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EDITORIAL

Circadian rhythms and mental illness

The possibility of looking at biology in terms of the timing of processes has been taken much more seriously in recent years. One aspect of this approach has emphasized that Claude Bernard's stress on the constancy of the *milieu intérieur* needs modifying, as man is also in part a complicated collection of oscillating systems. A particularly important group of oscillations produces the so-called circadian (*circa die*, approximately 24 hourly) rhythms (Aschoff, 1965).

An individual isolated in a cave or chamber develops circadian rhythms of sleep and wakefulness, steroid secretion, electrolyte metabolism, and so on, and, in fact, 24 hours plus or minus 0 to two hour cycles will be adhered to fairly precisely. In our normal environment entrainment of these endogenous rhythms occurs through the effects of time clues (*Zeitgeber*) (Aschoff, 1965), given in most plants and animals by light, but in man and other higher mammals by social factors as well. The actual state of the individual is the product of the underlying 'clocks' and the environment. Changes in this state should probably be called diurnal unless there is evidence that they are essentially dependent on the endogenous circadian 'clocks'.

One uses the plural 'clocks' because desynchronization (Lobban, 1964) can occur between behaviour and other factors, and even between, for example, excretion of various electrolytes. With increasing age in early childhood the adult pattern of the phase relationships of the many variables emerges. The rhythms themselves develop sequentially, and at first they are out of phase with each other (Hellbrügge, 1965). Changes due to time shifts in travel also cause desynchronization; each variable adjusts at its own rate to the new environment. The desynchronized states probably reduce mental efficiency.

Unicellular organisms show circadian rhythms of metabolism (Mayersbach, 1967), as do individual cells, including neurones in higher animals (Strumwasser, 1968). The hypothalamus, however, probably contains centres synchronizing rhythms of different variables and of individual cells (Slusher, 1964; Kakolewski *et al.*, 1971). In this editorial, it is not possible to say much about the exciting search for the true function of the biogenic amines, except to comment that reputable theories of sleep, depression, arousal, psychopharmacology, and of control of menstruation and circadian rhythms can be developed which are dependent on the selective concentration of amines in the terminal vesicles of neurones in the upper brain stem and the hypothalamus.

Circadian rhythms and the menstrual cycle are among the most well-authenticated rhythms in man, but ultradian (of less than whole day periods) and other infradian cycles (of longer than one day) have been widely reported. For psychiatry the 90 minute cycle of rapid eye movement sleep (associated with dreaming) (see Blake and Gerard, 1937; Lubin *et al.*, 1973) is of special interest. It is claimed that it occurs throughout the day, as is shown by oral behaviour (Friedman, 1965; Friedman and Fisher, 1967; Oswald *et al.*, 1970; Globus *et al.*, 1973) and by the EEG (Kripke, 1972). Halberg (1969), who coined the term 'circadian', suggests a circaseption (weekly endogenous rhythm) (Halberg *et al.*, 1969), as well as 20 and 30 day cycles. To demonstrate this, he has used his cosiner analysis based on fitting sine waves to the crude data (Halberg *et al.*, 1967). Despite its importance, this method has limitations and its 'statistically significant' rhythms may not always be biologically significant (see, for example, Sollberger, 1965; and Cauter and Huyberechts 1973).

Over several centuries, observations of comparatively rare examples of remarkably predictable recurrences of periodic psychoses have stimulated interest and raised the hope that studies of these patients might help us understand important aspects of the pathophysiology of psychoses (Testa,

1787; Kraepelin, 1899; Pilcz, 1901; Gjessing, 1932–1960; Menninger-Lerchenthal, 1960; Richter, 1965; Jenner, 1968). Gjessing's work on periodic catatonia, however, is really the only example which has borne therapeutic fruit, but even so only for a few patients and in a condition the nosological position of which remains obscure (Mall, 1960; Hatotani *et al.*, 1962). Though the timing may well—we think clearly does—demonstrate the existence of an organic component to the illness, it does not of itself explain much about the condition. It cannot even be claimed that a 'clock' is revealed, any more than it would be appropriate to say that the 'predictable vibrations' of a damaged railway carriage revealed an underlying clock.

This, however, raises the fundamental question in this field. Halberg, as has been stated, seems to believe that normal man is very significantly controlled by a number of oscillators, and that some illnesses represent their expression to a pathological degree.

Richter (1965) also, in a somewhat different fashion, sees the body as a collection of desynchronized oscillators which, because of their desynchronization, maintain a smooth performance of the whole organ or organism. In this 'Shock Phase Hypothesis', he felt that psychoses may arise from the synchronization of the phases of the oscillators, thus, as it were, rocking the boat. Richter (1965) sees health as the comparative absence of rhythmic alteration in overall function. However, the absence of a diurnal change in performance of a normal man seems difficult to accept even in our own everyday experience and, indeed, very wide variations of steroid levels are present in health.

Without clear evidence to the contrary, precisely recurring psychotic states could arise *de novo* because negative feedback mechanisms are altered and lead to oscillations. A fairly sophisticated mathematical model based on an almost completely conjectural view of the significance of thyroid stimulating hormone and thyroxine in the system has been produced by Jean Cronin (1975) (see also Rashevsky, 1964). The importance of this model depends not on its probably mistaken endocrinological assumptions, but on the fact that it shows that an approach divorced from research on classical biological rhythms is attractive—one which does not make too much of the idea of 'clocks', or of the methods of modern chronobiology. It is of interest that Abe (1965) is able to show that, despite the fact that precise periodicities of psychosis are rare, there is, nevertheless, a marked statistical tendency to approach such a timetable in large numbers of patients. If it were not for all the more than conceivably correct psychoanalytical and sociological theories of the origins of affective psychoses, we might take such models producing various timing schedules more seriously.

In the rat the time of ovulation (in the middle of the dark period) seems to depend on its circadian rhythm, and its oestrous cycle is therefore four or five whole days (Alleva *et al.*, 1970). There seems little evidence yet that this is true of the human menstrual cycle, which is very little affected in those who—for example, air hostesses—experience frequent time shifts (Preston *et al.*, 1973).

The similarity of period to the lunar cycles must not be more than mentioned for fear of what others might say, but in some animals rhythms of behaviour and of ovulation do seem to be synchronized with these cycles (Richter, 1968). One is immediately reminded of Benjamin Rush's (1812) observation that silence fell in the mental hospital during the eclipse of 16 June 1806; perhaps due to the darkness!

The degree to which the circadian clock is 'used' to measure time for the menstrual cycle, and perhaps other cycles, requires more attention. The change in mental state of some very well recorded recurrent psychotic states can certainly show a persistent tendency to occur at the same time of the day (Gjessing, 1932–1960; Jenner, 1968). This could be a conditional response (Fraisse, 1964) and it is perhaps appropriate here to be reminded of Pavlov's (1927) view that time of day is part of the stimulus in conditioning studies in which the state of the metabolism is, as it were, 'noted'. The early Russian school thought that this use of clues from metabolism both explained how a dog could distinguish even between 29 and 30 minutes (Feokritoff, 1912), and why at the same time conditioning could not lead to responses which were delayed for more than 24 hours (Fraisse, 1964).

Stroebel (1967) made some extremely interesting studies based in part on this approach and showed that deconditioning was much more efficient if performed at the time of day at which

conditioning had occurred. He also showed (Stroebel, 1969) that speed of learning—at least in the rat—correlates with steroid levels, an effect which could be blocked by adrenalectomy or metopirone, an inhibitor of the 11-β-hydroxylase in the adrenal cortex.

When Stroebel (1969) tried to repeat his rat studies using rhesus monkeys, he produced animals with 48 hour rhythms of body temperature, (the normal temperature rhythm during hibernation of some animals (Strumwasser, 1960).) In fact, he found that two methods could be used to produce such animals. One was simply to remove the neonate from its mother whom it could see but not approach. The other method he used depended on teaching animals to use a lever to stop physical stressors, such as hot and cold blasts of air, loud noises, etc. When the animal was well trained, the lever was moved beyond its reach but not out of sight. Animals either responded with desynchronized circadian rhythms of brain temperature with peptic ulceration, asthma, skin lesions, and polydipsia, or by developing 48 hour rhythms of brain temperature. It was also of interest that the 'desynchronized' group of animals returned to normal when access to the lever was restored or when tranquillizing drugs were given; those with 48 hour rhythms were more difficult to treat.

Many further studies of this sort are required as they clearly suggest a relationship between behavioural abnormalities, unusual biological rhythms, and circadian rhythms. Richter (1965), of course, at a much earlier period also showed that many cerebral lesions in rats lead to predictable recurrent cycles of behaviour. Personal experience has convinced us of the importance of his studies but has also shown how difficult it is to repeat them.

While we have presented reasons why much of current research on biological rhythms could be misleading if too optimistically applied to studies of periodic psychoses, it must be conceded that the rare examples of 48 hour, 72, 96, and 120 hour cycles must lead one at least to try to understand whether they depend on the circadian rhythm of the individual. Such patients have been reported repeatedly by Kraepelin (1899), Menninger-Lerchenthal (1960), Mayer Gross (1961), Bunney and Hartman (1965), Richter (1965), and Jenner (1968). The change of state at 02.00 hours in one study seems strongly in favour of a dependence on the circadian rhythm, at least for the patient's symptoms (Jenner, 1968). However, one experiment, in which a 48 hour patient lived to a time schedule in which day and night were of 22 hour duration, demonstrated very clearly a desynchronization of the renal electrolyte excretion rhythms and the psychosis, which quickly showed a 44 hour rhythm (Jenner *et al.*, 1968). In Bleuler's (1911) very influential book *Dementia Praecox oder Gruppe der Schizophrenien*, there is a remarkable history of a patient living in an ordinary environment with a clear 50 hour cycle. This is perhaps an example of a free-running circadian rhythm and a doubled rhythm of psychosis. A too-simple model, based on the analogue of a computer's binary system and doubling circuits, has, however, to be rejected, as 48 hour cycles can change to 72 hour cycles in the same person (Jenner, 1965).

In field studies so many other factors operate that it is difficult to assess the significance of the circadian rhythms for the findings obtained (Menzel, 1962). Conroy and Mills (1970), for example, found an interesting difference between night workers in engineering and journalism. The former do not adjust their steroid rhythms, the latter do, because, the authors suggest, the family adjusts differently and because they spend their off-duty times differently.

Such problems need to be remembered when we consider the diurnal changes in mood and so on that were described by Kraepelin (1899) in affective psychoses, and the interesting observation that men seem to be of two types, the morning and the evening types. The former rise early and wilt: they are introverts and have a typical temperature curve; the latter rise with difficulty to improve to overt extroversion in the evening (Colquhoun, 1971).

The nosological significance of the diurnal changes in affective psychoses has been questioned, as has even the consistent pattern within individuals (Stallone *et al.*, 1973). This field has been very well reviewed by Waldman (1972) who, while pointing out the complexities involved, nevertheless makes it quite clear that Kraepelin had as usual, discovered an important phenomenon, but one which requires a review for itself, It is equally true that the changes of diurnal rhythms of steroids due to stress, and depending on personality types, could have been emphasized in this note (Montagner

et al., 1973; Henry *et al.*, 1973). The toxicity and effectiveness of drugs in relation to the time of administration is also important and has been well reviewed by Moore Ede (1973).

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REFERENCES

Abe, K. (1965). Patterns of relapse in remitting psychotics. *Psychiatria et Neurologia*, **150**, 129–140.

Alleva, J. J., Waleski, M. V., and Alleva, F. R. (1970). The Zeitgeber for ovulation in rats: non-participation of the pineal gland. *Life Sciences*, **9**, 241–246.

Aschoff, J. (ed.). (1965). *Circadian Clocks*. North-Holland Amsterdam.

Blake, H., and Gerard, R. W. (1937). Brain potentials during sleep. *American Journal of Physiology*, **119**, 692–703.

Bleuler, E. (1911). *Dementia Praecox oder Gruppe der Schizophrenien*. Deuticke: Leipzig.

Bunney, W. E., Jz., and Hartmann, E. L. (1965). Study of a patient with 48-hour manic-depressive cycles. 1. An analysis of behavioral factors. *Archives of General Psychiatry*, **12**, 611–618.

Cauter, E. van, and Huyberechts, S. (1973). Problems in the statistical analysis of biological time series: the Cosinor test and the periodogram. *Journal of Interdisciplinary Cycle Research*, **4**, 41–57.

Colquhoun, W. P. (ed.) (1971). *Biological Rhythms and Human Performance*. Academic Press: London.

Conroy, R. T. W. L., and Mills, J. N. (1970). *Human Circadian Rhythms*. Churchill: London.

Cronin, J. (1975). A mathematical model for catatonic schizophrenia. *Annals of the New York Academy of Sciences*. (In press.)

Ede, M. C. Moore (1973). Circadian rhythms of drug effectiveness and toxicity *Clinical Pharmacology and Therapeutics*, **14**, 926–935.

Feokritoff, Y. P. (1912). *Time as a Conditioned Stimulus to the Salivary Gland*. Thesis: St. Petersburg.

Fraisse, P. (ed.) (1964). *The Psychology of Time*. Eyre and Spottiswoode: London.

Friedman, S. (1968). Oral activity cycles in mild chronic schizophrenia. *American Journal of Psychiatry*, **125**, 743–751.

Friedman, S., and Fisher, C. (1967). On the presence of a rhythmic, diurnal, oral instinctual drive cycle in man. A preliminary report. *Journal of the American Psychoanalytic Association*, **15**, 317–343.

Gjessing, R. (1932–1960) Beiträge zur Kenntnis der Pathophysiologie des katatonen Stupors. *Archiv für Psychiatrie und Nervenkrankheiten*, **96**, 319–392, 393–473; (1935) **104**, 355; (1939) **109**, 525–595; **191**, 191, 220, 247, 297; (1960) **200**, 350, 366.

Globus, G. G., Phoebus, E. C., Humphries, J., Boyd, R., and Sharp, R. (1973). Ultradian rhythms in human telemetered gross motor activity. *Aerospace Medicine*, **44**, 882–887.

Halberg, F. (1969). Chronobiology. *Annual Review of Physiology*, **31**, 675–725.

Halberg, F., Engeli, M., Hamburger, C., and Hillman, D. (1965). Spectral resolution of low-frequency, small-amplitude rhythms in excreted 17-ketosteroids; probable androgen-induced circaseptan desynchronization. *Acta Endocrinologia*, **50**, Suppl. **103**.

Halberg, F., Tong, Y. L., and Johnson, E. A. (1967). Circadian system phase. An aspect of temporal morphology: procedures and illustrative examples. In *The Cellular Aspects of Biorhythms*, pp. 20–48. Edited by H. von Mayersbach. Springer: New York.

Hatotani, N., Ishida, C., Yura, R., Maeda, M., Kato, Y., Nomura, J., Wakao, T., Takekoshi, A., Yoshimoto, S., Yoshimoto, K., and Hiramoto, K. (1962). Psychophysiological studies of atypical psychoses—endocrinological aspect of periodic psychoses. *Folia Psychiatrica et Neurologica Japonica*, **16**, 248–292.

Hellbrügge, T. (1965). Zeitliche Strukturen in der kindlichen Entwicklung. *Monatsschrift für Kinderheilkunde*, **113**, 252–263.

Henry, E. E., Montagner, H., and Cardot, N. (1973). Étude préliminaire du rythme circadien des 17-hydroxycorticostéroïdes chez les jeunes enfants d'une crèche. *Compte Rendu de l'Academie des Sciences*, **276**, 3453–3456.

Jenner, F. A. (1965). A psychotic analogue. In *Biomechanics and Related Bio-Engineering Topics*, pp. 467–478. Edited by R. M. Kenedi. Pergamon Press: Oxford.

Jenner, F. A. (1968). Periodic psychoses in the light of biological rhythm research. *International Review of Neurobiology*, **11**, 129–169.

Jenner, F. A., Goodwin, J. C., Sheridan, M., Tauber, I. J., and Lobban, M. C. (1968). The effect of an altered time regime on biological rhythms in a 48-hour periodic psychosis. *British Journal of Psychiatry*, **114**, 215–224.

Kakolewski, J. W., Deaux, E., Christensen, J., and Case, B. (1971). Diurnal patterns in water and food intake and body weight changes in rats with hypothalamic lesions. *American Journal of Physiology*, **221**, 711–718.

Kraepelin, E. (1899). *Psychiatrie. Ein kurzes Lehrbuch für Studirende und Aerzte*. 6th edn. Barth: Leipzig.

Kripke, D. F. (1972). An ultradian biologic rhythm associated with perceptual deprivation and REM sleep. *Psychomatic Medicine*, **34**, 221–234.

Lobban, M. C. (1965). Dissociation in human rhythmic clocks. In *Circadian Clocks*, pp. 219–227. Edited by J. Aschoff. North-Holland: Amsterdam.

Lubin, A., Nute, C., Naitoh, P., and Martin, W. B. (1973). EEG delta activity during human sleep as a damped ultradian rhythm. *Psychophysiology*, **10**, 27–35.

Mall, G. (1960). Katamnestische Ergebnisse nach der Gjessingschen Thyroxinbehandlung periodischer Katatonien. *Archiv für Psychiatrie und Nervenkrankheiten*, **200**, 390–401.

Mayer-Gross, W. (1961). Biologische Rhythmen und ihre Bedeutung für psychiatrische Probleme. In *Probleme der phasischen Psychosen*, pp. 15–23. Edited by H. Bürger-Prinz. Forum der Psychiatrie, No. 2 Enke: Stuttgart.

Mayersbach, H. von (ed.) (1967). *The Cellular Aspects of Biorhythms*. Springer: Berlin.

Menninger-Lerchenthal, A. (1960). *Periodizität in der Psychopathologie*. Maudrich: Vienna.

Menzel, W. (1962). *Menschliche Tag-Nacht-Rhythmik und Schichtarbeit*. Schwabe: Basel.

Montagner, H., Henry, E., and Cardot, N. (1973). Sur quelques variations du rythme circadien des 17-hydroxycorticostéroïdes urinaires chez les jeunes enfants en fonction de leur profil comportemental. *Comptes Rendus Hebdomadaires de l'Académie Séances*, **277**, 101–104.

Oswald, I., Merrington, J., and Lewis, H. (1970). Cyclical "on demand" oral intake by adults. *Nature*, **225**, 959–960.

Pavlov, I. (1927). *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex*. Oxford University Press: London.

Pilcz, A. (1901). *Die Periodischen Geistesstörungen*. Fischer: Jena.

Preston, F. S., Bateman, S. C., Short, R. V., and Wilkinson

R. T. (1973). Effects of flying and of time changes on menstrual cycle length and on performance in airline stewardesses. *Aerospace Medicine*, **44**, 438–443.

Rashevsky, N. (1964). *Some Medical Aspects of Mathematical Biology*. Thomas: Springfield, Ill.

Richter, C. P. (1965). *Biological Clocks in Medicine and Psychiatry*. Thomas: Springfield, Ill.

Richter, C. P. (1968). Inherent twenty-four hour and lunar clocks of a primate—the squirrel monkey. *Communications in Behavioral Biology*, part A, **1**, 305–332.

Rush, B. (1812). *Medical Inquiries and Observations upon the Diseases of the Mind*. Kimber and Richardson: Philadelphia.

Slusher, M. A. (1964). Effects of chronic hypothalamic lesions on diurnal and stress corticosteroid levels. *American Journal of Physiology*, **206**, 1161–1164.

Sollberger, A. (1965). *Biological Rhythm Research*. Elsevier: Amsterdam.

Stallone, F., Huba, G. J., Lawlor, W. G., and Fieve, R. R. (1973). Longitudinal studies of diurnal variations in depression. *British Journal of Psychiatry*, **123**, 311–318.

Stroebel, C. F. (1967). Behavioral aspects of circadian rhythms. In *Comparative Psychopathology, Animal and Human*, pp. 158–172. Edited by J. Zubin and H. F. Hu. Grune and Stratton: New York.

Stroebel, C. F. (1969). Biologic rhythm correlates of disturbed behavior in the Rhesus monkey. *Bibliotheca Primatologica*, **9**, 91–105.

Strumwasser, F. (1960). Some physiological principles governing hibernation in *Citellus beecheyi*. *Bulletin of the Museum of Comparative Zoology*, **124**, 285–320.

Strumwasser, F. (1968). Membrane and intracellular mechanism governing endogenous activity in neurons. *Physiological and Biological Aspects of Nervous Integration*, pp. 329–341. Edited by D. F. Carlson. Prentice-Hall: Englewood Cliffs, N.J.

Testa, A. J. (1787). *Vitalibus Periodis Aegrotantium et Sanorum Elementa Dynamicae Animalis*. Davis: London.

Waldmann, H. (1972). Die Tagesschwankung in der Depression als rhythmisches Phänomen. *Fortschritte der Neurologie Psychiatrie und Ihrer Grenzgebiete*, **40**, 83–104.