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EDITORIAL

Reactive rhythms and endogenous clocks[1]

Ever since Falret (1853) and Baillarger (1853) described *folie de deux périodes* there has been a belief that affective disorders involved a disturbance of periodicity (Sampson & Jenner, 1975; Wehr & Rosenthal, 1989). In recent years it has become clear that there is only one important endogenous period in the human body and that this is *circa diem* (circadian) in length. This has focused attention on the question of circadian rhythm disturbances in the affective disorders, especially the severe or endogenomorphic depressions rather than milder or neurotic depressions (Checkley, 1989). The mild quality of the latter and their lack of biological stigmata are taken to imply that they constitute a psychological problem rather than a clearcut illness. In the case of the severe or biological depressions, it has been argued that there is a modest amount of evidence in favour of an endogenous disturbance of rhythmicity in these disorders (Checkley, 1989).

The endogenous period is produced by a master oscillator, the body-clock, located in the hypothalamic suprachiasmatic nucleus (SCN) (Rusak & Zucker, 1979; Minors & Waterhouse, 1981). The hierarchical organization of circadian rhythmicity resembles cardiac rhythmicity. All body cells oscillate and these oscillations are capped by the SCN, which pacemakes just as the sino-atrial node does in the heart. Just as the sino-atrial node can be modulated by extracardiac influences, so also the SCN is modulated by the environment. Indeed it serves two functions, one to pacemake and the other to detect and respond to environmental cues (Wever, 1979). Under normal circumstances, the circadian period of the SCN is adjusted to an exact 24-hour period by *zeitgebers* (= timegivers) in the environment. This ensures that the body clock and environment are in phase and that day length can be estimated in the case of migrants, animals that hibernate and seasonal breeders, for example.

To date, work on a circadian pathophysiology in affective disorders has been dominated by the notion that endogenous depressions arise as a result of an aberrant body-clock. The best known proposal has been the phase advance hypothesis (Wehr & Goodwin, 1981). This posits a clock pathology, which drives some but not all internal rhythms out of phase with the environment. Some evidence has been provided in favour of the rhythms in cortisol and temperature being advanced, as the theory predicts (Checkley, 1989). Clinical features such as early morning wakening, diurnal variation of mood as well as the seasonality of affective disorders have been cited in favour of the hypothesis, as has the clinical response of some depressed subjects to phase advance of their sleep onset or to partial sleep deprivation. Further support has been claimed from studies pointing to a phase delaying effect of antidepressants (Wehr & Wirz-Justice, 1982; Wirz-Justice & Campbell, 1982).

While there is an accumulating body of evidence that there is a disturbance of circadian rhythms in the affective disorders (Healy, 1987; Souetre *et al.* 1989; Tsujimoto *et al.* 1990), the disturbances in rhythmicity currently reported do not offer clear support for a body clock hypothesis (Healy & Waterhouse, 1990). An alternative possibility arising from the structure of the circadian system outlined above is that disturbances of rhythmicity may arise from a mismatch between the endogenous period and the environment caused by an inappropriate response to exogenous *zeitgebers*. The effect of such a mismatch is illustrated by jet lag and shift work, which produce rhythm disorders in which the body clock is not the source of the problem – indeed the resolution of these disturbances points to an essentially normal clock. Of interest is that these states of

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mismatching of exogenous and endogenous components to rhythmicity result in listlessness, dysphoria and anergia – symptoms also at the core of the affective disorders.

Recently Ehlers *et al.* (1988) and Healy & Williams, (1988) have proposed that the circadian disturbances found in the affective disorders arises not as a result of a clock pathology but rather in response to altered *zeitgebers*, i.e. significant environmental changes. While both argue for breaks in social routines as the precipitant of an affective disorder, Ehlers *et al.* (1988) posit roles for ongoing social disorganization and additional biological risk factors in the development of the initial disturbance into a disorder of clinical intensity. Healy & Williams (1988) stressed the interaction of physical disturbances and cognitive factors in the transformation of the initial disturbance from a shift-work maladaptation type of picture to a typical affective disorder. Combining aspects of the Ehlers *et al.* (1988) and Healy & Williams (1988) proposals, it is possible to offer a shift work model of the affective disorders. This involves arguing that it is in the milder depressive disorders that we should look for the common biological disturbance in depression.

GENERAL PRACTICE DEPRESSION

The debate about reactive and endogenous components to rhythmicity has been overshadowed in psychiatry by the larger debate about reactive and endogenous affective disorders. This latter debate has probably influenced the kind of circadian models put forward to account for depression. The body-clock model could be seen as receiving support from older notions of a biological depression, that arises endogenously, that leads to hospitalization by virtue of its severity, that is liable to persist for over a year, that is not open to modification by psychosocial influences and that is given to abrupt switches between depressed and manic poles. Such an affective disorder would not be compatible with a disorder such as jet lag or shift work, which is a phase disorder caused by an altered lifestyle acting in conjunction with an essentially normal body-clock.

There has, however, been a notable shift in the clinical picture of the affective disorders in recent years and accordingly of the requirements that must be met by any biological hypothesis that would account for those disorders. Increasingly the old dichotomy of endogenous and reactive seems inappropriate in that depressions with endogenomorphic features and responsive to antidepressants are likely to have been precipitated by psychosocial changes (Hirschfeld, 1981; Paykel, 1985).

More importantly, beginning with the early community studies of Shepherd *et al.* (1966) and progressing through the work of Goldberg & Huxley (1980), Sireling *et al.* (1985) and many others (Blacker & Clare, 1987; Fahy, 1989), it has become apparent that the older picture of the hospitalized endogenous depressive is unrepresentative of the majority of sufferers from depression. Increasingly it would seem that the majority of antidepressant-responsive major depressive disorders are relatively mild and often go undetected by general practitioners (GPs) (Blacker & Clare, 1987). In part this seems to be because the presenting complaints are of a physical dysphoria, listlessness and anergia rather than the unhappiness and guilt that are more commonly associated with a diagnosis of depression.

A further change in the stereotype of the typical major depressive disorder has stemmed – or is currently stemming – from work on the psychotherapy of these disorders. Following the introduction of antidepressants, the belief that psychotherapy might have anything to offer sufferers from major depressive illnesses waned to reach a nadir in the late 1970s. Since then, however, with the introduction of cognitive and interpersonal therapies, this picture has been changing. Now it would appear that a number of focused treatments can modify even depressions with endogenomorphic features, that would otherwise be treated with antidepressants (Wilkinson & Blackburn, 1981; Simons *et al.* 1984; Teasdale *et al.* 1984; Blackburn *et al.* 1986).

Healy & Williams (1988) suggested that a cognitive therapy might be expected to work for even an endogenomorphic depression by removing cognitive blocks to recovery, if the natural history of the underlying disorder was one of spontaneous resolution in most instances, as would be the case for a phase rather than a clock disorder.

There is a further possibility. Recently Teasdale (1988*a*). has argued that a common feature of

currently successful psychotherapy programmes for depression, whether interpersonal, cognitive or behavioural, appears to be the induction of motivated activity. Subjects are instructed to be active rather than passive – to undertake tasks and monitor their own performance. The generation of a sense of control over their affairs, be they interpersonal or more general, appears to be important therapeutically.

From a circadian rhythm perspective such activity will necessarily lead to a reconstituting of *zeitgebers*. A similar 'therapy' is of benefit in jet lag and shift work maladaptation syndrome (Minors & Waterhouse, 1981). There is, in addition, some recent experimental support for claiming that such a therapy might specifically lead to a correction of rhythmic disturbances. Unlike the sino-atrial node, it appears that there is a complex interaction between the environment, the SCN and behavioural rhythms. It now seems that the SCN can have its time adjusted not only by such clearly exogenous cues as sunrise and sunset but also by behaviour, the rhythm of which it itself influences and that motivated activity can lead to a more rapid realignment of mismatched internal rhythms and environmental cues than would occur if the animals were simply given light cues (Mrosovsky *et al.* 1989; Van Reith & Turek, 1989).

THE SHIFT-WORK MODEL OF AFFECTIVE DISORDERS

There are, therefore, a number of areas of overlap between this emerging clinical profile of the affective disorders and the type of disturbances that result from shift work. Both jet lag and more particularly shift work commonly bring about physiological disturbances and impairments of well-being that bear notable similarities to the disturbances enshrined in current operational criteria for affective disorders. Typically they produce irritability, decreased physical and mental efficiency, fatigue but also poor sleep, apathy and restlessness, poor appetite and gastro-intestinal disturbances along with a generalized anxiety and increased awareness of physical difficulties that may appear out of proportion to any obvious physical disability (Meers *et al.* 1978; Froberg, 1981; Holley *et al.* 1981; Reinberg *et al.* 1983; Winget *et al.* 1984).

Although there appears to have been no explicit attempt to see whether workers who have a shift-work maladaptation syndrome meet with DSM-III-R (APA, 1987) or RDC criteria (Spitzer *et al.* 1978) for major depressive disorder or whether shift work causes psychiatric disorder (Cole *et al.* 1990), a number of studies suggest either that the core phenomenological features found in subjects having difficulties with shift work would meet current criteria for affective disorders or that shift work actually predisposes to affective disorders. Tasto *et al.* (1978) have found increased depression scores on the Profile of Mood States (POMS) in nurses working rotating shifts. Costa *et al.* (1981) found a 5–15% increase in a category of 'neurotic disorders', which included depression, in shiftworkers. Bohle & Tilley (1989) found that shift work leads to increased scores on the 12-item (mental state) version of the General Health Questionnaire in nurses starting shift work.

The comparisons between shift-work maladaptation syndrome and affective disorders are not simply phenomenological. There appears to be a predisposition to having difficulties with shift work. In general subjects who are neurotic – as defined by instruments such as Eysenck's personality inventory – adapt least well to shift work and jet lag (Meers *et al.* 1978; Wever, 1979; Haider *et al.* 1981; Bohle & Tilley, 1989; Redfern, 1989) and seem to be predisposed to developing depression of clinical intensity (Martin, 1985). Dissecting the causal chain in these disorders is difficult – just as it is in depression (Teasdale & Dent, 1987). On the one hand it appears that a high 'neurotic' score is associated with delayed normalization of physiological indices after phase shifting (Wever, 1979). On the other it seems that shift work can alter subjective perceptions of health, especially if there are concomitant psychosocial problems (Koller *et al.* 1978). However, it seems unlikely that problems with shift work are merely a manifestation of a primary neurotic difficulty as typically subjects who have initial difficulties with shift work avoid recruitment to long-term shift working (Koller *et al.* 1978; Wedderburn, 1981; Cole *et al.* 1990).

In addition to a possible similarity in predisposition to affective disorders or shift-work maladaptation syndrome, there appears to be some similarity in the circumstances under which

these disorders become severe and long-lasting. In particular, while shift work causes problems for all shift workers, the social situation of the sufferer has a considerable impact on the difficulties experienced (Koller *et al.* 1978; Wedderburn, 1978, 1981; Waterhouse *et al.* 1987; Bohle & Tilley, 1989). The degree of problems reported appears to be negatively related to the availability of social supports to the shift worker (Thierry & Jansen, 1982; Bohle & Tilley, 1989).

It can be seen, therefore, that the affective disorders and the type of problems brought about by clear mismatches of endogenous clocks and exogenous inputs share a number of features in common. However, while there may be a phenomenological umbra and a psychosocial penumbra that shift-work maladaptation syndrome and the affective disorders share in common, there seem to be at least two problems in the way of accepting that all there is to the pathophysiology of depression is a disturbance that closely resembles that induced by shift work. In the first place, such a disturbance will appear to many to be altogether too brief and too mild to account satisfactorily for the scale of the problem that is a full-blown affective disorder. Secondly, shift-work disturbances and jet lag appear to lack the cognitive features of hopelessness, guilt and suicidal ideation that are found in depression.

FROM DYSRHYTHMIA TO DEPRESSION

Blacker & Clare (1987) have estimated that a typical affective disorder in general practice lasts for approximately 14 weeks. While this comes much closer to the timescale of post-shift-work dysphoria than does the older stereotype of an affective disorder, it is considerably longer than the 2 to 10 day disturbances brought about by jet lag or a spell of shift work. There are several factors that may help to account for this discrepancy.

First, this estimate by Blacker & Clare was drawn from a sample that did not include the recently identified brief depressive disorders (Angst *et al.* 1984; Angst & Dobler-Mikkola, 1984*a*, *b*; Dobler-Mikkola & Angst, 1989). In a community survey of depressive episodes in 21–24-year-olds, Angst and colleagues found that depressive episodes that meet all the criteria for a diagnosis of major affective disorder but last less than 2 weeks outnumber episodes that last for 2 weeks or more by over 3:1. Given current research criteria, such cases would not come into the reckoning when the mean duration of affective disorders is being calculated, as these criteria have required the disorder to last at least 2 weeks. In response to the findings of Angst and others, the most recent revision of ICD has incorporated the category of brief depressive episodes into their framework. The inclusion of these briefer depressions would almost certainly considerably reduce the estimate of the mean duration of a typical affective episode.

Secondly, when considering the duration of shift work induced disturbances, it must be kept in mind that subjects who tolerate shift work poorly can and do drop out (Koller *et al.* 1978; Wedderburn, 1978; Cole *et al.* 1990). We have no good estimate for the duration of disturbances in subjects who tolerate shift work poorly. However, even in subjects who apparently tolerate it well for some years, recent research indicates that repeated desynchronosis may lead to a relatively permanent psychosomatic disturbance (Koller *et al.* 1978; Frese & Semmer, 1986). Thus, the notion that shift work induced disturbances differ qualitatively from the affective disorders by virtue of their transient and innocuous nature is open to question.

There is a further set of factors that might significantly affect the perception of the disturbances found in the affective disorders causing both sufferers and observers to overlook the similarity of these disturbances to those found in shift work. When subjected to life stress, individuals attempt to account for what is happening to them. The reformulated model of learned helplessness argued that depressed subjects show an attributional style biased towards attributing responsibility for failures or disasters to themselves and that this leads to helplessness and hopelessness (Abramson *et al.* 1978). Such a bias, however, would have to be pre-existent to the illness.

In contrast Healy & Williams (1988) argued that current evidence suggests that helplessness arises during the course of an affective episode. Such a picture could be expected, they argued, as the disruptions of sleep, appetite, motivation, interest, concentration and libido consequent on

dysrhythmia introduce unpredictability and uncontrollability into the most intimate areas of personal functioning. In attempting to account for what is happening, subjects then have to make judgements under uncertainty and this leads to the mobilization of biases of the type described by Kahneman and colleagues – a representativeness bias, an availability bias, an anchoring bias and a fundamental attributional error (Kahneman *et al.* 1982). The operation of these biases on the primary abnormal experiences, Healy & Williams argued, would transform a dysrhythmia into a presentation more typical of a depressive disorder and can be expected to give rise to a range of presentations (Healy & Williams, 1988, 1989; Healy, 1990).

A RESEARCH PROGRAMME

Five consequences follow from this formulation. First, there should be some evidence that all depressions involve a core dysrhythmia-related experience of the type encountered in jet lag or a shift-work maladaptation syndrome, some of which later develop the cognitive features of hopelessness, helplessness, guilt and suicidality. The studies from general practice, cited above, would appear to offer a considerable amount of evidence in favour of this possibility.

Secondly, this model proposes that there will be reactions to the dysrhythmic state. This can be expected to lead to the illness appearing to arise endogenously for two reasons. One is that these reactions will in many cases appear out of all proportion to the apparent triggering event. The other is that in the absence of a clear and comprehensible external cause, dysrhythmia is liable to be attributed to personal dispositions, leading to the presumption that the distress is somehow arising endogenously (Healy & Williams, 1988).

A third consequence is that depressions should start as relatively mild disorders and become more severe and potentially chronic with the addition of cognitive distortions. Indeed for cognitive distortion to be a significant factor in the pathogenesis of the affective disorders, the initial experience must almost of necessity be noticeable but not disabling. This follows as the processes of cognitive distortion are here taken to give rise to illness behaviours and such behaviours are most readily developed in response to provoking disorders that are mild and ambiguous (Mechanic, 1972).

A fourth implication regards the duration of an affective disorder. It is being postulated that disturbances of rhythm lead to dysphoria, lethargy and apathy, and that demoralization arises as a consequence of this initial disturbance. It would seem likely that this demoralization might persist for some time after the provoking disturbance has cleared up and persisting would be rated on depression rating scales and be interpreted as a persistence of the full-blown illness. In favour of this argument are findings from pattern analysis of the response to antidepressants that features of depression such as sleep and appetite disturbances typically clear up within 2 to 3 weeks of antidepressant treatment, whereas impairments of self-esteem and lack of self-confidence take longer (Quitkin *et al.* 1984; Kravitz *et al.* 1989). On this basis the actual duration of the core of a typical depressive disorder, even without including brief depressive episodes, is likely to be somewhat less than Blacker & Clare's (1987) estimate of 14 weeks.

Conversely, one can propose that travellers and shift workers do not develop comparable cognitive distortions in response to dysrhythmia because they have clear external culturally sanctioned attributions that can be made regarding the origin of their physical symptoms and mental dissatisfaction. There is a question of cognitive dissonance also. In the case of shift work, the evidence suggests that those who perceive only the disadvantage of shiftwork but none of the advantages and so cannot respond positively to it, drop out early on, or as early as social and financial considerations permit. This leaves committed workers, who are willing to reorganize their lives to maximize the advantages in terms of free time and money to be gained. Those not prepared to re-organize appear to be the ones who encounter difficulties (Waterhouse *et al.* 1987). In the case of depression, however, there is no opting out.

A final implication is that cognitive reactions rather than an immutable clock pathology may be what determines the chronicity of an affective disorder as well as its severity. It has been shown that

depressed mood differentially activates global self-devaluative concepts in subjects who have previously been depressed (Teasdale & Dent, 1987). This, Teasdale (1988*b*) has argued, is the kind of cognitive processing that might transform a mild and transient depressive episode into a more severe and persistent one. Some evidence in favour of this has been provided by Williams *et al.* (1990), who found that dysfunctional attitudes predisposed to the persistence of depressions that otherwise have endogenomorphic features.

The central aspect of this proposal is that there is a mismatch between exogenous and endogenous influences on rhythmicity and that this mismatch give rise to the core experiences of dysphoria, lethargy and listlessness found in depression and after shift work. This mismatch has been demonstrated for shift work (Minors & Waterhouse, 1981) and can be presumed to give rise to the core disturbances in a shift-worker's condition. The mismatch has also been demonstrated in the affective disorders – giving rise to the phase advance hypothesis. The correlation of altered rhythms with core subjective states in depression has not yet been conclusively demonstrated. However, there is some evidence in favour of such a correlation. Souetre *et al.* (1989) and Tsujimoto *et al.* (1990) have both recently reported negative correlations between Hamilton rating scale scores in depressed subjects and the circadian amplitudes of rhythms in temperature and a variety of hormones.

The task of correlating altered rhythms with subjective states will require a comparison of shift-work-induced disturbances and depression, aimed at establishing the initial physiological and cognitive responses to desynchronosis. This will entail prospective rather than cross-sectional studies of shift work, to include those subjects who may have difficulties tolerating the change, and a detection of early episodes of hypomelancholia in younger subjects, to minimize contamination by factors making for severity or chronicity. In addition both populations would need to be rated on a common scale, aimed as much at measuring the experience of purposiveness, expectancies and incentives as it is of sleep and appetite disturbances or aches and pains.

There are a number of other projects that might critically test the model being offered. A central prediction of this proposal is that subjects who become depressed after life events do so by virtue of the socially disorganizing consequences of these events. It follows that there should be evidence of increased disruption of social routines in subjects who become depressed following life events compared to those also exposed to such events but who do not become depressed. There is some preliminary evidence in favour of this position (Ehlers *et al.* 1988) but this area needs considerably more research. Accordingly some form of diary-keeping would seem indicated. A number of predictions can be made. One is that a correlation with social disorganization will be strongest for initial affective episodes as the initial establishment of cognitive distortions will create a vulnerability that will lead to a more rapid emergence of distress of clinical intensity in subsequent episodes. A second prediction is that ongoing social disruption will correlate with chronicity of affective disorders. A third is that the rate at which subjects otherwise being treated equally with antidepressants and in comparable therapeutic milieux respond to treatment will correlate with the regularity or perceived regularity of routines in their environment.

Another testable implication of this proposal is that subjects who have had an affective disorder should be less tolerant of shift work and jet lag than subjects who have not been affected. This follows as the proposed similarity of the core phenomenological experiences between these states and the affective disorders might be expected to overcome to some extent the influence of attributions as to the cause of the disorder. There is some evidence in favour of this as regarding plane travel (Jauhar & Weller, 1982) and in response to sleeplessness (Wehr *et al.* 1987).

To return to the central question: how much does a reactive disturbance of rhythms contribute to the phenomenology and pathophysiology of depression? This question seems worth pursuing, as whether or not the primary core of a depressive disorder involves such a disturbance, the social events that trigger depression and the dislocations the illness itself gives rise to, must in turn lead to reactive changes in circadian rhythms, which may obscure the true outlines of the primary lesion, if they are not taken into account. Shift work provides a suitable natural experiment in which such effects may be assessed without the confounding effects of co-existent pathology.

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