concentration was followed in each case by the finding of a diagnostic enteropathy. We do not know, of course, whether or not abnormal intestinal histology could have been found before the fall in xylose absorption. The one-hour blood xylose test, used in this way, avoids the problem about the lower limit of normal for the test,^{10 11} because it is a sustained fall in blood xylose, rather than an absolute value, that is the indication for biopsy.

In group 2 there were three children in whom a sudden drop in one-hour blood xylose occurred which was not confirmed. We therefore recommend that two abnormal results are obtained before ending the challenge with a biopsy.

One of our patients (case 18) was an adolescent outside the age range of the other children in this study. Although gluten administration caused a fall in the one-hour blood xylose concentration and some change in small-bowel histology the evidence was not sufficient to establish the diagnosis of coeliac disease beyond doubt although this remained a strong possibility. Therefore the normal biopsy result after a year on a normal diet was unexpected. These findings might be explained by "patchy lesions" in the mucosa or by a dose-dependent enteropathy such that even 20 g of gluten a day for eight weeks was insufficient to cause severe damage and such that the variable amount of gluten in a self-selected "normal" diet allowed recovery.¹² Previous reports¹³ have suggested that during adolescence there may be a refractory period when the effects of gluten are unpredictable and any challenge studies in this age group must be interpreted with reservation.

This study clearly separated, with one exception, two distinct populations—group 1 and group 2. There was no clinical difference between the groups at the time of the challenge and patients in both groups exhibited mild symptoms during the challenge. The fact that six children in group 2 had symptoms but were shown to have normal post-challenge histology indicates that symptoms alone cannot be used as proof of gluten sensitivity. Symptoms were never severe enough to require termination of the challenge, but had they been abnormal biopsy findings would still have been required to make a firm diagnosis. The difference in the two populations is underlined by their HLA status. Of those children tested 82% in group 1 and 22% in group 2 were HLA-8. These figures are similar to published figures for a coeliac and a normal population respectively.¹⁴ It is not possible to state with certainty that the children

in group 2 might not have developed mucosal damage if gluten administration had been continued beyond three months. It seems unlikely, however, since they seemed to be a different genetic population, follow-up showed them to be thriving on a normal diet, and biopsy specimens from eight of them taken a year or more after returning to a normal diet were normal. The factors that determined the speed of relapse in patients in group 1 are not known. Speed of relapse was not related to age, duration of gluten-free diet, pre-challenge small bowel histology, or HLA status.

In this study only half the 35 "coeliac" children could be proved to have coeliac disease. If these proportions exist elsewhere many children, diagnosed as having coeliac disease on inadequate grounds, are being subjected unnecessarily to a gluten-free diet. This study shows the usefulness of a standardised approach to gluten challenge and emphasises the importance of jejunal biopsy in the initial diagnosis of coeliac disease.

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Change in diurnal temperature rhythm in manic-depressive illness

GEORGIA NIKITOPOULOU, JOHN L CRAMMER

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Summary

The temperatures of six manic-depressive patients were taken every three hours consecutively for many weeks, covering at least one depressive and one manic episode

in each patient. While the daily temperature curve was essentially normal in manic phases, with pronounced 24-hour rhythm, during depression the daytime temperatures appeared disorganised, often falling during the morning instead of rising, and with suggestions of a 12-hour rhythm. It may be useful to look on manic-depressive illness as resulting from a desynchronisation of circadian rhythms and to compare the pharmacologies of temperature regulation and mood regulation in psychosis.

Introduction

In spite of many years' study no clear picture has emerged of any brain disorganisation that might underlie manic-depressive

Metabolic Unit, Maudsley Hospital and Institute of Psychiatry, London SE5

G NIKITOPOULOU, MD, British Council scholar (now senior lecturer in physiology, University of Athens)

J L CRAMMER, MA, FRCPsych, senior lecturer in psychiatry, Institute of Psychiatry

illness. Drugs such as imipramine, haloperidol, and lithium carbonate influence various aspects of such illness, and biochemical hypotheses, some implicating deficiencies of noradrenaline or serotonin at central nervous synapses, have been proposed to explain their effects. Such neuronal or subcellular theories do nothing to explain the clinical phenomena of the illness—why, for instance, depressive episodes are often characterised by early morning waking and by a diurnal variation in depth of depression.¹ These disturbances in circadian rhythm require a neurological theory, one that views the illness as a disturbance in brain centres or organ function rather than in synapses or cellular function.

If psychoses are illnesses with mental and behavioural symptoms arising from limited brain disorganisation it may be possible to detect other signs of disorganisation by examining the working of physiological processes normally regulated by the brain. Body temperature, for instance, is narrowly controlled (by systems involving both noradrenergic and serotonergic synapses) so that it oscillates in a circadian curve with a peak around 1800 and a minimum at 0600. This is a stable pattern characteristic for the individual and largely unaffected by lying in bed all day or by food;²⁻³ it takes four days for the temperature to readjust to the new activity and eating schedule when a person makes an east-west jet flight between time zones 10 hours apart.⁴ Mental function, as shown by reaction times or tests of working performance, correlates highly with body temperature.³⁻⁵⁻⁶

The body temperatures of psychiatric patients in a drug-free and physically healthy state do not appear to have been examined for many years, certainly not several times a day for several days to show up the diurnal rhythm. We decided to observe the circadian temperatures of manic-depressive patients spontaneously switching between depressive and manic episodes, so that the different phases could be compared in each individual, thus avoiding all the difficulties of group variability and choice of controls.

Patients and methods

Six manic-depressives of long standing (table) were admitted on different occasions to a metabolic ward. Their temperatures were

Clinical details of patients. All patients had had electric convulsion therapy at some time and two (cases 2 and 6) had made serious attempts at suicide

Case No	Age and sex	First illness occurred:		Illness continuous for (years)	Approximate cycle length (weeks)
		Age	No of years earlier		
1	55 F	29	26	18	Manic 3, depressive 3, normal 10
2	40 F*	31	9	3	Manic 2, depressive 2
3	50 F*	21	29	13	Manic 3, depressive 3, normal 4
4	31 M	19	12	4	Manic 2, depressive 2, normal 3
5	54 F	50	4	4	Manic 2, depressive 2, normal 2
6	69 F	22	47	14	Manic 4, depressive 4, normal 2

*Still having regular menstrual cycles not in step with mood rhythm.

recorded every three hours day and night—that is, at 0300, 0600, . . . 2400—by experienced nurses using the same clinical thermometers, which were left for at least three minutes in the axilla. All patients were weighed daily and rated daily on a Phipps clinic behaviour chart for 43 signs—about 10 depressive and 10 manic and some indicating normality. All were up by day and in bed at night. The ward temperature varied little, although the study was made from March to October. Drugs were mostly avoided, although subject 6 was maintained throughout on a constant lithium carbonate 1200 mg/day. Subjects 1 and 2 received thioridazine (300 mg/day) to dampen excitement on a very few days, on which temperatures were discarded. Another patient (subject 3) had four weeks on amitriptyline between the depressive records 3c and manic records 3d, and another (subject 4) received 30 mg diazepam daily for panicky feelings in the first part of his depressive phase.

Inevitably in a long series of observations some were lost. Nevertheless, the measurements were analysed in blocks of days or time series (6–18 days) chosen to accord with mental states assessed at psychiatric interview or by Phipps rating. The analysis of such data is considerably simplified when there are no missing values in the series. Consequently, when a single value was missed out of 24—that is, in three days—an average value was put in, calculated from the other measurements at that time of day in the whole block, provided that it was the only omission for that time of day in the whole series. Otherwise the whole day or days were omitted.

Results

The daily temperature charts showed considerable variability, which made direct analysis difficult. When, however, all the values in each time series were averaged to give an average 24-hour tempera-

FIG 1—Average body temperature curves over 24 hours. Vertical axis marked in 0.5°C steps and horizontal axis time in three-hourly segments; shaded areas=1800-0600. Each curve is average of all complete days observed in series; number of days is given in parentheses against successive phase a, b, c, etc for each particular subject. Global mental state given for each as M (manic), D (depressed), or MD (changeover period). Severity of state given by height of columns in accompanying histogram made from average of Phipps ratings: m=manic signs; n=normal signs; d=depressive signs.

FIG 2—Autocorrelograms of body temperature time series of the six patients. Vertical axis shows size of correlation coefficient; horizontal axis shows time gap between data, vertical lines marking 1200 and 2400 on each plot. Length of time series and mental phases as in fig 1.

ture curve for the subject in that mental state several important features emerged (fig 1). The manic phases (1c; 2c, h, and i; 3d; 4b; and 6c and d) showed an essentially normal pattern, with a fall of about 1°C between 1800 and 0300. In contrast, the depressive phases showed a smaller temperature swing ($0.5\text{--}0.75^{\circ}\text{C}$), and although the night course was similar the day course was very different. Instead of a steady morning and early afternoon rise, as seen in normal people^{2,3} and in the manic phases, the temperature dropped when the patient got up (1b; 2a, d, e and f; 3b and c; 4a; and 5c). The patient on lithium carbonate (subject 6), showed a very flat curve rather than a drop or a steady rise.

The autocorrelogram and power spectrum of each series were found (figs 2 and 3). The correlogram is a plot of the autocorrelation coefficients of the data compared with themselves 3, 6, 9, ... 36 hours later, and the power spectrum evaluates the importance of periodicities in the time series, yielding a peak for any pronounced periodicity.⁷ In manic phases the temperature curve had a 24-hour periodicity, with a smooth minimum at half-cycle; in depression a second peak at 12 hours tended to appear, and the striking 24-hour rhythm was much diminished (fig 3).

Discussion

Values for each patient can be compared with other values for the same patient, and two (subjects 2 and 6) who repeated part of their cycles while under observation gave the same results twice. All the patients were in the ward for different periods, and if they overlapped were in different mental phases. Subject 4 lost weight in depression, but the others remained steady. Even if one supposes the amplitude of temperature swing to be a consequence of activity because of mental state, it seems hard to imagine how a small decrease in activity in depression could produce a morning fall in temperature and the appearance of a 12-hour rhythm.

The circadian rhythm of temperature is endogenous, a biological clock, though it is normally entrained to a particular 24-hour periodicity by the day-night pattern of life. If this 24-hour periodicity weakens, and a new periodicity emerges, the implications are that this clock has become disorganised and

FIG 3—Power spectrum of temperature measurements for the six subjects. Horizontal axis shows increasing frequency of periodicity of temperature values from left to right (circles mark values for 24-hour and 12-hour periodicity). Vertical axis shows proportion of all observations showing that periodicity. Length of time series and mental phases as in fig 1.

probably desynchronized vis-a-vis some of the other clocks controlling circadian rhythms of hormone release and urinary excretion.

Some workers⁸⁻⁹ have suggested that normal mammalian and avian circadian rhythms may result from the locking together of two 12-hour rhythms, one entrained to dawns, the other to dusks, which can be separated under certain experimental conditions. This may have relevance for human disease.

The depressive phase of our patients may therefore be characterised physiologically as one of temperature-clock desynchronisation. The short-term desynchronisation of human circadian rhythms produced by east-west and west-east flight is experienced partly as a dysphoria, and perhaps the subjective unpleasantness of depressive illness is partly the awareness of desynchronisation. Electric convulsion therapy could be regarded as a powerful external synchroniser; would it be therapeutically equivalent if given always at midnight, or randomly at any hour instead of (commonly) always between 0900 and 1200? Sufferers from depressive illness are often unable to work, particularly in the mornings, while in normal people work performance and body temperature are closely correlated.⁵ We have some preliminary results with card-sorting as a test of performance suggesting that this correlation will hold also for depressed people and that performance drops in parallel with temperature during the morning in the depressed.

Possibly these six subjects, although their earlier histories, symptom-pictures, and drug responses in no way distinguish them, may represent only some rare clinical subgroup and not be typical of manic-depressive patients in general. Even normal people may differ constitutionally in their overall circadian pattern—for example, the morning people and evening people of Kleitman.³ It is necessary to examine many more people, not only depressives but other categories, and to look not only at temperature and performance tests but also at rhythms of

hormones¹⁰ and urinary electrolytes.¹¹ Halberg¹² has suggested that the rhythm of recurrence of manic-depressive episodes may be determined by the extent to which two circadian rhythms are out of phase.

Our observations of a reversible abnormality of daily temperature cycle during depressive episodes support the hypothesis that manic-depression is the manifestation of disordered circadian rhythms and suggest this as a potentially fruitful approach to the pathology of mental illness.

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Polyarthritis in adults with hypogammaglobulinaemia and its rapid response to immunoglobulin treatment

A D B WEBSTER, G LOEWI, R D DOORMASHKIN, D N GOLDING, D J WARD, G L ASHERSON

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Summary

Five patients with primary hypogammaglobulinaemia developed a severe polyarthritis that had some features in common with rheumatoid arthritis. Their joint disease could be distinguished from rheumatoid arthritis, however, by the dramatic improvement after gamma-globulin treatment. The arthritis of hypogammaglobu-

linaemia can, therefore, be included among the few potentially curable polyarthritides.

Introduction

The association of non-septic arthritis and primary hypogammaglobulinaemia was first described in children.¹ Others have subsequently described the association in both children and adults and some authors have regarded the pathogenesis of the joint disease as identical to that of classical rheumatoid arthritis.² We have studied five adults with primary hypogammaglobulinaemia and polyarthritis and have attempted to distinguish their disease from rheumatoid arthritis. The most clear-cut difference is that the arthritis in patients with hypogammaglobulinaemia improved rapidly after gammaglobulin replacement therapy.

Patients

The five patients all developed recurrent infections as adults and were classified as having adult onset "variable" primary hypogammaglobulinaemia.³

Clinical Research Centre, Harrow, Middlesex HA1 3UJ

A D B WEBSTER, MRCP, consultant physician
G LOEWI, DM, FRCPATH, consultant pathologist
R D DOORMASHKIN, DM, head of section of electron microscopy
G L ASHERSON, FRCP, FRCPATH, head of division of immunology

Princess Alexander Hospital, Harlow, Essex CM20 1QX

D N GOLDING, FRCP, consultant rheumatologist

Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire SY10 7AG

D J WARD, MRCP, consultant rheumatologist