement as to the intensity of the complaint of abnormal mood. Frequently as sadness (a symptom of depression) may be seen as more intense than apprehension (a symptom of anxiety), depression is diagnosed in favour of anxiety states (Mendels et al., 1972). According to Hamilton (1983), for example, a typical depression is easy to distinguish from an anxiety state in this way. It is only
the anxious depressive, that is the borderline case, which causes difficulties. There is evidence to suggest that the excessive reliance on the present state of symptoms on their own may not be helpful. Whilst this position may be applicable to the diagnosis of more severe cases, these are relatively rare (Snaith, 1987) in the majority of cases where the characteristic symptoms are not present in clear form which give rise to difficulties. There is evidence to show that a high proportion of patients with milder forms of affective disorders show both anxiety and depression. About 95% of depressive patients complain of psychological symptoms of anxiety. This includes not only anxious mood but also tense feelings, inability to relax, irritability, difficulty concentrating, etc. Somatic symptoms of anxiety are found in 85% of depressed patients (Hamilton, 1983). This finding is supported by Van Valkenburg et al. (1984). They examined the validity of the anxious-depressive syndrome in a sample of 114 patients who met the diagnostic criteria for anxiety neurosis (DSM-III panic disorder) and for depression. The groups in which there was a mixture of anxiety and depression showed a marked similarity, with observed differences attributed to severity. In contrast, significant differences between the groups of anxious depressives and those with primary anxiety or primary depressive disorder were reported for treatment response and prognosis.

The usefulness of the concept of mixed anxiety-depression has been investigated for those neurotic outpatients who received treatment for some mixture of anxious and depressive symptomatology. Paykel (1972) provided evidence that anxious depressives need to be distinguished from other subtypes of neurotic depressives. He showed
that they did not respond to antidepressant medication as did other groups of depressives. However, the concept of mixed anxiety-depression as a working diagnosis has not proved to be useful (Downing and Rickels, 1974). It increased the heterogeneity of the diagnostic concept not only in terms of the severity and chronicity of the condition, but also in terms of the configuration of symptoms they display. The present diagnostic systems (DSM-III-R in particular) ignore the uncertain areas of overlap between anxiety states and non-psychotic depression, and it is therefore of little use to the clinician when it comes to differential diagnoses between anxiety and depression.

Therefore, in order to study the relationship between anxiety and depression it should be remembered that in investigating mood states in affective disorders we are dealing with multiple component constructs which have patterns of relationship, that is some symptoms of anxiety and depression will fluctuate together, others fluctuate independently, and some may be causally related. In a longitudinal study, Russell and De Silva (1983) tried to answer the question whether there was a clear demarcation between anxiety states and minor depressive illnesses or whether it was better to consider them as laying along a continuum of disturbed mood. They measured anxiety and depression in 3 subjects weekly over a 4-month period using standardized self-rating instruments. They concluded that depressive and anxious mood fluctuate in a similar fashion. However, the study by Russell and De Silva suffers from several methodological flaws. Firstly, the rating scales used do not clearly distinguish between depressed and anxious symptomatology. The scales used were: the
Wakefield Depression Inventory, the Beck Depression Inventory (BDI),
the Zung Depression Rating Scale (ZDS), and two further rating scales
of anxiety which are not described in any detail. Several studies
attempted to deal with this problem by omitting two items pertaining
to anxiety (panic attacks and anxiety feelings) from the Wakefield.
But the criticism still applies to the BDI and the ZDS. Secondly, two
of the measures used are not independent of each other. The Wakefield
is a shortened version of the Zung scale. It incorporates ten items
of the ZDS plus two items concerned with psychological feelings of
anxiety. It is therefore not surprising that these two measures
correlate with each other. A third criticism is that none of the
three well-known scales is useful in distinguishing moderate from
severe conditions (Lader, 1981; Kearns et al., 1982; Snaith, 1987).

Furthermore, in order to study the relationships of anxiety and
depression longitudinally, it would be useful to measure the condition
more than once a week and in more than three subjects. In addition,
anxiety and depression are not only experienced by people who are
diagnosed as suffering from a morbid form of these but so-called
'normal' people. One could expect anxious and depressed moods in
normal subjects to be distinguishable from neurotic subjects in terms
of severity, permanence and frequency. Thus, four possible
relationships may be distinguished:

1) Anxiety and depression are two independent psychological
manifestations which co-occur in all affectively disordered patients
as well as normals. For example, Gresh and Fowles (1979) conceive of
them as two symptomatic stages of affective disorder with the ratio
of anxiety and depressive symptoms varying over time such that the diagnosis depends on when in the course of illness the evaluation is made (Russell and De Silva, 1983).

2) Anxiety and depression are two independent psychological processes where anxiety can elicit (cause) depression in severe cases of anxiety. Studies of patients suffering from anxiety neurosis have found a high prevalence of depressive symptoms, severe enough to qualify for a secondary diagnosis of depression (Fawcett and Kravitz, 1983). Estimates of depressive symptoms in anxious patients are as high as 65% (Roth et al., 1972).

3) Anxiety and depression are two independent psychological processes where depression can cause anxiety in severe cases of depression. Dealy et al. (1981) reported that 33% of their patients had diagnosis of secondary anxiety. An association between panic attacks (anxiety neurosis) and depression has also been found: Van Valkenburg et al. (1984) reported that 29% of their depressed sample had concomitant panic attacks.

4) Anxiety and depression are two independent processes which happen to co-occur in some people who are more seriously affected but there is no systematic relationship between the two states. In agreement with this position is the Newcastle group studies (Roth et al., 1972; Gurney et al., 1972; Kerr et al., 1972). These studies showed a separation between clinical symptoms, personality, treatment and treatment response, course and outcome, prognosis, and rating scales. This group, while cognisant of the overlapping of
symptomatology between anxiety and depression, suggested that with the use of appropriate statistical methods, the two states could be shown to differ on certain dimensions.

It seems perfectly possible to suppose that there are patterns of relationships between anxiety and depression rather than just correlations or no correlations. Hence, even if anxiety and depression can be identified as independent psychological processes, they may still be related in some predictable fashion. For example, if (2) was the case then in primarily anxious patients anxiety should predict depression; or in the case of (3) primarily depressed patients depression should predict anxiety; or if (4) was the case anxiety should correlate with depression in all psychiatric cases but not in normals. Only statistical analyses taking the correlations between time series at serial lags into account can identify patterns of dynamic interaction between anxiety and depression. Four different patterns of relationship are considered:

1) Anxiety and depression are derivatives from the same set of processes. If this was the case, a co-variation of anxious and depressed moods would be expected in all groups.

2) Anxiety causes depression in severe cases of anxiety. If this was the case, anxious mood would precede depressed mood in anxious patients.

3) Depression causes anxiety in severe cases of depression. If this was the case, depressed mood would precede anxious mood in
depressed patients.

4) Anxiety is unlike depression except in extreme cases of psychiatric disturbances. If this was the case, anxious and depressed mood would vary independently from each other in normals.
Table 8.1. Clinical and Demographic features of the subjects

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<td>Antidepressant</td>
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<td>Benzodiazepines</td>
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METHOD

Design

Mood changes were assessed over a period of four weeks. During this period, subjects were asked to fill in a mood rating scale twice a day. An initial clinical interview was conducted with each subject during which a number of interviewer-administered and self-rated scales were completed for each subject. Weekly meetings with the experimenter were held during the four weeks of the study where further self-rated tests were completed. In the final clinical interview interviewer and self-rated measures were given.

Subjects

The design called for seven anxious, seven depressed and seven normal subjects. Fourteen patients were referred. The diagnosis of the referring agent, GP or psychiatrist was taken to make up the groups. Subsequently diagnoses were confirmed by structured interview and psychiatric assessment, and subject's history and current mental state were compared with RDC criteria (Spitzer et al., 1978). Information elicited in this manner confirmed the majority of initial diagnoses. One patient referred as suffering from anxiety met RDC criteria for major depression but not for panic disorder. A further patient referred as anxious dropped out of the study after 1 week and is
excluded from this report. This left eight patients diagnosed as depressed and five patients diagnosed as anxious. All patients included in the study had drug treatment in the past or were on medication at the time of the study. But none of them received any form of psychological help.

Seven normal subjects served as the control group. Normal was defined as never having been treated for any psychiatric condition including anxiety and depression. An attempt was made to match subjects by age and sex. Table 8.1 gives details of demographic and clinical features of the subjects.

Procedure

A standard clinical interview was conducted with each subject. Appropriate changes were made when interviewing control subjects. Then a series of interviewer-administered rating scales were given to subjects in the form of a semi-structured interview. Ideally, these interviewer-administered rating scales ought to be administered by two raters who rate the subject's responses independently and subsequently compare ratings. However, in the present study this was impractical and only the experimenter's ratings are available for analysis.

During the twenty-eight days of the study, the subjects were seen at weekly intervals. The purpose of weekly meetings was to collect the rating scales and to ask subjects to report on events during the week and to say whether they were pleasant or unpleasant. Subjects
were also given the questionnaires described below. In order to shorten administration time, subjects only filled in the state-anxiety form of the STAI during these weekly meetings. In the last meeting, both self-rated and interview-rated rating scales were administered. The initial interview took approximately two hours. Weekly interviews took 20-40 minutes.

**Personality Measures**

At the end of the initial interview, subjects were asked to fill in a personality questionnaire, and a number of rating scales of anxiety and depression. These assessment instruments are briefly described below.

**Eysenck Personality Questionnaire:** developed by Eysenck and Eysenck (1975), which yields four factors: P, E, N, and L. Roth and Mountjoy (1982) showed that depressives have significantly lower scores on neuroticism and higher scores for extraversion compared with anxious patients.

**Beck Depression Inventory (BDI):** This inventory contains 21 items referring to symptoms and attitudes of depression, with four ranked statements to each item. The patient chooses the response which best matches his/her state at the time. The maximum score is 62 with scores of 10 or below reflecting no significant clinical depression. The measure was developed by Beck (1978). It is widely used as the best current questionnaire measure of depressive symptomatology.

**The Hopkins Symptoms Checklist (HSCL):** Derogatis et al. (1974) designed this checklist as a general scale for assessing symptoms in
psychiatric outpatients. It covers five main areas of psychopathology: somatic symptoms; obsessive-compulsive phenomena; interpersonal sensitivity; depression; anxiety. In the present study the overall score was used as a measure.

Wakefield Self-Assessment Depression Inventory: Developed by Snaith et al. (1971). The Wakefield consists of 15 items asking how the respondent feel at the time of test on a four-point response scale ranging from "Yes, definitely" to "No, not at all". Scoring on each item is 0, 1, 2, or 3 according to the response underlined. Total score is a simple process of addition of item scores. Items 2, 5, 7, and 13 are reversed so that the response of "Yes, definitely" scores 0 and "No, not at all" scores 3. The Wakefield has been devised to measure the severity of the depressive syndrome in patients diagnosed as suffering from that illness.

State-Trait Anxiety Inventory (STAI): Developed by Spielberger et al. (1970). The STAI is comprised of separate self-report scales for measuring two distinct anxiety concepts: state anxiety (A-state) and trait anxiety (A-trait). The A-state scale consists of 20 statements that ask people to describe how they feel at a particular moment in time. The A-trait scale also consists of 20 statements, but the instruction require subjects to indicate how they generally feel.

Mood Measures

Changes in mood were assessed by asking subjects to fill in a mood scale twice a day, in the morning and in the evening. Approximate times of day were specified (8am and 8pm) but because of
people's different routines, these times could not always be rigidly adhered to. As subjects were asked to fill in rating scale frequently, the instrument chosen had to be easy to understand and quick to administer. The measure which best met these requirements was the Profile of Mood States (POMS). This is a 65-item adjective checklist which yields 6 factors: tension-anxiety; depression-dejection; anxiety-hostility; vigour; fatigue and confusion. The rating scale was developed by McNair et al. (1971). Norms are available for an outpatient psychiatric sample and for a normal population. The measure is purported to be able to distinguish depressed and anxious patients.

Observer-ratings

Hamilton Depression Scale (HDS): Developed by Hamilton (1960). This is a most widely used observer rating scale. Ratings are made on the basis of semi-structured psychiatric interview. The time span considered when the ratings are made is the previous few days. A possible disadvantage of using this scale in the present study is that the scale is considered more appropriate for rating endogenous depression as it contains many items pertaining to somatic symptoms. Patients in the present study are equally likely to be endogenously or reactively depressed.

Hamilton Anxiety Scale (HAS): Developed by Hamilton (1959). This scale covers a wide spectrum of anxiety. In the present study, the ratings were made on a visual analogue scale (100mm line). Individual ratings were added up to produce one overall score.

Brief Psychiatric Rating Scale (BPRS): Developed by Overall and Gorham
(1962). It provides a rapid assessment of a wide range of psychopathology including anxiety and depression. It is useful as an additional wide-range instrument in non-homogenous groups of patients. Guidelines on the use of the scale are given by the authors. A total pathology score is obtained by summing up the ratings which are made on a 7-point scale.

American College of Neuropharmacology (ACNP): Checklist for anxiety and depression. Developed by Wittenborn and published by Lipman (1977). ACNP anxiety guidelines require 'moderate' or higher levels of the first two manifestations of anxiety (feeling nervous, jittery, jumpy, feeling fearful, apprehension, anxious, panicky) and at least three other symptoms or signs of anxiety. The syndrome definition of depression requires dysphoric mood plus four or five of the associated symptoms. There are overlaps of symptomatology of the anxiety and depression checklists. For example, restlessness and agitation. The authors have found that symptom levels of non-patient groups are 'remarkably low very significantly different statistically' than observed levels in anxious and depressed groups. Experimenter completed the observer-rated rating scales in the first and last interviews.
RESULTS

Personality Measures

The results on the EPQ and Spielberger's Trait Anxiety Inventory are shown in Table 8.2. Anxious and depressed patients scored comparably with non-psychiatric controls on the P and E scales of the EPQ. The means of the groups were similar to those published by Eysenck and Eysenck (1975); it should be noted, however, that the scores on all scales were somewhat higher in the present sample although this difference was not statistically significant. The N scale of the EPQ distinguished the combined neurotic group (anxious and depressed patients) from non-psychiatric controls ($t=2.54$, df=18, $P<0.02$). There was no significant difference between the N scores of the anxious and depressed groups. Neither group could be independently significantly distinguished from the control group, probably because the difference in means was too small to yield significant $t$ values with the current sample sizes.

Spielberger's Trait inventory turned out to be more sensitive. It significantly distinguished the neurotic group from the control group ($t=4.76$, df=18, $P<0.0002$). Both the anxious and the depressed group could be separately distinguished from the control group in terms of their trait anxiety scores ($t=4.52$, df=10, $P<0.001$; $t=3.75$, df=13, $P<0.004$ for anxious and depressed groups respectively). There was no difference between levels of trait anxiety in patients in the anxious
and depressed groups. Thus, whilst trait anxiety levels of neurotic patients can be shown to be substantially elevated on Spielberger's test the degree of predisposition to anxiety does not distinguish the anxious from the depressed group.

Observer-Ratings of Patient Behaviour

Five observer rating scales were used. All five were administered on two occasions and the average scores obtained from these two assessments were also calculated. The group means for the first and second administration and their average are shown separately for the three groups in Table 8.3 for all five measures.

The Hamilton Depression Inventory distinguished highly significantly between control and neurotic subjects. The mean levels of all patient groupings were 3 or more standard deviations above that of the control group. Both anxious and depressed groups could be independently distinguished from non-psychiatric controls on both occasions when the test was administered (t=9.24, df=10, P<0.001; t=6.43, df=13, P<0.001 for anxious and depressed groups respectively). It is important to note, however, that the difference between the anxious and depressed groups was not significant although depressed patients scored consistently higher. It is likely that with larger sample sizes the observed difference would have reached statistical significance.
The results yielded on Hamilton's Anxiety Inventory paralleled closely the observer ratings of depression. Here too both anxious and depressed groups could be distinguished on all occasions from the control group (see Table 8.3). Anxious symptomatology was indeed more marked in the anxious group compared with the depressed group but with the degree of variability observed. The two groups could not be statistically significantly distinguished from each other.

The Brief Psychiatric Rating Scale is not a measure which is particularly applicable to neurotic patients. It is to be expected therefore that distinctions between the neurotic patients and control groups would be of a smaller order than for the Hamilton scales. Nevertheless the BPRS was very efficient in pinpointing clinical cases. As Table 8.3 illustrates, the BPRS yielded comparably elevated scores for both anxious and depressed patients on both administrations.

The ANCP Anxiety and Depression measures were clearly specifically sensitive to anxious and depressed symptoms respectively than either of the Hamilton measures. On both occasions it distinguished the combined neurotic group from the control group. The difference between neurotic and control groups was of a much smaller order, however, than that between the control group and anxious patients. As Table 8.3 shows the scores of anxious patients were markedly raised. A significant difference was observed between the scores of anxious and depressed patients on each testing session (t=3.68, df=11, P<0.004 for the combined means). The picture yielded using the depression scale of the same instrument was more or less
the inverse of that produced by the anxiety scale. Depressed patients had substantially elevated scores on this scale and although the scores of anxious patients were higher than those of the control group in most comparisons, this difference was not statistically reliable. Depressed patients scored significantly higher than anxious patients on first administration \((t=2.81, \text{df}=11, P<0.01)\). On the second occasion this difference between the two groups was not statistically significant as both groups seemed to have shown some degree of regression towards a common mean. Overall, however, the instrument did distinguish between the two groups \((t=2.50, \text{df}=11, P<0.03)\). Thus, the ACNP seems to be the most specific of these observer rated scales. The anxiety and depression scales in combination were able to identify the patient groups relatively adequately. Both scales seemed to go some way towards distinguishing the two forms of neurotic reaction.
Table 8.2. Group means (with standard deviations) of anxious and depressed patients and non-psychiatric control.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anxious (n=13)</th>
<th>Depression (n=17)</th>
<th>Control (n=10)</th>
<th>T-Test</th>
<th>NS</th>
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Note: NS indicates non-significant differences.
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<th></th>
<th>Neurtic vs control</th>
<th>Squared depression</th>
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<th>N=13</th>
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### Table 8.4: Group means with standard deviations on self-reported inventories of depression and anxiety for anxious and depressed patients and non-psychiatric controls.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Depressed Controls</th>
<th>Anxious Controls</th>
<th>Depressed + Anxious Controls</th>
<th>Neuritic Controls</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.4</td>
<td>11.0</td>
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<td>Std. Dev.</td>
<td>2.1</td>
<td>2.5</td>
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Note: Significant t-values
Self-Ratings

On the whole the self-rated measures yielded disappointing results (see Table 8.4). These measures were administered weekly and group means for each week as well as the score averaged across the five administrations are to found in Table 8.4 separately for each group and each of the four measures.

The Wakefield turned out not to be a specific measure of depression. Both anxious and depressed patients scored higher than controls on this measure at each of the five weekly assessments but the differences between the two neurotic groups were small and largely in the wrong direction. The differences between the two neurotic groups were, however, of a very small order with again the anxious group tending to score more highly (in at least two out of five weekly assessments).

Spielberger's State Anxiety was similarly not specific to the anxious patients. On three out of the five occasions on which this instrument was administered the mean score of the depressed group for state anxiety was higher than that of patients referred primarily for an anxiety condition. Finally, The Hopkins Symptoms Checklist although it differentiated neurotic patients from controls with a high degree of effectiveness, seemed insensitive to the differences between anxious and depressed patients.
The Relationship of Self-rated and Observer-rated Measures

The association between measures of anxiety and measures of depression was examined for the whole sample using Pearson's Product-moment Correlation. These correlations are shown in Table 8.5. As this table indicates, the overall associations between measures of anxiety and depression were very high and consistent across several occasions of administration. The Hamilton Depression Scale showed a significant association with almost all measures of anxiety except for the Hopkins Symptoms Checklist. The ACNP for depression again was notably specific in that its relationship to the ACNP anxiety scale was small. The Wakefield related to all anxiety measures except for the Hopkins Symptoms Checklist. The Beck Depression Inventory was also strongly associated with anxiety measures.

The Study of Subjects Mood Self-rated Twice Daily over 28 Days

The measure of mood applied in this study was POMS which has seven mood factors. These are tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, confusion-bewilderment and a total mood disturbance score. The purpose of using these measures was to see if individuals different patterns of mood changes can be clinically differentiated. The mean scores for each factor over 28 days were calculated for each subject and along with the average of these for the three groups are shown in Table 8.6. This table shows that there were no significant differences in reported mood over 28 days between any of the groups. There is a
slight trend for the neurotic groups to score higher across all the scales but this is also true for the vigour-activity scale which is negatively keyed for mood disturbance. Thus the slightly higher scores are likely to reflect a slight yes saying response bias rather than a genuine difference between the groups. The lack of sensitivity of this mood measure to psychopathology may be an important observation despite the relatively small number of subjects. This is because firstly, other psychometric measures reveal differences not only between the neurotic and control groups but also between the anxious and depressed subjects; secondly, even though the number of subjects was small the number of measures taken from each subject was high (the POMS was completed 56 times by each subject). Thus, if differences existed these should have manifested themselves over 28 day period. Thirdly, the POMS is a valid measure of mood which is purported to have substantial discriminative power both between and within individual variation in moods.

The evaluation of this negative finding must await the final discussion but it should be noted at this stage that an absence of a difference in overall mood levels need not mean that the instrument is insensitive to differences between the two groups. It is both possible and likely that psychopathology is not synonymous with or even correlated with mood disturbance. It is the interpretation of subjective states by the individual rather than the states themselves that may constitute a psychological complaint. Thus dysphoria, for example, may be experienced in equal measure by so-called normal and neurotic individuals but whereas in one case dysphoria may be interpreted by the individual as a reasonable response to adverse
circumstances an equal amount of sadness may be regarded as cause for complaint in a neurotic individual. Furthermore, the absence of overall differences does not preclude important differences in the pattern of mood changes and it is such possible differences in pattern that might differentiate the neurotic individual from the normal as well as the different reaction types from each other.

The Association of POMS factors with each other and other measures

The product-moment correlation coefficients between mean scores on each of the six POMS scales were calculated for the whole sample and the results of this analysis are shown in Table 8.7. On the whole the correlations were substantial. The key correlation between mean level of depression and mean level of anxiety was 0.91 (df=18, P<0.001). This implies that to a large measure the average level of tension over the study period was a powerful predictor of average depression. It should be remembered, however, that this does not imply that the two moods occurred together since these correlations refer to mood ratings averaged over 28 days. Confusion, fatigue and anger were also significantly associated with tension and anxiety. Depression and dejection had very much the same order of associations with these scales. Only vigour and activity failed to relate.

The association of the tension-anxiety and depression-dejection POMS factors with the other psychometric measures for the whole sample are shown in the table of correlations presented in Table 8.5. The depression-dejection factor seems more specific than the tension-
anxiety factor. Depressed mood averaged over 28 days is significantly associated with anxiety level averaged across 5 weekly observation (based on the Spielberger State Anxiety score). The tension-anxiety measure, however, seems to be substantially associated with the Wakefield and the BDI and slightly associated with the Hamilton observer rating of depression.

**Distributional properties of mood scale ratings**

One manner in which the pattern of moods may differ across subject group is in terms of the distributional properties of moods across time. The variability of mood may be greater. An extreme case of this is undoubtedly manic depression in which periods of vigour, activity and elation alternate with periods of extreme dysphoria. It is possible that a less marked expression of this may be found in neurotic depression. Neurosis may also be marked by unusually extreme moods. Patients with anxiety, for example, might be identified not by an overall increase in level of tension but by a few extreme instances of anxious states (e.g. panic attacks). If this was the case the positive skewness of distribution of mood ratings should reveal differences between the groups. It is also possible that neurotic patients are distinguished by the flatness of the distribution of their moods. In other words their moods deviate from the normal distribution in that no particular level is characteristic of the individual. For example, in depression the individual has no characteristic level of vigour but observed levels occur fairly evenly around the central point of the distribution.
Table 8.6. Mean levels and Averaged Distributional Properties of Mood Scale Ratings (POMS) over a 28 day period.

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<th></th>
<th>Anxious N=5</th>
<th>Depressed N=8</th>
<th>Neurotic N=13</th>
<th>Control N=7</th>
<th>Significant t-value and probabilities</th>
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<td>0.92</td>
<td>1.82</td>
<td>NS</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.76</td>
<td>3.37</td>
<td>2.37</td>
<td>4.99</td>
<td></td>
</tr>
<tr>
<td>Depression/Dejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36.47</td>
<td>40.69</td>
<td>39.06</td>
<td>38.65</td>
<td></td>
</tr>
<tr>
<td>Variation</td>
<td>3.37</td>
<td>4.05</td>
<td>3.92</td>
<td>2.24</td>
<td>NS</td>
</tr>
<tr>
<td>Skewness</td>
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<td>1.54</td>
<td>1.68</td>
<td>1.83</td>
<td></td>
</tr>
<tr>
<td>Kurtosis</td>
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<td>3.85</td>
<td>4.78</td>
<td>5.49</td>
<td></td>
</tr>
<tr>
<td>Anger/Hostility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.89</td>
<td>41.88</td>
<td>41.50</td>
<td>38.77</td>
<td></td>
</tr>
<tr>
<td>Variation</td>
<td>3.65</td>
<td>4.81</td>
<td>4.36</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
<td>2.01</td>
<td>1.68</td>
<td>1.81</td>
<td>3.25</td>
<td>2.42 P&lt;0.02</td>
</tr>
<tr>
<td>Kurtosis</td>
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<td>4.19</td>
<td>4.45</td>
<td>13.42</td>
<td>2.54 P&lt;0.02</td>
</tr>
<tr>
<td>Vigour/Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>51.63</td>
<td>51.37</td>
<td>45.56</td>
<td></td>
</tr>
<tr>
<td>Variation</td>
<td>7.19</td>
<td>7.56</td>
<td>7.42</td>
<td>6.54</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
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<td>0.39</td>
<td>0.43</td>
<td>0.64</td>
<td>NS</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.24</td>
<td>0.01</td>
<td>0.08</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Fatigue/Inertia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>39.70</td>
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<td>42.52</td>
<td>39.54</td>
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<tr>
<td>Variation</td>
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<td>5.06</td>
<td>4.92</td>
<td>5.17</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
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<td>1.46</td>
<td>1.67</td>
<td>1.41</td>
<td>NS</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.26</td>
<td>3.43</td>
<td>2.21</td>
<td>3.15</td>
<td></td>
</tr>
<tr>
<td>Confusion/Bewilderment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>38.39</td>
<td>43.61</td>
<td>41.59</td>
<td>36.24</td>
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<td>4.05</td>
<td>3.88</td>
<td>2.86</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
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<td>1.02</td>
<td>0.96</td>
<td>1.73</td>
<td>NS</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>2.10</td>
<td>2.39</td>
<td>2.28</td>
<td>3.83</td>
<td></td>
</tr>
<tr>
<td>Total Mood Disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>141.56</td>
<td>159.83</td>
<td>152.80</td>
<td>144.95</td>
<td></td>
</tr>
<tr>
<td>Variation</td>
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<td>25.01</td>
<td>23.62</td>
<td>18.31</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
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<td>0.45</td>
<td>0.47</td>
<td>0.71</td>
<td>NS</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.70</td>
<td>1.39</td>
<td>1.12</td>
<td>1.25</td>
<td></td>
</tr>
</tbody>
</table>

Anxious vs Depressed df = 11
Anxious vs Control df = 10
Depressed vs Control df = 13
Neurotic vs Control df = 18
<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Depression</th>
<th>Hostility</th>
<th>Activity</th>
<th>Tension</th>
<th>Patience</th>
<th>Violence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.79</td>
<td>0.02</td>
<td>0.67</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: Values in the table are significant at the 0.05 level.

*Correlations are based on mean scores of each subject over 20 days on the Raskin-Eysenck measure of each of the six factors.*

*Table 8.7 Product-moment correlation coefficients for the six factor scales.*
The direction of the difference is indicated by for group above the median.

\[ \uparrow = \text{level higher for group above the median} \]

\[ \downarrow = \text{levels lower for the group below the median} \]

<table>
<thead>
<tr>
<th>Measure</th>
<th>1.68</th>
<th>1.71</th>
<th>1.43</th>
<th>1.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed</td>
<td>5.90 (09)</td>
<td>5.97 (09)</td>
<td>5.90 (09)</td>
<td>5.97 (09)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.71 (09)</td>
<td>4.71 (09)</td>
<td>4.71 (09)</td>
<td>4.71 (09)</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>9.38 (09)</td>
<td>9.38 (09)</td>
<td>9.38 (09)</td>
<td>9.38 (09)</td>
</tr>
<tr>
<td>Beck Scale</td>
<td>10.88 (09)</td>
<td>10.88 (09)</td>
<td>10.88 (09)</td>
<td>10.88 (09)</td>
</tr>
</tbody>
</table>

*Combined neurotic and non-psychotic sample. Values with parentheses in parentheses indicate subjects and contrasted with low scores on mean levels and depression. Depressed and depressed at 0.05 level of significance and depression to identity anxiety and hostility.

Table 8.5. Self-rated and Observer-rated measures of anxiety and depression.
### Table 8.9: Average correlation coefficients between POMS factors for the total sample

<table>
<thead>
<tr>
<th></th>
<th>Anxiety/Depression</th>
<th>Depression/Defection</th>
<th>Hostility/Defection</th>
<th>Interreactivity</th>
<th>Fatigue/Tension</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension</td>
<td>0.69</td>
<td>0.48</td>
<td>0.75</td>
<td>0.66</td>
<td>0.51</td>
<td>0.37</td>
</tr>
<tr>
<td>Anger</td>
<td>0.45</td>
<td>0.41</td>
<td>0.24</td>
<td>0.41</td>
<td>0.33</td>
<td>0.36</td>
</tr>
<tr>
<td>Activity</td>
<td>0.18</td>
<td>0.32</td>
<td>0.36</td>
<td>0.33</td>
<td>0.33</td>
<td>0.36</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.14</td>
<td>0.19</td>
<td>0.26</td>
<td>0.22</td>
<td>0.21</td>
<td>0.24</td>
</tr>
<tr>
<td>Tension</td>
<td>0.56</td>
<td>0.51</td>
<td>0.59</td>
<td>0.53</td>
<td>0.51</td>
<td>0.54</td>
</tr>
</tbody>
</table>

All coefficients are significant.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hood Disturbance</td>
<td>0.70</td>
</tr>
<tr>
<td>Depression/Confusion</td>
<td>0.48</td>
</tr>
<tr>
<td>Anger/Hostility</td>
<td>0.43</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.42</td>
</tr>
<tr>
<td>Anger/Hostility</td>
<td>0.46</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.45</td>
</tr>
<tr>
<td>Anger/Hostility</td>
<td>0.47</td>
</tr>
<tr>
<td>Depression/Confusion</td>
<td>0.54</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*Table 8.10* Average correlation coefficients between POMS factors for the neurotic sample.
|                          |  
|--------------------------|---
| **Depression/Defection** | 0.45  
| **Anxiety**              |  
| **Defection**             |  
| **Hostility**             |  
| **Activity**              |  
| **Hostility**             |  
| **Activity**              |  
| **Defection**             |  
| **Hostility**             |  
| **Activity**              |  

Table 6.11. Average correlation coefficients between POMS factors for the control sample.
To assess these aspects of the distribution of mood, the second, third and fourth moments of the mood distribution of each subject were calculated. This gave measures of variation, skewness and kurtosis of the distribution of each mood type for each subject over the 28 days. The means of these values for the three groups in this study are shown in Table 8.6. As this table demonstrates, these distributional properties were similar across the groups. The only statistically significant effect to emerge was in terms of the anger-hostility dimension. Here it seemed that non-psychiatric control subjects showed a slightly more positively skewed distribution for this mood than either of the neurotic groups although only the difference between depressed and control groups proved to be statistically significant \((t=2.42, \text{df}=13, P<0.02)\). This result indicates that control subjects experienced angry and hostile moods in occasional extreme outbursts whereas the hostility of neurotic groups was a much more constant feature. In view of the fact, however, that this is the sole significant finding in terms of the distributional properties of moods perhaps we should not place too much emphasis on it. On the whole the distribution of moods across the 28 days of neurotic and control groups may be considered as similar.

A Post-hoc attempt at validating the Mood Scales

In view of the disappointing finding with means levels and distributional properties of the POMS Scale it was felt that the validity of these measures should be established before further work would be carried out. Clearly, if the depressed and anxious groups
were not differentiated from each other and jointly from the non-neurotic group on these scales serious questions are raised about the quality of this instrument. On the one hand it is possible that the instrument is simply not sufficiently sensitive to mood changes to show significant differences with sample sizes as small as the present ones. It is possible, on the other hand, that the groups all presented with a mixture of disturbed moods that could not be distinguished from each other. In other words, that there was as much depression and anxiety with similar sorts of distribution in the non-psychiatric group as the psychiatric group.

One way of distinguishing between these two possibilities is to contrast high and low scorers on other measures of anxiety and depression on mean levels, standard deviations and skewness of distribution on the POMS factors. If insignificant results were found because of the impurity of the sample, when subjects were split in this post-hoc, empirical way, meaningful differences should start emerging. A large number of analyses were performed and as their results do not relate directly to the hypotheses these are only presented in summary form in Table 8.8. One way analyses of variance were carried out using the median score on each of the measures as the cut-point to separate high and low scorers. The pattern of results obtained is interesting but far from clear. Subjects scoring high in N on the EPQ seem more likely to report vigour and activity. The two groups also differed in terms of the distribution of their moods. The non-neurotic group showed a greater tendency for isolated, high values leading to greater positive skewness of the distribution. Measures specifically related to anxiety, however, on the whole did
not distinguish groups characterised by high tension and anxiety. The Spielberger scale, however, was an exception as high scorers on both the trait and state form of this questionnaire were more likely to produce isolated high values on this scale. This association provides some concurrent validity for the tension and anxiety measure and suggests that the absence of initial differences might have been due to impure groups. The measures of depression, however, were disappointing in that their relationship seemed to be primarily with fatigue and inertia rather than the depression-dejection scale. High scorers on both BDI and Wakefield were more likely to report moods of fatigue and inertia and not depression and dejection. The Hamilton scales seem both to relate to confusion and bewilderment rather than either tension or depression.

The Cross-correlation of Mood States Across Time

The correlation of each mood state with every other mood state was calculated for each subject over the 28 days period. The average correlation coefficients are shown in Table 8.9 for the combined group, Table 8.10 for the neurotic group and Table 8.11 for the control group.

On the whole coefficients were relatively high indicating that the moods measured by the POMS are strongly associated with each other. One finding is of particular importance, however, for the present study. Whereas the association of depression-dejection and tension-anxiety was significant for the non-psychiatric sample as well
as the total, the association was smaller and insignificant for the neurotic sub-group (t-test was used to assess significance of correlation coefficients). Confusion was also a strong correlate of both tension and depression whereas fatigue was a correlate of depression but not of tension. The correlations with total mood disturbance are illustrative only as this is a linear combination of the other variables.

In interpreting this correlation matrix it is important to comment on the strong association of tension and depression. The covariation of these two mood states across time in most people adds substantial support to a model of these states which would combine these moods into a single psychological structure.

Temporal Characteristics of Mood Scores

The temporal characteristics of mood scores were examined using simple time series analysis techniques. These consist of calculation of product-moment correlation coefficients between measures of a variable at Time 1 and measures of the same variable (or another variable) at a constant time interval from the first measurement. The time interval is referred to as lag and the correlation coefficients as lag correlations.

In the current analysis two attempts were made to examine the temporal structure of moods in the neurotic and non-psychiatric groups. Firstly, auto-correlation coefficients were calculated in
order to examine the extent to which mood at Time 1 could be used to predict the same mood half a day, a day, a day and a half, etc. The second analysis consisted of the calculation of lag cross-correlation coefficients where mood of one type at Time 1 was used to predict scores on another mood scale at Time 2. This form of cross-lagged correlational analysis has been extensively used to make causal inferences about the relative primacy of two variables.

Auto-correlation

The auto-correlation were calculated for each type of mood and for each group of subjects. As differences between these groups in terms of the size of correlations were small, only the correlograms for the combined group are shown in Figures 8.1 to 8.7. The standard error of the coefficient was used to test the significance of correlations at each lag for each group. These are graphically illustrated on the figures for each group separately as well as for the combined group. It should be clear that auto-correlations are to some extent ambiguous since correlations at lag 2 may be partly accounted for by significant associations at lag 1. For example, high correlations between mood scores on the mornings of day 1 and day 2 (lag 2 correlations) may be accounted for by correlations between the morning and afternoon scores and afternoon to morning scores (correlations at lag 1). In order to control for this effect, partial auto-correlation coefficients were also been calculated for each of the mood factors and each of the groups. The partial auto-correlations are also graphically illustrated in Figures 8.1 to 8.7.
Figure 8.1: Mean auto-correlations for the POMS Factor Tension-Anxiety for Data 1-24
Figure 8.2. Mean Autocorrelation for the POMS Factor Depression-Depression for Lags 1-24
Figure 6.2: Mean Autocorrelations for the POMS Factor Anger-Hostility for Ages 1-24

Significant Partial Autocorrelation (Total Sample)
Significant Partial Autocorrelation (Control Group)
Significant Partial Autocorrelation (Neurotic Group)
Figure 8.4. Mean Autocorrelations for the POMS factor Vigour-Activity for lags 1-24.
Figure B.6. Mean Autocorrelation for the POMS Factor Confusion-Bewilderment for IAGE 1-74.
Figure 8.7: Mean Autocorrelations for the POMS Factor: Total Mood Disturbance for Ages 1-24.
Examining the correlogram of tension-anxiety in Figure 8.1 we find significant auto-correlations at lag 1 for the total sample as well as for the normal and neurotic sub-samples. This means that level of tension in one half of the day predicted tension in the other half of the day, or that afternoon tension predicted tension the next day. Correlations at lag 2 were significant only for the normal sample and the total sample. This implies that level of tension in the morning predicted tension the next morning, and the evening tension predicted tension the next evening; and that the tension-anxiety moods of neurotic group changed between 2 days. The second important aspect of this correlogram concerns the appearance of slight but significant negative correlations towards the lags of 16 to 22. These tend to be significant for the total sample and for the neurotic group for both auto-correlations and partial auto-correlations. In fact when the correlations of depressed and control subjects were contrasted at these lags highly significant t values were found between these groups at lags 11 and 22 (t=-3.39, df=13, P<0.005; t=-3.54, df=13, P<0.005 respectively). The trend in the data is present at other lags as well. This is perhaps some indirect evidence for cyclic type change in tension and anxiety levels of depressed patients which is not found in either normals or anxious subjects. The latter provided too small a sample for the testing of this hypothesis. Thus, whilst for the normal and anxious group lags greater than five or six days produced correlations which were still positive, the depressed group changed moods with a tendency greater than chance.
A similar pattern was found in the case of the depression-dejection scale. Here the negative correlations in the depressed group at lag 17 (8 days onwards) was even more marked. The t-tests contrasting the depressed and control groups were highly significant at lags 17, 19, 20, 21 and 22 (t=3.19, df=13, P<0.008).

A different pattern emerged for anger and hostility moods. Here auto-correlations were only significant at lag 1 and the 1-2 week negative association appeared not to emerge. The peaking of the auto-correlation at lag 19 is out of line with the general trend of data but as this correlation is not significantly different from zero it is perhaps wiser not to attach too much importance to this.

The auto-correlations of fatigue and vigour and activity produce markedly similar correlograms. It is of interest that correlations at lag 2 are greater than those at lag 1 and that these continue to oscillate around zero primarily for the neurotic group up to about lag 19. This is clearly related to a daily cycle where fatigue is greater in the evening and vigour and activity is greater in the morning. Again it is the depressed patients that contribute most to this although it is to be found to some extent in the normal group as well. Despite the small numbers, significant differences emerge between the anxious and depressed group at some of these lags. These differences are due to the more marked oscillations in the correlogram of depressed patients than anxious ones. For example, at lag 18 the correlation coefficient for depressed patients was 0.16 and for the anxious group was -0.04 on vigour and activity (t=2.5, df=11, P<0.03).
The correlogram for confusion and bewilderment is somewhat similar to the pattern of tension and depression. This is not surprising in view of the high correlation between tension, depression and confusion at lags of 0 (0.51 and 0.44 respectively). The negative correlations after lag 1 apply primarily to the neurotic group, again more to the depressed sub-group than the anxious ones. Confusion therefore might be a part of the same set of mood states which we have seen includes tension-anxiety and depression-dejection.

The auto-correlations for total mood disturbance is difficult to interpret as it by definition includes the variation of all the above factors. It is indeed marked by the same oscillation around zero correlation that we have seen in the case of vigour activity and fatigue but also contains the initially highly positive and after about a week consistently negative correlations which were revealed in the correlogram of depression, tension and confusion.

Two effects seem to emerge sufficiently consistently to warrant comment. Firstly, on the whole brief term auto-correlations (i.e. lags of 2 or 3) seem more likely to be significant in the neurotic patients. This is an overall effect that seems to encompass both neurotic groups. Secondly, auto-correlations after a week, however, tend to become negative for depressed patients and this does not appear to be so marked in either anxious patients or controls. The latter effect could represent as one weekly cyclical variation of mood specific to patients with depression.
Figure 8.9. Cross-correlation of POMS factors: tension-anxiety and anger-hostility
Figure 8.16. Cross-correlations of POMS factors Depression-Dejection and Confusion-Bewilderment.
Cross-correlations

21 sets of cross-correlations were calculated which represent cross-correlations between all sets of mood variables. These coefficients were computed in order to examine the primacy of moods. In other words, given the association of tension and depression for example, can we find any evidence for a model of depression causing tension as opposed to tension causing depression? Lag cross-correlation coefficients were therefore calculated for all pairs of moods where each mood was used to predict the other moods at lags from 1 to 12. The cross-correlograms are shown in Figures 8.8 to 8.16. We are primarily concerned with tension-anxiety and depression-dejection and so shall restrict our discussion to the cross-correlograms of these two states.

The cross-correlogram of tension and depression offers further evidence in favour of the close psychological correspondence of these two states. In the left side of the correlogram which illustrates the adequacy of depression to predict tension significant values are found up to about a lag of 4. Similarly, correlations are significant up to about a lag of 3 when tension is used to predict depression. Thus we cannot say that across individuals one of these moods is primary to the other. The significant negative correlation at lag 9 for depression predicting tension is an isolated incident which is difficult to interpret. The cross-correlogram between tension and anger has similar shape and again primacy is impossible to attribute. Tension and vigour, however, do seem to show a more unilateral relationship where tension seems to predict vigour somewhat better.
than the other way round. This applies in a negative way in the short term where tension inhibits vigour and in a more positive way at lags of 3 to 4 days when tension predicts greater vigour. Tension and confusion produce a similar correlogram to tension and depression although interestingly confusion seems a somewhat better predictor of tension than the other way round. Overall, it seems that none of the mood states turned out to be powerful predictors of tension and anxiety although depression and confusion seemed to occur in association with it.

The most interesting associations were found in the case of depression. Analysis based on the total sample revealed that anger over lags of 1 and 2 was a significant predictor of depression whereas the same was not true for depression viz a viz anger. At lags of 2 to 3 days depression becomes a significant negative predictor of anger. This is probably interpretable in terms of the cyclical change in depression noted in the previous section. Further associations are shown in the correlogram of vigour and depression. It is surprising that vigour is a positive and highly significant predictor of depression over the short term. Vigour is seen to bring on depressed mood and less surprisingly depressed mood brings on decreased vigour. The cyclical nature of the process is illustrated by the significant values obtained for depression as a significant predictor of vigour at lags of 9 and 11. Depression and fatigue and depression and confusion appear to be associated to each other in a reciprocal way.
In summary then a number of precursors of depressed mood were identified which do not seem to be associated with tension. Anger, as well as episodes of vigour, seems to provide a prelude to depression. The fact that these moods are not associated with tension in this way might be thought to imply that at least in some instances depression may not be part of the same psychological framework as tension and anxiety.

The cross-correlations across the sub-group of patients were also studied. No significant differences emerged from this analysis indicating that the interrelation of mood states is not a function of psychopathology. This provides further evidence for psychological contensions that there is no discontinuity in terms of psychological processes between neurotic states and non-psychiatric conditions.

DISCUSSION

The results showed that some assessment measures of anxiety and depression used in this study did not discriminate satisfactorily between the two conditions. Observer-rating scales showed a trend in the appropriate direction in distinguishing anxious and depressed groups while self-rated scales did not even show a trend of specific responsiveness to the two neurotic complaints. Both types of scales did, however, discriminate neurotic (anxious and depressed group combined) from non-psychiatric subjects. But even in this, observer-rating scales were more effective than self-rating scales. It was not
surprising to find that the two types of measures correlated highly. These findings were not unexpected.

The explanation for these findings may perhaps be found in the non-specific nature of neurotic pathology where depressive and anxiety complaints occur together (Johnstone et al., 1980; Cloninger et al., 1981; Leckman et al., 1983; Coryell et al., 1988). Alternatively the measures themselves may be loaded highly on both anxious and depressive symptomatology or that the difference between the two groups is an artificial one in that depression and anxiety may be found in both groups in roughly equal measure (Fawcett and Kravitz, 1983). This latter possibility seems less likely since observer-rated measures, even if not yielding statistically significant differences, showed promising trends in the appropriate directions. Given more subjects this might well have proved to be significant.

Mood as measured by the POMS did not differ between the neurotic and the non-psychiatric control groups. This may be due to the lack of sensitivity of this main mood measures used in the present study. However, the POMS has been shown to be a reliable and valid measure of mood, flexible enough to reflect mood swings over time in patient and control samples (McNair et al., 1971). Also, the number of measures taken per subject was high, so that it can be assumed that differences of mood would have emerged from the data if there had been consistent differences.

An investigation of the relationship of the POMS factors with each other yielded disappointing results. The correlations were
substantial which implies that this main measure used in this study, the POMS, might load too highly on a general dimension of pathology to be able to meaningfully discriminate between depressed and anxious states. However, it was hoped that the analysis of patterns of mood change may reveal significant distributional and temporal aspects of mood.

The POMS factors were compared with the other psychometric tests used. Depression and tension factors were found to be significantly related to both measures of depression and measures of anxiety. Again, the measure did not distinguish between the two neurotic samples.

A post-hoc comparison between high and low scorers on the observer-rated and self-rated rating scales on mean levels of POMS factors provided some evidence that the tension-anxiety and fatigue-inertia scales distinguish between high and low scorers; but no such evidence was found for the other factors. This may mean that some of these factors are poor measures of the moods whose label they hold. On the other hand, these results may be a reflection of the impurity of the original sample.

The relationship of the POMS factors over time was investigated. Factors were found to be strongly associated with each other. One interesting finding was that the association between depression-dejection and tension-anxiety was significant for the control group as well as the total sample. This finding adds support to a dimensional model which would combine these moods into a single psychological structure (Eysenck et al., 1983). Furthermore, the association of
these two moods across time bears out the strong associations found between mean levels of these states across individuals and provides further support for informal observations of Russel and DeSilva (1983). However, we should bear in mind that the association was strikingly insignificant for the neurotic group.

Temporal relationships between mood factors were looked at. Firstly, auto-correlations were considered, i.e. the extent to which a mood could be used to predict the same mood at a later time. The second considerations were cross-correlations, i.e. the extent to which one mood is predictive for another mood at a later stage. The results of the auto-correlations indicated that tension-anxiety moods of normal subjects were more prolonged than those of neurotic group. There was some indication for a cyclic change in tension-anxiety in depressed patients but not in anxious or normal subjects. Strikingly, similar patterns were found for the depression-dejection factor. This provides strong support for the notion of equivalence of these two states as far as underlying psychological processes are concerned. Viewed in the concept of the relatively high association found between these two mood states where cross-correlation were calculated at the lag of 0 (0.49), the present results offer strong support for these states. Quite different patterns were found for anger-hostility, fatigue-inertia and vigour-activity. Fatigue-inertia was found to be greater in the evening and vigour-activity greater in the morning.

The causality of moods over time was investigated by using cross-correlation over time. The primary concern in the present study was the relationship between tension-anxiety and depression-dejection.
Depressed mood can be precipitated by a number of mood factors, such as anger and vigour, i.e. factors not necessarily associated with tension. This implies that at least in some instances depression may not be part of the same psychological framework as tension-anxiety. No significant differences were found between subgroups.

Overall, these findings give evidence in favour of a close psychological correspondence of the two conditions of anxiety and depression. Furthermore, they lend support to the contention that there is a continuity in terms of psychological processes between neurotic state and non-psychiatric conditions.

It appears that negative affect such as anxiety and depression is not different in people who have been diagnosed as pathologically depressed or anxious from non-psychiatrically ill people. At this stage it is left up to speculation why some people are pathologically depressed or anxious while others are not. One reason may be the issue of labelling. Psychologically well people may feel that they have a reason to feel depressed or anxious and subsequently label these negative feelings as 'normal' reactions to events. Neurotics may feel that their mood changes 'out of the blue'. Furthermore, the causal attribution between normals and neurotics may differ. The former seek external explanations, the latter internal ones. This idea stems from Abrahamson et al.'s (1980) reformulation of the learned helplessness model. They tried to explain depression in an attributional framework.
Another idea, more relevant to mood changes comes from Linville (1982). She related mood changes to complexity of knowledge structures that guide the processing of information about self and others. She maintains that simplicity in a person's thinking is associated with more extreme affective reactions; greater complexity is associated with more moderate affective reactions. Such a cognitive approach may in the future lead to a more meaningful differentiation between normal and neurotic, than an illness model does at present. Such a distinction could have implications for the treatment of neurotic conditions. This cannot be said about the present classification systems.
So far this thesis has been concerned with showing how psychophysiological and time-series analysis techniques have succeeded in clarifying the issue of delineating the clinical problem of depression. Psychophysiological measures have been shown to be valuable in discriminating different subtypes of depression in a group of drug-free patients with major depressive disorders. However, attempts to use psychophysiological methods as a diagnostic aid have produced conflicting results in many recent studies particularly for anxiety and anxiety-related disorders (e.g. Byrne, 1975; Mirkin and Coppen, 1980; Giedke et al., 1980; Ward et al., 1983). The relationship of psychophysiological findings to diagnosis may have been obscured in some recent studies by the inclusion of patients who had been prior to the study or some time before on psychoactive medication immediately. Psychotropic drugs, concurrently administered with psychophysiological assessment, not only affect underlying
physiological responses but also mental state, thus obscuring possible relationships between psychophysiological mechanisms and symptom profiles. Concurrent medication, however, is controlled in many studies and was carefully controlled in the investigations reported above. In some studies however only some of the patients were drug-free (Giedke et al., 1980; Ward et al., 1983) adding an unknown source of heterogeneity to the data. The long-term effects of past psychotropic medication upon psychophysiological responses are not known.

It has been suggested that conflicting results in this area of research may be due in part to inadequate control for the effect of past drug use in some of the previous studies with patient groups. Currently used controls consisting of temporary cessation of drug use may not be adequate if drug induced neurophysiological changes are permanent or at least persistent. For example, the "wash-out" period, if any, in most of the studies were probably insufficiently long, varying from 3-4 days (Byrne, 1975), up to 7 or 10 days (Lapierre and Butter, 1980; Mirkin and Coppen, 1980). The brevity of wash out periods appears particularly optimistic in the light of the time course of effectiveness of many types of psychotropic medications. Most major tranquillizers and antidepressants take at least two weeks before reaching their maximal effectiveness (Petursson and Lader, 1984). This implies that readjustment of neurotransmitter balance is a complex process, probably involving a large number of simultaneously interacting parameters. There is no reason to suppose that the reverse of this process, the reestablishment of neurotransmitter imbalance characteristic of the pathological state, should be any less complex.
Thus taking place over a shorter period of time.

Studies which attempted explicitly to examine the effects of past history of psychotropic drug use on patients' psychophysiological responses are few in number and have produced mixed results. Pishkin et al. (1978) in a controlled study of patients with anxiety disorders found no overall difference in terms of physiological activity between a group who had been medicated with benzodiazepines and a drug-free group. On the other hand, somewhat lower psychophysiological activity has been reported in patients after antidepressant medication than before the medication (Storrie et al., 1981) and than in unmedicated patients (Ward et al., 1983). However, no clear relationship was found between dose administered and physiological response magnitude (Storrie et al., 1981). In studies on electrodermal activity before and during medication in relation to clinical improvement (Stern et al., 1961; Heiman, 1978; Storrie et al., 1981), possible effects of the medication per se could not be investigated since comparison with unmedicated patients was not performed. On the whole, the effects of drug use on psychophysiological responses particularly in anxious patients have been insufficiently explored. The studies above, in any case, only deal with the short-term effects of medication primarily on neurotransmitter balance. Animal studies increasingly demonstrated that continuous exposure to psychotropic medication is likely to have consequences which go beyond the half-life of the drug. The observed increases in dopamine receptors in brains of chronic schizophrenic patients appear to be restricted to those who have received neuroleptics for at least two years (MacRae, 1982, 1984). What none
of the studies on psychophysiological responses of clinical group taken into consideration is the possibility that prolonged medication with anxiolytics and antidepressants may lead to persistent changes in the neural substrates which underly psychophysiological responding. No study has so far investigated the influence of past history of medication upon psychophysiological responses in clinically matched groups.

The observed prolonged withdrawal symptoms following long-term benzodiazepines administration (Petursson and Lader, 1983; Ashton, 1984; Higgitt et al., 1985; Rickels et al., 1988) is an indication of possible drug induced permanent changes of neural mechanisms (see Chapter 4 for further discussion) although it is possible that such symptoms may be found in untreated anxious populations (Rodrigo and Williams, 1986). Therefore, in order to examine the possible long-term effects of benzodiazepine treatment on psychophysiological responses we need to examine a number of psychophysiological dimensions where it is known that acute drug administration induces significant changes. Thus we need to compare a group with a history of benzodiazepine treatment with the following groups: 1) a clinically anxious group without benzodiazepine treatment; 2) a clinical group who should differ from the anxious group in known way (e.g. patients with conversion symptoms); and 3) a normal control group.

Lader and Sartorius (1968) and Lader (1969) using psychophysiological techniques distinguished patients with conversion disorder from anxious and phobic patients as well as normal controls. More recent studies confirm the finding of a unique pattern of
response, primarily in terms of skin conductance but also on other measures of autonomic and cortical arousal in anxious patients (Bond et al., 1974; Horvath and Meares, 1979; Horvath et al., 1980). These findings indicate that anxious patients should manifest elevated levels of autonomic but not central nervous system arousal relative to hysterical patients. If tranquillizer administration has long-term effects we may predict that the benzodiazepine treated group should show blunted responses by years of treatment compared to the untreated group. The present study aimed at replicating the Lader study on psychophysiological differences between a group of long-term sufferers from the benzodiazepine withdrawal syndrome with those of matched groups of anxious and conversion hysteria patients and normal controls.

METODO

Subjects

Benzodiazepine Withdrawn Group: Nine patients with continuing complaints of anxiety-like symptoms who had been benzodiazepine-free for at least 12 months were recruited for the study. They all met RDC criteria (Spitzer et al., 1978) for anxiety disorders and operational criteria for the benzodiazepine withdrawal syndrome drawn up by Higgit et al. (1988). Their mean age was 46.8 years (range 30-68). They were 4 men and five women. The clinical characteristics of this group are shown in Table 9.1. This group was smaller in size than three other groups. Primarily because of recruitment difficulties, it
was decided to match groups on mean age, socio-economic status and chronicity rather than individually in order to keep the number of subjects at a maximum.

Anxious Group: 24 patients known to be suffering from anxiety states were asked to participate in the study. All were outpatients whose primary complaint was of severe, pervasive, persistent anxiety. They were 10 men and 14 women with an age range of 30 to 55 years and a mean age of 45.4 years (SD=12.7).

Hysteric Group: 13 patients with conversion symptoms meeting the DSM-III-R criteria for conversion reactions were collected from the outpatient clinic and Neurology Unit of King's College Hospital. The group was composed of 4 men and 9 women with an age range of 28 to 68 years and a mean age of 43.5 years (SD=16).

Normal Group: 13 healthy paid volunteers took part in the study who were sought via advertisements placed in University College London. They were 4 men and 9 women with an age range of 17 to 56 years and a mean age of 41.3 years (SD=11.8). They were not selected for calmness and some admitted to anxiety symptoms.

Procedure

An extensive clinical assessment of patient groups using a battery of standardized psychiatric instruments preceded laboratory testing. Before the testing, the range of clinical, physiological and psychological tests were explained to each subject. On arrival at the laboratory EEG electrodes were applied to the scalp and skin conductance electrodes to the left forearm and thumb. Subjects then
were asked to perform a number of psychological tests and physiological measures were taken. The testing session lasted approximately 45 minutes for each subject.

Most tests were applied using an on-line PDP-12A laboratory computer for rapid and accurate acquisition, storage and analysis of data. The computer effectively ran the tests in a fixed order, sampling, processing, displaying, and storing the information on magnetic tapes for subsequent statistical analysis.

The testing conditions were kept as standard as possible and recordings were carried out in a sound-attenuated recording room. The experimental session started with the physiological measures (EEG, evoked responses, skin conductance) accompanied by a reaction time task and a measure of tapping speed and finally the psychological questionnaires were administered. However, it was impractical to administer questionnaires to the anxious group and therefore the norms for anxious patients are reported instead.
### Table 9.1. Clinical and Demographic characteristics of the patients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Length of Drug Usage (Years)</th>
<th>Drug Taken</th>
<th>Time Since Withdrawal (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>M</td>
<td>Anxiety</td>
<td>17</td>
<td>Diazepam</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>M</td>
<td>Anxiety, Depression</td>
<td>8</td>
<td>Diazepam</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>M</td>
<td>Anxiety</td>
<td>4</td>
<td>Diazepam</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>F</td>
<td>Postnatal Depression</td>
<td>14</td>
<td>Chlordiazepoxide</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>F</td>
<td>Agoraphobia Depression</td>
<td>6</td>
<td>Lorazepam</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>Social Phobia</td>
<td>12</td>
<td>Diazepam</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>F</td>
<td>Anxiety, Anorexia</td>
<td>14</td>
<td>Diazepam, Temazepam</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>F</td>
<td>Anxiety, Depression</td>
<td>15</td>
<td>Diazepam, Nitrazepam</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>F</td>
<td>Anxiety, Depression</td>
<td>11</td>
<td>Lorazepam</td>
<td>18</td>
</tr>
</tbody>
</table>
Physiological Measures

EEG

Recordings were made from bipolar electrodes attached to temporal and vertex sites (Cz and T3 in the 10-20 system). After amplification, the EEG was fed into 4 parallel band-pass filters with the respective upper and lower frequencies set as follows: 2.4-4.0 Hz, 4.0-7.5 Hz, 7.5-13.5 Hz and 13.5-26 Hz. Each filter output was sampled 16 times for 5 second periods whilst the subject was at rest with his eyes open. Periods with marked interference and artefact were rejected on the basis of visual analysis by the experimenter. The 4 waveband samples were rectified and averaged and the mean rectified voltage in each waveband was calculated. The 4 values were added together and each was expressed as a percentage of the total.

AER

The recording procedure for evoked responses were identical to those for the EEG. Subjects were instructed to press a key as fast as possible in response to a series of 32 click stimuli of about 70 db presented at intervals varying between 8 and 12 seconds. The 500 msec epochs of the EEG following each of the 32 clicks were averaged by the computer and displayed on the computer oscilloscope. The 4 peaks of the averaged responses (P1, N1, P2, and N2) were identified semi-automatically with the experimenter adjusting computer estimates for each peak. The latency at each peak and the P1-N1, N1-P2, and P2-N2 peak-to-peak amplitudes were computed and recorded.
Skin Conductance

This test represents an indirect measure of palmar sweat gland activity. Skin resistance was measured from the left thumb. A self-adhesive foam ring maintained a constant area. Electrode jelly (0.05 M sodium chloride) was applied to the skin in the ring. A constant current of 14 amp/cm was passed through this electrode to an earth electrode strapped on the forearm. The voltage developed was proportional to the skin resistance of the thumb. The amplified output was fed into an analog-to-digital converter of the computer, and the voltages converted to the corresponding skin conductances. Skin conductance was measured simultaneously with the reaction time task used to measure cortical evoked responses. The basal skin conductance level and the number of fluctuations in conductance were assessed.

Performance Measures

Reaction Time

Simple auditory reaction time was measured to 32 clicks of moderate intensity. The mean reciprocal value was calculated. This test provides a measure of sensory and motor speed.

Key Tapping Rate

Using the first two fingers of the preferred hand, the subject was asked to tap a one-inch diameter key as fast as possible. The
computer recorded the number of key depressions made during 60 seconds, and the inter-tap-interval was computed in milliseconds. This task is a measure of pure motor speed.

**Self-report Measures**

The subjects completed the following questionnaires immediately after the laboratory testing:

1. The Crown-Crisp Experiential Index (CCEI): The CCEI consists of 48 questions which the testees pick the answer applying to them. It is designed so that a total score can be obtained to provide a measure of general emotionality or neuroticism together with a profile of six sub-scale scores. The six sub-scales measure free-floating anxiety (FFA), phobic anxiety (PHO), obsessionality (OBS), somatic concomitants of anxiety (SOM), depression (DEP) and hysterical personality (HYS). Each of these sub-scale dimensions is measured by eight questions (Crown and Crisp, 1979).

2. The Hostility and Direction of Hostility Questionnaire (HDHQ): The HDHQ consists of 51 true or false questions. It is designed to sample a wide range of possible manifestations of aggression, hostility or punitiveness. It is comprised of five tests which measure aspects of hostility like urge to act out hostility (AH), criticism of others (CO), projected delusional (i.e. paranoid) hostility (PH), self criticism (SC) and guilt (G) (Caine et al., 1967). Total hostility scores, which is the sum of all five tests, and Direction of hostility, which is the sum of intropunitive tests (with SC counted twice over) less the sum of the extrapunitive tests, were computed.
The Hysteroid-Obsessoid Questionnaire (HOQ): A 48-item form based on the assumption that hysterical and obsessional traits can be dichotomized along a single dimension (Caine and Hope, 1967). An item is scored 0 if answered in the obsessoid direction and 1 if answered in the hysteroid direction. Low scores thus indicate obsessoid response patterns.

RESULTS

One-way analyses of variance was applied to all the measures for the four groups in order to examine the differences between the four groups. Subsequent paired comparisons were made using Scheffe Method which is the most conservative available.

EEG

There were no significant differences between the four groups in the total voltage of the EEG as the voltage in all four wavebands (see Table 9.2).

When the voltage in each waveband was expressed as a percentage of the total voltage, the proportion of activity in the Alpha (7.5-13.5 HZ) waveband was the only one to show a significant difference (F=9.65, df=3,55, P<0.001) (see Table 9.2). From pairwise comparisons it appeared that the benzodiazepine withdrawal group had significantly more activity in this waveband than anxious group (P<0.05), with no
significant difference between the benzodiazepine withdrawal group and hysterics and normal control groups. However, the anxious group could be significantly distinguished from hysterics (P<0.05) and normal controls (P<0.05).

AER

The P1 and N2 latencies and P1-N1, N1-P2 and P2-N2 amplitudes did not show consistent differences between the groups. Group differences in averaged evoked responses emerged following the first negative component (N1) and second positive component (P2) of the AER. As shown in Table 9.3, N1 and P2 latencies were found to be significantly different between the groups (F=7.31, df=3,55, P<0.001 and F=3.95, df=3,55, P<0.05 respectively). Paired comparisons revealed that the anxious patient group showed a significantly smaller N1 component than the benzodiazepine withdrawal group (P<0.01) and the hysterics (P<0.05) but the anxious group and the normal controls could not be significantly distinguished on this measure. P2 latency was significantly lower for the anxious patients (P<0.05) and normal controls (P<0.05) than for the benzodiazepine withdrawal group and the hysterics, with no significant difference between the benzodiazepine withdrawal and the hysterics groups.
<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
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</thead>
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<tr>
<td>SN</td>
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<td>1.07 (0.68)</td>
<td>1.04 (0.70)</td>
<td>1.02 (0.67)</td>
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<tr>
<td>SN</td>
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</tr>
<tr>
<td>SN</td>
<td>1.06 (0.72)</td>
<td>1.07 (0.68)</td>
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<tr>
<td>SN</td>
<td>1.06 (0.72)</td>
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<tr>
<td>SN</td>
<td>1.06 (0.72)</td>
<td>1.07 (0.68)</td>
<td>1.04 (0.70)</td>
<td>1.02 (0.67)</td>
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</tbody>
</table>

**Table 9.2**: Waveband analysis of the EKZ: Group mean and standard deviation.
<table>
<thead>
<tr>
<th></th>
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<th>Mean (SD)</th>
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<td>SN</td>
<td>17.1 (6.3)</td>
<td>SN</td>
<td>17.0 (6.4)</td>
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<td></td>
<td>(9)</td>
<td></td>
<td>(9)</td>
<td></td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>17.1 (6.1)</td>
<td></td>
<td>17.0 (6.2)</td>
<td></td>
<td>16.2 (6.3)</td>
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<td>(9)</td>
<td></td>
<td>(9)</td>
<td></td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>17.1 (6.1)</td>
<td></td>
<td>17.0 (6.0)</td>
<td></td>
<td>16.2 (6.2)</td>
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<td></td>
<td>(9)</td>
<td></td>
<td>(9)</td>
<td></td>
<td>(9)</td>
</tr>
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<td></td>
<td>17.1 (6.2)</td>
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<td>17.0 (6.1)</td>
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<td>(9)</td>
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<tr>
<td></td>
<td>17.1 (6.1)</td>
<td></td>
<td>17.0 (6.0)</td>
<td></td>
<td>16.2 (6.2)</td>
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<td></td>
<td>(9)</td>
<td></td>
<td>(9)</td>
</tr>
</tbody>
</table>

Table 3. Intervals and amplitudes of the ANR: Group means and standard deviations.
| NS | 210.56 (33.95) | 199.32 (28.25) | 300.76 (30.64) | 200.28 |
| NS | 3.16  (1.24)  | 1.16  (1.13)  | 3.03  (1.39)  | 3.73  |
| P  | 5.73  (3.37)  | 3.26  (3.27)  | 5.13  (3.88)  | 7.32  |
| NS | 12.28 (6.28)  | 9.40  (6.89)  | 13.17 (9.24)  | 9.75  |

Skin conductance level (microsiemens)

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Anxiotone (N = 24)</td>
<td>11.54 (4.51)</td>
<td>11.54 (4.51)</td>
<td>11.54 (4.51)</td>
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<td>Normotone (N = 17)</td>
<td>11.54 (4.51)</td>
<td>11.54 (4.51)</td>
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<td>Withdrawn (N = 13)</td>
<td>11.54 (4.51)</td>
<td>11.54 (4.51)</td>
<td>11.54 (4.51)</td>
</tr>
</tbody>
</table>

Table 9.4: Skin conductance measure and performance tests: group means and standard deviations.
Skin Conductance

Mean basal skin conductance levels did not differ significantly between the groups. Significant skin conductance abnormalities only emerged in terms of number of fluctuations per minute in skin conductance ($F=2.96$, $df=3,55$, $P<0.05$). As Table 9.4 shows, the benzodiazepine withdrawal and hysteric groups differed hardly at all on this measure whilst both showed deviations from the anxious group which in their turn were not statistically significantly different from the normals. The anxious group showed the highest level of fluctuations but this was not statistically significant when contrasted with each one of the other three groups.

Performance Tests

There were no significant differences between groups on either mean reciprocal of Reaction Time task or on mean Tapping Rate per minute (see Table 9.4).

Self-report Measures

CCEI

There was no significant difference between the groups on phobic anxiety (PHO) subscale score. Highly significant differences were found, however, on free-floating anxiety (FFA) subscale score
(F=10.24, df=3,55, P<0.001), on somatic concomitants of anxiety (SOM) subscale score (F=21.88, df=3,55, P<0.001), on hysterical personality (HYS) subscale score (F=8.93, df=3,55, P<0.001) as well as significant differences on depression (DEP) subscale score (F=7.66, df=3,55, P<0.01) and obsessionality (OBS) subscale score (F=3.58, df=3,55, P<0.05) between the groups. As can be seen in Table 9.5, the benzodiazepine withdrawal group tend to score less than unmedicated anxious population almost on all subscales except for SOM and DEP subscales. Paired comparisons showed a significant difference between the benzodiazepine withdrawal group and normal controls on FFA (P<0.01), SOM (P<0.01), OBS (P<0.05) and DEP (P<0.01); but no significant difference was found on these subscales between the benzodiazepine withdrawal and anxious groups. There was a significant difference, however, between the anxious group and normal controls on FFA (P<0.01), OBS (P<0.05), SOM (P<0.01), DEP (P<0.05) and HYS (P<0.05) subscales. Comparisons between the benzodiazepine withdrawal group and hysterics showed significant differences on DEP (P<0.05) and HYS (P<0.05). Overall these results indicate that the benzodiazepine withdrawal group suffer from anxiety almost equally as the unmedicated anxious population.
Table 9.5. Psychological questionnaires data (mean score with standard deviation in parenthesis)

<table>
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<tr>
<th></th>
<th>Withdrawn (N=9)</th>
<th>Anxious (N=24)</th>
<th>Hysterics (N=13)</th>
<th>Normals (N=13)</th>
<th>Sig</th>
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<tr>
<td><strong>CCEI</strong></td>
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<tr>
<td>FFA</td>
<td>9.7 (3.3)</td>
<td>10.0 (2.7)</td>
<td>7.2 (3.5)</td>
<td>3.8 (2.8)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>PHO</td>
<td>5.4 (3.5)</td>
<td>4.6 (3.1)</td>
<td>5.1 (3.1)</td>
<td>3.2 (2.5)</td>
<td>NS</td>
</tr>
<tr>
<td>OBS</td>
<td>7.7 (3.4)</td>
<td>8.3 (3.9)</td>
<td>6.6 (4.5)</td>
<td>4.0 (1.7)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>SOM</td>
<td>9.8 (3.2)</td>
<td>6.7 (2.9)</td>
<td>3.5 (4.1)</td>
<td>2.7 (1.1)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>DEP</td>
<td>7.7 (3.3)</td>
<td>6.3 (2.3)</td>
<td>4.5 (2.6)</td>
<td>3.3 (1.3)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>HYS</td>
<td>4.7 (3.1)</td>
<td>5.3 (3.3)</td>
<td>7.7 (3.3)</td>
<td>2.8 (1.5)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td><strong>HDHQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Hostility</td>
<td>18.6 (7.6)</td>
<td>20.2 (7.5)</td>
<td>18.4 (7.7)</td>
<td>12.1 (5.3)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Direction of Hostility</td>
<td>2.1 (4.8)</td>
<td>3.1 (4.7)</td>
<td>3.0 (4.6)</td>
<td>3.7 (5.2)</td>
<td>NS</td>
</tr>
<tr>
<td>HOQ</td>
<td>13.4 (3.5)</td>
<td>21.8 (6.2)</td>
<td>22.8 (2.7)</td>
<td>14.7 (2.8)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>
The groups did not differ significantly on Direction of Hostility scale of the HDHQ. Total Hostility score, however, was significantly different for the four groups (F=3.59, df=3,55, P<0.05), with anxious group scoring more than the other three groups (see Table 9.5). Comparisons between groups showed a significant difference between anxious patients and normal controls on the Total Hostility score (P<0.05), while there was no significant difference either between the benzodiazepine withdrawal and anxious groups or between the benzodiazepine withdrawal and normal control groups. The results therefore show heightened hostility in both the benzodiazepine withdrawal group and unmedicated anxious patients.

There was a highly significant difference between the groups on the HOQ mean score (F=40.71, df=3,55, P<0.001), with hysteric group scoring more than other three groups (see Table 9.5). Pairwise comparisons showed a significant difference between the benzodiazepine withdrawal group and hysterics (P<0.01) and between the benzodiazepine withdrawal group and anxious patients (P<0.01), but no significant difference between the benzodiazepine withdrawal group and normal controls.
DISCUSSION

The possible long-term effects of medication on psychophysiological responses were examined in a group of long-term users of benzodiazepines now withdrawn from medication. The central and autonomic nervous systems responses of this group were compared with those of clinically matched groups of unmedicated anxious and conversion patients and normal controls. Of the EEG measures significant differences were found in amount of alpha activity. Whereas the anxious group showed the typical low alpha activity found by a number of studies (e.g. Lindsley, 1950; Roubicek, 1969; Bond et al., 1974; Gaebel and Ulrich, 1988) in anxious patients, the benzodiazepine withdrawal group could not be differentiated either from the hysterical group or from the normal controls.

Averaged evoked responses of the benzodiazepine withdrawal group were indicative of a continual state of low arousal at the cortical level which is consistent with previous observations (Meares and Horvath, 1972; Bond et al., 1974; Shagass, 1983). The benzodiazepine withdrawal group had a longer N1 and P2 latencies, which shows their continual state of low arousal at the cortical level. Long latency components of the AER are sensitive to the importance of the stimuli in the subject's cognitive field (Satterfield, 1965). Increase in these components are said to be responsive to stimuli that are relevant (Wilkinson and Lee, 1972) or are thought to require selective attention (Naatanen, 1982; Hillyard and Kutas, 1983; Donald, 1983; Hansen and Hillyard, 1984). Acknowledging this association of
cognitive mode and changes in long-latency AER, the results suggest that abnormally low level of cortical arousal in the benzodiazepine withdrawal group may be associated with some cognitive dysfunction (such as inattention) in these patients, or it is a function of a withdrawal response resulting from termination of benzodiazepine therapy. The latter explanation is more likely and suggests the difference between the benzodiazepine withdrawal group and the unmedicated anxious population at cortical level is evidence for the long-term effect of medication. However, the results of self-report measures indicated these two groups to have almost equivalent levels of self-reported anxiety.

Higher mean skin conductance levels were found for the anxious group although overall mean skin conductance levels did not reach significant level. Skin conductance fluctuations showed the benzodiazepine withdrawal group more closely to resemble hysterics and normal controls than the unmedicated anxious patients. Lader and Sartorius (1968) obtained results similar to the present study. Their neurotic subjects as a group did not show any tendency to habituate to repeated auditory stimuli. In this respect, they differed from groups with other neuroses studied by Lader (1969), all of whom show a delay but not an absence of habituation of skin conductance response. However, the Lader and Sartorius study differed from the present study in one important respect: their neurotic subjects showed remarkably high levels of arousal, as indicated by spontaneous fluctuations in skin conductance, in excess of 11 per minute, a level greater than that found in any other neurotic group studied by Lader. This seems to explain habituation because Lader showed in a series of
normal subjects and groups with different neuroses an inverse relationship between habituation and the rate of spontaneous fluctuation in skin conductance. In the Lader and Sartorius study, the failure to habituate could be understood in terms of remarkably high arousal level. In the present study it cannot. The level of arousal, manifested by spontaneous fluctuations in skin conductance, was significantly lower in the benzodiazepine withdrawal group than in the anxious group. This indicates that the withdrawn patients in this study showed little anxiety and physiological arousal in their symptoms. In support of this Horvath and Meares (1979) and Horvath et al. (1980) reported higher number of spontaneous fluctuations in skin conductance in anxious patients in comparison with normal controls.

Thus the results offer no support for the hypothesis as the re-emergence of the anxiety-related disorder for which the benzodiazepines were originally prescribed. No evidence was found that psychophysiological indicators of anxiety were marked in the previously long-term drug users. Yet self-report measures and psychiatric assessments showed this group of patients to have a very similar pattern of reactions to other patients with diagnosis of anxiety-related disorders. Confusion between re-emergence of the original anxiety and a true withdrawal syndrome is attributed to the fact that anxiety is accompanied by widespread bodily changes. Characteristic somatic, physiological, autonomic, biochemical and behavioural changes occur (Lader, 1975; 1980). Consequently, a variety of symptom patterns is found in anxious patients (Tyrer, 1976).
In conclusion, the present findings emphasize the differences between patients withdrawn from long-term benzodiazepine therapy and unmedicated anxious patients in terms of their anxiety and physiological arousal. It seems that the benzodiazepine withdrawal group and the patients with conversion symptoms have more in common (at least in terms of some psychophysiological indices) than the unmedicated anxious patients. However, the observation that patients with withdrawal symptoms are psychophysiological hard to distinguish from normal controls on a highly sensitive index of autonomic arousal (i.e. skin conductance fluctuations) suggests that it is unlikely to be an affective disturbance and lends support to the view that it represents a genuine iatrogenic condition which may be best treated as a complication of benzodiazepine therapy. The present study has failed to elucidate the mechanisms underlying these patients' problems, and therefore further data are necessary in order to clarify the ambiguities in the present findings.
CHAPTER 10

EXAMINATION OF PSYCHOPHYSIOLOGICAL RESPONSES AS A CONSEQUENCE

OF LONG-TERM BENZODIAZEPINE MEDICATION

INTRODUCTION

In the previous chapter differences between groups of neurotic patients on a battery of physiological and psychological measures were examined. It was shown that patients withdrawn following long-term benzodiazepine treatment could be differentiated significantly from a non-medicated anxious population in terms of some of the physiological responses. Skin conductance fluctuations, which are a highly sensitive index of autonomic arousal, showed the withdrawn group more closely to resemble the normal than the unmedicated anxious sample. No evidence was found that psychophysiological indicators of anxiety were marked in the benzodiazepine withdrawal group. Yet the results of psychological questionnaires and psychiatric assessment showed them to be anxious in comparison with non-anxious group and clinically anxious patients. However, no evidence was found to indicate persistent changes in the neural substrates which underly psychophysiological responses of long-term benzodiazepine patients.
Some of the ambiguities in the present findings concerning the nature of this problem of prolonged medication with benzodiazepines need further clarification. We need further proof that the long-term medication group is different from unmedicated group. Thus comparing the patients with a history of benzodiazepine treatment studied in the previous chapter with a group of normal controls might help to elucidate the issue. In this way it was hoped to determine whether this particular patient group who had been chronic benzodiazepines users would respond normally to a challenge dose of diazepam. Even though they are now anxious on psychological tests and psychiatric assessments, we may predict that they will show no differences in psychophysiological tests except when diazepam challenged.

Perhaps the most probable explanation for the differences observed between the patients withdrawn following long-term benzodiazepine treatment and untreated anxious populations would be expected to be in the mechanisms that involve benzodiazepine metabolism. Increased numbers of benzodiazepine receptors following chronic benzodiazepine administration have been reported (e.g. Wilkinson et al., 1980; Mennini et al., 1984). Evidence, however, is strongest for a reduction in benzodiazepine binding capacity following chronic benzodiazepine administration (Rosenberg and Chiu, 1979; File, 1982; Sher et al., 1983, Aranko, 1985). Reduced sensitivity to GABA postsynaptically (Petursson et al., 1981; Sher et al., 1983; Waterhouse et al., 1984) and an uncoupling of the benzodiazepine-GABA receptor complex such that GABA ceases to enhance benzodiazepine binding (Mele et al., 1984) have both been reported as a consequence of prolonged benzodiazepine intake. Furthermore, Little
et al. (1987) have demonstrated that chronic benzodiazepine administration leads to tolerance to acute effects of benzodiazepines but enhanced sensitivity to inverse agonists, suggesting that an explanation merely in terms of receptor numbers, or sensitivity, would be too simplistic. The benzodiazepine receptor is unusual in that as well as the benzodiazepines that act there to lower anxiety, it can also mediate the action of the so-called 'inverse agonists' which have behavioural effects in the opposite direction (Gray, 1982; Hinson and Siegal, 1983), that is they increase anxiety. Although there is evidence that both a benzodiazepine-like and an inverse agonist-like ligand might exist, they provide no information as to the underlying mechanisms consequent upon long-term medication for the following reasons. Benzodiazepines may appear to continue to be effective when measures during treatment are compared with post-treatment measures because continued medication suppresses withdrawal symptoms. Furthermore, the need to increase doses to produce a given effect in order to maintain anxiolysis reported in some studies (e.g. Haefely, 1983; Haskell et al., 1986) is indicative of development of tolerance. In addition, a number of studies report the re-emergence of symptoms, primarily of anxiety, while patients are still taking benzodiazepines, which also suggests tolerance development (Greenblatt and Shader, 1978; Ashton, 1984; Higgitt et al., 1986). There is therefore some evidence for possible effect of the repeated administration of the drug. Although the nature of the effect is not invariably demonstrated, the observation that increased plasma benzodiazepine concentrations in negative studies are not associated with increased deficits implies that the drug has decreasing effects over years of treatment.
The processes to account for the observed prolonged medication with benzodiazepines are little understood. Pharmacodynamic and behavioural factors have both been suggested to play a part but their respective importance is unclear. However, testing the patients with a history of benzodiazepines treatment with a challenge dose of diazepam and comparing them with an untreated group on a battery of psychological and physiological tests might provide us with some clues concerning their respective contributions. The aims of the present study therefore were:

1) to determine whether this patient group who had been chronic benzodiazepines users show any differences in psychophysiological tests in comparison with a normal control group matched for age and sex;

2) to demonstrate the extent to which the long-term effects of medication found in the previous study are due to prolonged alteration in responses to benzodiazepines.

METHOD

Subjects

The same 9 patients who suffered from benzodiazepine withdrawal syndrome studied in the experiment presented in the previous chapter were used. Details concerning patients' selection are given in Chapter 9.
The control group comprised of an equal number of drug-free, healthy adult paid volunteers in the same age range who were sought via advertisements placed in the Psychology Department of University College London. They matched the patient group for sex and none of them had had chronic exposure to benzodiazepines.

Design

The study was a two-stage, double-blind placebo-controlled investigation. Subjects were tested on two occasions two weeks apart. On one of these occasions they were administered 5mg diazepam orally and on the other a matching placebo. The effects of the drug were compared with those of placebo on a battery of physiological and psychological measures and the differences between the two groups were examined. The study also incorporated an extensive clinical assessment of the patient group using a battery of standardized psychiatric instruments.

Procedure

Ethical Committee approval was sought and obtained for the following procedure. Subjects were informed that the experiment was aimed at investigating the presence of long-term effects of benzodiazepine administration and involved a single administration of 5mg of diazepam orally. Subjects were not aware, however, which of the two occasions of attending the laboratory would involve active
medication. The clinical assessment of patients preceded laboratory testing and included a full psychiatric and drug history, a history of the withdrawal from benzodiazepine medication as well as an assessment of current withdrawal symptoms by interview and self-ratings.

Subjects were instructed not to drink alcohol the night before testing. On arrival at the laboratory EEG electrodes were applied to the scalp and skin conductance electrodes to the left forearm and thumb. Subjects were then asked to perform a number of physiological tests and psychological measures were taken. Following this pre-test a tablet was administered and subjects rested for 30 minutes. The battery of tests were then re-administered. Subjects were asked to continue daily mood, sleep and bodily symptoms ratings for the 7 days following each testing session. The testing session lasted approximately two and a half hours on each occasion.

Most tests were applied using an on-line PDP-12A laboratory computer for rapid and accurate acquisition, storage and analysis of data. The computer administered the tests in a fixed order, sampling, processing, displaying and storing the information on magnetic tapes for subsequent statistical analysis.
Physiological Measures

EEG and AER

Recordings were made using the techniques described in detail in Chapter 9. The latency at each peak and peak-to-peak amplitudes were computed and recorded automatically. Reduction in amplitude and increases in latency are indicators of reduced responsiveness to stimuli and are frequently correlated with subjective decreases in alertness.

Fourier analysis of EEG

A fourier analysis was performed on 16 EEG samples taken with the subject resting with eyes open. The experimenter rejected any samples with muscle artefact present on visual analysis. The samples were filtered between 2.0 and 32.0 Hz after which online power spectral analysis was performed. The spectrum was estimated by calculating the auto-correlation function followed by fourier transformation. Each of the 16 records was analysed in sections of 4.8s duration and smoothed to give values at 0.5 Hz intervals. The power was analysed and log values taken for the four bands. The peak frequency in each band was also calculated.

Skin Conductance

Skin conductance was monitored using the techniques described in Chapter 9. Basal skin conductance level and the number of fluctuations
in conductance were recorded during the reaction time task.

**Blood Pressure**

Blood pressure was measured using a mercury sphygmomanometer (Accoson) attached to the right upper arm. Standard procedures were used to obtain values of systolic and diastolic pressure.

**Pulse Rate**

Pulse rate was determined via palpitation of the radial artery.

**Performance Measures**

**Reaction Time**

The simple auditory reaction time to 32 clicks of about 70 db was measured by the computer. The reciprocal transformation was applied to normalize the distribution and the mean calculated. This test provides a measure of sensory and motor speed.

**Key Tapping Rate**

Using the first two fingers of the preferred hand, the subject was asked to tap a key as quickly as possible. The computer recorded the number of key depressions made during 60 seconds, and the inter-tap-interval was computed in milliseconds. This task is a measure of
Cancellation Task

This is a measure of attention to close detail at speed and accurate scanning. The task involved the cancellation of 4s in a table of numbers in which the frequency of 4s was 40 in 400 random digits. The time to complete the task and the number of errors incurred were computed. 4 equivalent forms of the test were used, one for each testing occasion (see Appendix 1).

Digit Symbol Substitution Test

This test is a sub-test of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1958) and is a good measure of new learning ability. The test includes motor and cognitive components but the latter predominate. It entails the subject coding symbols for numbers. The table was presented as in the WAIS manual with number of correct codings in 90-second period used as a measure (i.e. 90/no. of items completed). Alternative equivalent forms of the test were administered on each testing occasion (see Appendix 2).

Symbol Copying Test

This test was devised by Kornetsky et al (1959) as a strictly motor test. The same symbols are used as in the Digit Symbol
Substitution Test, but the subject has only to copy and not code them. This gives a measure of writing skills and the motor component of the Digit Symbol Substitution Test. Again the score was the mean time (in seconds) it took to complete each correct item during the 90-second test period (see Appendix 3).

**Self-ratings**

**Mood Rating Scale**

Mood states was assessed using the Bond and Lader (1974) Mood Rating Scale which subjects were asked to complete prior to and 45 minutes post drug ingestion. The scale consists of 16 bipolar analogue scales with 2 opposed mood-related adjectives anchoring the ends of the scales. The Mood Rating Scale has been shown reliably to yield 3 mood factors: alertness, contentedness and calmness. These factors scores were used as dependent variables (see Appendix 4).

**Bodily Symptoms Scale**

A 12-item visual analogue scale was constructed to measure bodily symptoms (possible withdrawal symptoms). Subjects were asked to rate themselves along 100mm lines between symptom absent and very severe. This was completed at the same time as the Mood Rating Scale (see Appendix 5).
Sleep Rating Scale

The quality of subjects' sleep was assessed using a specially designed self-rating scale consisting of 4 bipolar visual analogue scales aimed at assessing subjective experience of quality of sleep, speed of sleep onset, speed of awakening and feeling upon awakening. Subjects completed this questionnaire each morning upon awakening for 7 days in each occasion at their homes (see Appendix 6).

Clinical assessment

Hamilton Anxiety Scale (Hamilton, 1960) was completed by the experimenter once on each testing occasion prior to drug taking for both the experimental and the control subjects. The Hamilton Scale is widely used psychiatric instrument designed to assess the severity of anxiety. It covers a wide range of visceral and muscular symptoms, insomnia, cognitive dysfunction and interview behaviour. These are grouped as 15 variables, each rated on a 5-point scale.

Statistical Analysis

Most of the data were transcribed from magnetic tapes, but clinical details, rating scale data, and psychological measures were punched on cards for computer analyses.
The data were analysed using the analysis of variance model with subjects, groups, occasions, drugs (diazepam vs placebo) and time (pre and post drug) as main source of variance. Differences in response to the diazepam challenge between the two groups could be obtained from the groups by drug by time interactions. In the case of home ratings, both the group by drug and group by drug by time interactions could be examined under the hypothesis. Polynomial components of the time factor were extracted for each subject and the linear, quadratic and cubic effects were tested using further analysis of variance to identify significant trend effects.

RESULTS

Physiological Measures

The spectrum analysis of the EEG revealed a near significant group by drug by time interaction for beta peak frequency as shown in Figure 10.1 (F=3.26, df=1,13, P<0.06). This figure shows that an increase in beta frequency occurred in the EEG of control subjects following ingestion of diazepam. There was a slight decrease in the experimental group. No other significant differences on the EEG, AER variables, other physiological measures emerged between the groups in their response to diazepam.
Performance Measures

There was no significant difference on the performance measures between the groups in their response to diazepam (see Table 10.2). However, the patients performed worse than the controls throughout the study on almost all the measures of performance.

Self-Ratings

The analysis of mood ratings revealed that control subjects responded significantly more to the diazepam challenge than did the experimental group. Figure 10.2 shows the mean scores of both groups on factor 1 of the Mood Rating scale (drowsiness). The control group showed a marked increase in drowsiness in response to the diazepam challenge and the group by drug by time interaction on the analysis of variance confirmed this (F=5.04, df=1,14, P<0.05). On the feeble-strong, the energetic-lethargic and the clumsy-well-coordinated dimensions control subjects responded significantly more (F=4.49, df=1,13, P<0.05; F=6.13, df=1,13, P<0.01; F=11.46, df=1,13, P<0.005 respectively) with experimental group showing little or no response (see Figures 10.3, 10.4, 10.5). Ratings on the clear-headed-muzzy and dreamy-attentive scales followed a similar pattern although on both these dimensions the experimental group showed a tendency to respond in the same direction as the control group but to a lesser degree (F=4.66, df=1,13, P<0.05; F=5.02, df=1,13, P<0.05 respectively) (see Figures 10.6 and 10.7).
Figure 10.1. Mean Peak Beta Frequency of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.2. Mean Self-rating on Drowsiness Mood Factor of 2 Groups Following 5mg Diazepam or Placebo.
Figure 10.4. Mean Self-rated Energy of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.3. Mean Self-rated Calmness of 2 Groups Following 5mg Diazepam or Placebo.
Figure 10.5. Mean Self-rated Coordination of 2 groups Following 5mg Diazepam or Placebo.

Figure 10.6. Mean Self-rated Clear-Headedness of 2 groups Following 5mg Diazepam or Placebo.
Figure 10.7. Mean Self-rated Attentiveness of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.8. Mean Self-rated Muscle Cramps of 2 Groups Following 5mg Diazepam or Placebo.
This pattern was reversed on one of the measures of benzodiazepine withdrawal symptoms (see Figure 10.8). On this dimension, relating to presence of muscle cramps, the experimental group showed a marked reduction in symptoms while the control group was unaffected by the active diazepam. The three-way interaction was significant ($F=6.11$, $df=1,14$, $P<0.03$) implying that diazepam led to a significant reduction in muscle cramps in the experimental group. A similar three-way interaction emerged for the symptoms of eye-soreness ($F=4.19$, $df=1,14$, $P<0.05$, as shown in Figure 10.9) and the happy-sad dimension of the Mood Rating Scale ($F=6.30$, $df=1,13$, $P<0.03$). The diazepam challenge was associated with an increase in happiness and reduction in eye-soreness in the experimental group while no drug effect was apparent for the control group (see Figure 10.10).

The analysis of home ratings indicated that the diazepam challenge had greater effects on the experimental than on the control group. The significant three-way interaction between groups, drug and time on Mood Factor 1 (drowsiness) is shown in Figure 10.11 ($F=7.37$, $df=1,12$, $P<0.02$). The experimental group remained more drowsy in the week following the diazepam challenge than did the control group. The discrepancy between the experimental and control group was particularly marked for the calm-excited dimension (see Figure 10.12) and quadratic component of the three-way interaction was significant ($F=10.97$, $df=1,12$, $P<0.007$); a marginally significant result emerged for the clumsiness dimension as shown in Figure 10.13 ($F=3.81$, $df=1,12$, $P<0.07$). The pattern was less clear-cut for ratings on the strong-feeble dimension as shown in Figure 10.14 ($F=4.85$, $df=1,12$, $P<0.05$).
Withdrawal Symptoms

Measures of withdrawal symptoms rated over the seven days following diazepam challenge produced surprisingly clear-cut results. Figure 10.15 shows the three-way interaction between groups, drug and time on self-ratings of impaired concentration (F=4.58, df=1,12, P<0.05). While the diazepam challenge had relatively little effect on the control group's self-rated concentration, substantial impairment in concentration was reported by the experimental group following diazepam. Figure 10.16 shows the same patterns for eye soreness scale which also yielded a significant three-way interaction (F=4.98, df=1,12, P<0.05). A somewhat less clear-cut picture with a similar pattern was observed in self-ratings of muscle cramps (Figure 10.17) where the diazepam challenge was followed by increased self-rated cramps for the experimental group only (F=5.06, df=1,12, P<0.04).

The only withdrawal symptom not to reflect this pattern of results was self-rating of depression where a brief period of decreased depression followed the diazepam challenge for the experimental group but not for the control group (F=9.09, df=1,12, P<0.01). This is shown in Figure 10.18.
Figure 10.9. Mean Self-rated Eye-Soreness of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.10. Mean Self-rated Dysphoria of 2 Groups Following 5mg Diazepam or Placebo.
Figure 10.11. Mean Daily Self-rated Mood Factor of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.12. Mean Daily Self-rated Calmness of 2 Groups Following 5mg Diazepam or Placebo.
Figure 10.13. Mean Daily Self-rated Strength of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.14. Mean Daily Self-rated Calmness of 2 Groups Following 5mg Diazepam or Placebo.
Figure 10.15. Mean Daily Self-rated Concentration of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.16. Mean Daily Self-rated Eye-Soreness of 2 Groups Following 5mg Diazepam or Placebo.
Figure 10.17. Mean Daily Self-rated Muscle Cramps of 2 Groups Following 5mg Diazepam or Placebo.

Figure 10.18. Mean Daily Self-rated Dysphoria of 2 Groups Following 5mg Diazepam or Placebo.
DISCUSSION

The question of whether the long-term effects of benzodiazepine medication found in the previous chapter were due to prolonged alteration in responses to benzodiazepines was examined in a group who had all been withdrawn from medication but who had previously chronically ingested them. The increase in beta spectrum activity in the EEG characteristic of the effects of benzodiazepine (Bond and Lader, 1982; Bond et al., 1983; Higgit et al., 1986) was absent in this group although present in the control group. No drug effect was observed on the other physiological and performance measures, but small and insignificant drug effects were found for the control group. However, on the more sensitive mood measures control subjects responded significantly more to the diazepam especially in terms of the sedative effects of the drug (Bond and Lader, 1981; Baldessarini, 1985). Similarly, Hommer et al. (1986) demonstrated that symptom rating scales constitute unambiguous indicators of true long-term drug effects than many physiological indicators when the criterion is sensitivity at receptor level.

It was also striking, given the length of time since withdrawal from the benzodiazepines, that on some withdrawal symptoms (namely depression and muscular cramps) some amelioration occurred in the experimental group in response to the diazepam in the absence of apparent change in the control group. These results may be interpreted as suggesting that 5mg dose of diazepam served to suppress ongoing withdrawal symptoms (see Ashton, 1984; Schopf, 1983). Alternatively,
it is possible that experience with benzodiazepines is necessary before symptom suppressive effects become apparent (Sepinwall et al., 1978). This may be viewed as sensitization to drug effects due to pharmacodynamic changes at receptor level (Rago et al., 1983; Stephens and Schneither, 1985). However, the observation that withdrawal symptoms did not increase in association with reductions in benzodiazepine intake for the vast majority of those treated (Higgitt et al., 1987) indicates that these observed drug effects is not consistent with an interpretation solely in terms of pharmacodynamic changes (Ashton, 1984).

The persistence of some withdrawal symptoms in the week following the diazepam challenge is more difficult to account for. It is not possible that even such a small dose of the drug might have triggered a withdrawal reaction by destabilising the homeostasis between receptors and the putative endogenous ligand (Costa, 1985). However, a behavioural account may well be more parsimonious (Gray, 1982). It is likely that withdrawal symptoms conditioned to small doses of the drug had not been completely extinguished and were triggered by the subjective effects of the challenge (see File, 1982; Siegal and MacRae, 1984). It has indeed been suggested that withdrawal symptoms may be related to pavlovian conditioning processes. Hinson and Siegal (1983) have suggested that after abstinence drug associated environmental cues may produce drug mirroring conditioned responses.

In light of the persistence of some of these withdrawal symptoms for at least a week following the experimental test it is more likely that cognitive factors may have played an important part. Most
experimental subjects who had experience of severe withdrawal symptoms from benzodiazepines may have been primed to label subsequent minor symptoms as withdrawal. Or symptoms may be due to a new psychological or medical disorder which developed during the period of benzodiazepine treatment whose symptoms were masked or modulated by the benzodiazepine usage (Wesson and Smith, 1982; Higgitt et al., 1987).

The persistence of some of these withdrawal symptoms over periods of months as reported by other workers has important treatment implications. It suggests that a state of dependence might readily be re-established on recommencement of regular intake of benzodiazepines. Regardless of whether the origin of withdrawal symptoms is psychological or pharmacodynamic, this group of patients seems very likely to be prone to experience complications if benzodiazepine treatment were recommended.
GENERAL DISCUSSION AND CONCLUSIONS

In the previous chapters, the results of several experiments were presented and points of relevance to each chapter were discussed. The purpose of this chapter is to attempt to draw together the various observations into a coherent pattern and to relate the results to previous work as reviewed in Chapters 2 to 4. A model of emotion will also be presented making use of the results of previous studies as well as the present set of investigations.

Summary of Main Findings

Skin conductance

Evidence was presented in Chapters 5, 6 and 7 which confirmed the hypothesis of abnormal electrodermal activity in depressive patients. The main findings were 1) a high proportion of patients had abnormal skin conductance; 2) those patients classified as neurotic on the Newcastle scale had significantly higher spontaneous electrodermal responsivity than either the endogenous patients or the normal subjects; 3) the abnormalities of electrodermal activity may be due to
increased output of thyroid hormones.

Generally speaking, these findings are in accordance with previous studies, with one exception (Toone et al., 1981). Toone and his co-workers suggested that their patients may have lacked the severity of symptoms described in earlier studies. In another study (Giedke et al., 1980), the differences in electrodermal activity between the patients and the normal subjects were observable only during baseline period but not during the experimental period.

Speaking in terms of individual skin conductance variables, the spontaneous fluctuations is the variable that has consistently shown higher values in neurotic depressives. This lends validity to a link between the spontaneous fluctuations and level of physiological arousal (Lader and Wing, 1966; Bond et al., 1974; Chapter 9).

The question as to whether anxiety and depression are separate psychological processes or part of the same psychological process has been raised frequently but never been conclusively answered. Chapter 8 attempted to answer this question by measuring mood changes of anxious, depressed and normal subjects over a period of 4 weeks. It was found that overall mood did not differ significantly between groups. Patterns of mood change over time were investigated and strikingly similar patterns emerged for anxious and depressed moods in all three groups.

These findings support the contention that there is a continuity of psychological processes between neurotic and normal conditions.
Furthermore, the observed similarities between anxious and depressed moods and the link between anxiety and abnormality of skin conductance in depression (Chapter 5), perhaps suggest that the levels of anxiety might have predicted the abnormal skin conductance observed in depression.

Long-term Medication Effects

Chapter 10 contained evidence suggesting that altered responses to benzodiazepines persist in long-term benzodiazepine users for several months. Such patients appeared to be less affected by diazepam in terms of its commonly observed effects regardless of their original medication. However, these patients were more likely to manifest two specific types of effects: 1) immediate symptom reduction and 2) exacerbation of withdrawal symptoms over the subsequent week.

Chapter 9 reported the relative differences between these long-term benzodiazepine users and patients with anxiety-related disorder. Although these patients showed little anxiety and physiological arousal in comparison with anxious patients in terms of a highly sensitive index of autonomic arousal, other psychophysiological indices such as the AER components largely supported the view that these ex-users of benzodiazepines have a very similar pattern of reactions to other patients with conversion symptoms.

These results require a primarily cognitive account although in some respects they are also likely to be the result of simple artefacts. Firstly, it is likely that patients who have complained of
and found a certain degree of sympathy for their withdrawal symptoms should label any bodily experiences subsequent to this as a re-emergence of withdrawal (Pennebaker, 1982). Secondly, the reduced effectiveness of the drugs in inducing immediate effects may require an account in terms of the pharmacodynamic effects of long-term medication with benzodiazepines. Thirdly, the greater responses elicited from the patients may at times be attributable to response bias or sensitization to bodily states following repeated psychiatric assessments.

Theoretical Issues

In summarising the results the following theoretical issues emerged:

Differentiation between healthy individuals and patients with anxiety states at rest is best seen with skin conductance measures. Moreover, the more anxious the individual, the higher his physiological activity.

Patients with anxiety states adjust much more slowly than normals to the contingencies of the experimental situation. Similarly, anxious patients after exposure to a stimulation procedure are slower to return to pre-stimulation levels as monitored by skin conductance. Thus, if one wants to maximise differences between anxious and calm subjects, a stimulation procedure should be applied but particular attention be paid to the immediate post-stimulation period. Moreover,
if subjects are exposed to a repetitive series of identical stimuli, anxious patients will usually show a marked increment in their responses whereas normals tend to maintain their responses. This is another aspect of the generally maladaptive response systems which anxious subjects have and the further implications of this are explored in the next section.

Differentiation between subtypes of depression (Chapter 5) advocates the clinical evaluation of depressed patients in terms of neurotic and endogenous. Neuroticism may be defined as an excess of activity and over-responding. Both are observable in the patients, can be rated and make no assumption regarding aetiology or pathological mechanisms. This dichotomy seems as useful as any. However, the two conditions can occur together and the clinical picture may alternate between them.

Nevertheless, the equating of "endogenous" with lowered arousal is not justified. As demonstrated in Chapter 7 there is an inverse relationship between the spontaneous electrodermal responses and thyroid function in depression. It often appears that there is a lowering of resting levels of activity with reactivity sometimes diminished. Yet although behaviourally depressed patients are often slow and inhibited, there is no evidence of inhibition centrally (Shagass, 1972). If the peripheral effectors by which central processes are detected are altered in function or impaired, no inferences about the level of central activity can be drawn. It is possible that such a state of affairs exists in endogenous depressives.
One hypothesis that may evaluate depressive illness in physiological terms is the following. The basic pathological mechanism in depression is physiological retardation. This manifests itself as slowness of speech and movement, and as depression of glandular function such as sweating. Retardation of affect is experienced first as depression and then, as the retardation increases, an absence of affect, characteristic of deeply depressed patients. The retardation can be endogenous, that is cause unknown, or in response to external events (reactive) or an interaction between external events and a predisposition towards retardation in the individual. As a response to the general bodily and affective changes, anxiety is engendered which may reach the dimensions of agitation but which is superimposed on and may completely mask the retardation as demonstrated in the experiment reported in Chapter 5. Psychophysiological indicators of depressive illnesses then reflect an amalgam of the retardation and agitation.

A Cognitive Psychophysiological Formulation of Emotions

What conclusions can be drawn from the current findings and those of previous studies? Almost all studies suggest that anxious subjects are in a state of overarousal. This has been shown for peripheral autonomic measures such as electrodermal activity and central correlates, the EEG. Moreover, the more anxious the individual, the higher his/her physiological activity, and clinical improvement is associated with a lessening of this overarousal.
The concept of general arousal is of a behavioural continuum ranging from drowsiness to extreme emotions of anger or fear. Psychophysiological variables reflect the intensity of behavioural arousal but are themselves subject to a variety of constraints. For example, the pulse volume of the finger-tip subserves a primary thermoregulatory role in contrast to the sweat-glands of the finger-tip which are more responsive to psychological influences (Christie, 1980). The problems in obtaining meaningful patterns of physiological responses reflect the idiosyncrasies of each measure both in psychological and physiological terms.

One may therefore assume that the skin conductance would give a measure of the level of arousal, the spontaneous skin conductance responses a measure of the physiological arousing mechanisms (Lader and King, 1966; Raskin, 1975). The proposed physiological arousing mechanisms would represent "internal" arousing mechanisms in conjunction with any forms of stimulation which would be "external" arousing mechanisms. Using this model it is possible to go a little further in attempting to explain the difference between patients with anxiety states and healthy individuals. It may be remembered that in anxious patients and in neurotic depressives both the basal skin conductance levels and the number of spontaneous fluctuations increased, whereas in the normal subjects these measures decreased significantly (as did in endogenous depressives). If we examine the patients, we find that the level of arousal increases, habituation fails to occur to the stimuli ("external" arousing mechanisms) and the spontaneous fluctuations ("internal" arousing mechanisms) also increases because there is a need to maintain a higher level of
This model (Figure 11.1) is an amalgam of many authors' suggestions, especially those of Spielberger et al. (1971), Lader (1983) and Lazarus (1966,1985). In this formulation, external stimuli impinge on the organism. The stimuli can be physical, such as trauma and noise, or social, such as poor living conditions, inadequate nutrition, etc., or psychosocial, such as marital discord and problems at work. Internal stimuli are also important and consist of thoughts, needs, aspirations, and so on. Both external and internal stimuli are appraised for possible threats to the organism or individual. The internal stimuli are modified by genetic endowment and past experience, nature and nurture, which themselves interact. The internal stimuli modify the appraisal of both themselves and the external stimuli.

If either a potential advantage or potential disadvantage is detected, two processes follow. First, the activity of certain parts of the CNS increases but remains co-ordinated and integrated. This is arousal. Second, an affect is experienced which is appropriate to the stimulus in both qualitative and quantitative terms. Thus, a dangerous stimulus would result in fear, an obnoxious one in disgust, etc.

How is the emotional state recognised and described verbally? Although both the development of emotional expression in children and their acquisition of language have been carefully studied, there have been relatively few studies on the acquisition of emotional language. It appears that a child learns to describe his feeling state...
appropriately as fear, anger, etc., because his mother teaches him the correct word inferring his mental state from his situation, his behaviour and his facial expression. Thus although the experience of an emotion is presumed to be innate, the use of the generally accepted words to describe the feeling is a learned skill. Because of the rewarding properties of the mother’s attention, overt signs of the emotion may be reinforced: consequently, over demonstrative mothers would be expected to have overdemonstrative offspring. Nevertheless, some mothers may be insensitive to their children’s emotional feelings and diagnose them wrongly. Thus a child may associate an inappropriate word to his feeling and in later life may complain of anxiety when he is depressed or vice versa.

The CNS arousal is accompanied by widespread physiological changes (Tyrer, 1976; Lader, 1980). These changes are relayed back to the CNS by proprioceptive pathways but can also be consciously perceived by the subjects (Lader, 1983; Dienstbier, 1989). These may reinforce the emotion by acting as internal stimuli and may constitute a potential positive feedback loop.

Methods for coping with heightened emotional states, especially unpleasant ones, interact with many points of the model. Thus, external stimuli apparently producing the emotion can be identified and removed by environmental manipulation. Appropriate coping behaviour can be learnt, thus adding to and modifying past experience; the most fundamental form of coping behaviour is adaptation or habituation. There may be re-appraisal of the properties of the stimulus. Also, there are the wide range of psychological mechanisms
studied by Freud such as denial, repression, regression, projection and reaction formation.

Can such a model explain morbid emotions and their accompanying physiological changes? Pathological trait anxiety and depression can be regarded as extreme deviations, as the upper end of a normally distributed continuum of personality factors (Fonagy and Higgitt, 1985). As mentioned before, genetic factors are important here and interact with previous experience to render an individual particularly liable to experience certain emotions under stress. This forms the basis of a type of specificity in that particular emotions will be characteristic of particular individuals. The existence of individually specific physiologic response patterns is well documented (Lacey and Lacey, 1958; Engel, 1972).

Another aspect of the theoretical model is its applicability to the problem of withdrawal response from long-term benzodiazepine treatment. It is established that much of what has been learned about the perception of the external environment is paralleled by perception of physical sensations and internal states (Pennebaker, 1982). We use schemata to monitor internal sensations and may selectively attend to certain internal cues depending on their salience and relevance. For example, changes observed in AER components in patients withdrawn following long-term benzodiazepine treatment were found to be responsive to stimuli that are relevant and require selective attention (see Chapter 9).
The implication of such finding is that noxious, neutral or pleasant sensory stimuli undergo a process of cognitive appraisal and this cognitive process has the power to amplify or attenuate sensory experiences (Chapman, 1978). This may occur in one of two ways: 1) prior expectations may influence current sensory experience, 2) labelling of physical experiences may influence the effects of drugs. For example, in a classical study, Schachter and Singer (1962) demonstrated that the effect of adrenaline greatly depended on the labels or situation within which the symptoms occurred. Linden et al. (1986) found that relatively enduring personal characteristics may determine the likelihood of an individual labelling physical symptoms as complaints.

Through these processes of expectation and labelling, the thoughts an individual has about his/her physical state and the idea supplied by others may influence the level of distress experienced by that individual as well as equally influencing concurrent physiological arousal (Sternbach, 1978).

This cognitive account was shown to be particularly useful in the understanding of the reaction of currently drug-free subjects with a history of benzodiazepine dependence (Chapter 10). These individuals were led by their past experience to expect a worsening of their condition consequent upon the experience of drug-related effects and did report more withdrawal symptoms in the week following 5mg diazepam than following placebo.
In conclusion, this thesis has concentrated on the psychophysiological aspects of patients with anxiety and depression and the changes effected thereon by prolonged benzodiazepine therapy. Overall the review of the literature and the present findings suggest that it is confusing and difficult in the majority of cases to make a clinically relevant distinction by symptom configuration between atypical anxiety and atypical depression. Although the physiological data favour a distinction between symptoms of anxiety and depression in patients with major depressive disorder (i.e. endogenous vs neurotic), the psychological evidence favours a close correspondence between anxiety and depression.

When an apparent distinction can be made clinically between anxiety and depression (Downing and Rickels, 1974; Prussof and Klerman, 1974; Leckman et al., 1983; Coryell et al., 1988), it is unlikely to be borne out later by longitudinal analysis (Russel and De Silva, 1983; Chapter, 8). What appeared at first to be a distinct diagnostic entity will become blurred over time as it merges with other diagnostic categories.

The present classification categories fail the first test of a good classification scheme — that of providing categories that are inherently mutually exclusive. The independence of the present diagnostic categories from each other does not appear to hold up on empirical testing. In the absence of inherently mutually exclusive categories, further empirical investigation is obstructed since statistically valid analysis of the nominal data and any useful multivariate analysis will be difficult if not impossible.
The existing categories need to be collapsed to a more useful, practical, and comprehensive classification that allows better prediction, control, and scientific study and, like nature, is simple and economical.

Figure 11.1. A cognitive psychophysiological model of emotion


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APPENDICES

5.1) Skin conductance equipment layout and electrode placements.

1)Cancellation Task.

2) Digit Symbol Substitution Test.

3) Symbol Copying Test.

4) Mood Rating Scale.

5) Bodily Symptoms Scale.

6) Sleep Rating Scale.
APPENDIX 5.1

Skin conductance equipment and electrode placements
VERSION I

1. CROS OUT ALL THE 4's:

9954781317260743808765555620287663074873512642206
77341879170471100582907255221083974299526585139857
5049033765555657113651317209757357556222415466436667
412533393126148232441359744235119747392863593104
110257265198008962003558516422553061642340729124935
6485689169352437345578785478178995012635759352470
7651059204527646554329023491724728555147776273092
2771566410493264923839191322199955516816522719243
Display

14  occs

15  drugs

17  time

18  occs x time

19  drugs x time

21  linear occs

22  quadratic occs
VERSION II

1. CROSS OUT ALL THE 4's :-

37479153294147953142388416291342182704324616883522
66138530029501567076253997386210598871873784123340
14665177229037267774185750271316341756555673809405
75811740719781437760224621537804703667820265566780
83470624718187459931385629992479380122552709285009
3333211764834651482265573758269800009156273201140
13953682984537875543738425396198658465395688276271
943208235364672540332284591722561861595999122311
VERSION III

1. CROSS OUT ALL THE 4's:

99730555368485529060092507965673211915674259527958
3013010248638529880205221805962008737088351736103
4279117955556399099643127200455931061153872728166
3947556942535892056287358345031858418345496180234
51038206552941744d37480132555521246355092046892157
896349624247617184510829514992256307616074951889656
20103774903181577627653560591263396674735856873984
200486845584656504204688057099827075233356262062
1. CROSS OUT ALL THE 4's:

93418229025194271603039733044584385015297854
760470509968325425964525405885271846635885833
511558481768559971555229218769900147508951660889631
200927071024838609097325225134312313560273468
71242008998606595066955985550521769425207051256932
9816392952338103824921818876797013660136851775718
56456014007278559733483423253328909835761553912161
6607788882232098767682293291131690506055863847642
1. Please rate the way you feel in terms of the dimensions given below
2. Regard the line as representing the full range of each dimension
3. Rate your feelings as they are AT THE MOMENT
4. Mark clearly and perpendicularly across each line

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>impaired memory</td>
<td></td>
</tr>
<tr>
<td>impaired concentration</td>
<td></td>
</tr>
<tr>
<td>insomnia</td>
<td></td>
</tr>
<tr>
<td>lack of energy</td>
<td></td>
</tr>
<tr>
<td>metallic taste in mouth</td>
<td></td>
</tr>
<tr>
<td>blurred vision</td>
<td></td>
</tr>
<tr>
<td>eye soreness</td>
<td></td>
</tr>
<tr>
<td>light / touch / noise sensitivity</td>
<td></td>
</tr>
<tr>
<td>derealization</td>
<td></td>
</tr>
<tr>
<td>cramps</td>
<td></td>
</tr>
<tr>
<td>pins and needles</td>
<td></td>
</tr>
<tr>
<td>pains</td>
<td></td>
</tr>
</tbody>
</table>

- very severe impairment of memory
- very severely impaired concentration
- very severe insomnia
- very severe lack of energy
- very severe metallic taste in mouth
- very severe blurred vision
- very severe eye soreness
- very severe light / touch / noise sensitivity
- very severe derealization
- very severe cramps
- very severe pins and needles
- very severe pains
MOOD RATING SCALE

NAME:..........................................................

DATE...........................................

1. Please rate the way you feel in terms of the dimensions given below

2. Regard the line as representing the full range of each dimension

3. Rate your feelings as they are AT THE MOMENT

4. Mark clearly and perpendicularly across each line

ALERT _______________________________________________ DROWSY

CALM _______________________________________________ EXCITED

STRONG _______________________________________________ FEEBLE

MUZZY _______________________________________________ CLEAR-HEADED

WELL-COORDINATED ___________________________________ CLUMSY

LETHARGIC _______________________________________________ ENERGETIC

CONTENTED _______________________________________________ DISCONTENTED

TROUBLED _______________________________________________ TRANQUIL

MENTALLY SLOW _______________________________________________ QUICK WITTED

TENSE _______________________________________________ RELAXED

ATTENTIVE _______________________________________________ DREAMY

INCOMPETENT _______________________________________________ PROFICIENT

HAPPY _______________________________________________ SAD

ANTAGONISTIC _______________________________________________ AMICABLE

INTERESTED _______________________________________________ BORED

WITHDRAWN _______________________________________________ GREGARIOUS
SLEEP QUESTIONNAIRE

SEX: M  F  DATE: .................................................. TIME: ....................

TYPE OF SLEEP

very bad ........................................................................................................ very good

OF SLEEP

very abrupt ...................................................................................................... very slow

OF AWAKENING

very slow ........................................................................................................ very fast

ON AWAKENING

very alert ........................................................................................................ very sleepy