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CIRCADIAN RHYTHMS AND MANIC-DEPRESSION

DEAR SIR,

I recently suggested (Skutsch, 1973) that manic-depression might be caused by the large, *irregular* temperature changes of spring and autumn. Later it occurred to me that such changes might cause temporary disturbances in the circadian rhythms of normal persons, and I decided to monitor my own physiological rhythms for one year.

While so engaged a 'lucky' accident occurred. I had an acute virus attack which resulted in (mild) depression. The symptoms were: almost total loss of the sense of taste; poor appetite; fatiguability and anhedonia. I was thus able to note the effect of this on the aforesaid rhythms.

The first was a diurnal temperature change. Over the three months prior to the attack (Dec.–Mar.) my temperature swung between 97° and 99°F daily. During the week of the fever it never dropped to normal at all. When it finally did so (at the onset of depression) there was a new rhythm with a smaller amplitude and a higher mean; also the shape of the curve was different (see Fig. 1). This lasted for ten days, corresponding almost exactly to the depressive symptoms. The amplitude corrected itself gradually over three weeks, but the wave-like curve did not return for six.

I also measured overnight urine volumes, because it is possible that prolactin may be involved in manic-depression (Horrabin, 1974). Prolactin is anti-diuretic (Buckman and Peake, 1973) and *may* liberate anti-diuretic hormone (Manku, 1972). Its blood level is high during sleep (Nokin, 1972)—when urine volume is low—and I thought the two might vary inversely.

For three months before the virus attack the mean overnight urine volume was 515 ml. (mean deviation ±120). During the fever it dropped to 200–300 ml., due, no doubt, to sweating. But when the temperature returned to normal the urine volume remained low and on the third night dropped to 142 ml. The next day my mood began to improve; that night the volume was 446 ml. The values for the next seven nights, during which the depression cleared up were 875, 750, 625, 284, 994, 625 and 852 ml. These figures do suggest that depression is associated with fluid retention and that improvement in mood is accompanied by off-loading of the surplus water. As with temperature rhythm, the abnormal urine volumes continued for six weeks. The mean values for the weeks following the one shown in detail above were 590, 588, 641, 570, 571 and 494 ml. Perhaps lithium ameliorates manic-depression because it causes diuresis.

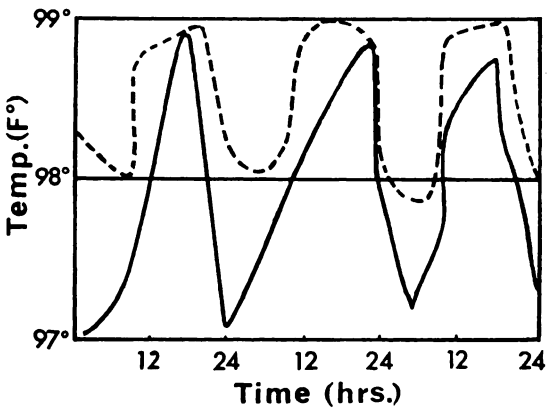

FIG. 1— ——— normal curve.
– – – – depressive curve.

Before one could deduce that prolactin is involved in depression it would be necessary, of course, to show that overnight urine volumes are inversely correlated with overnight prolactin levels.

The disorder of taste suggests that gonadotrophins were involved in this depressive attack, because, in men at least, low pituitary gonadotrophins may be associated with anosmia (Price, 1972).

The simplest explanation for this attack would be low dopamine levels. Dopamine inhibits prolactin output (MacLeod and Lehmeyer, 1974), stimulates that of gonadotrophin (Kamberi *et al.*, 1969; 1970) and causes hypothermia (Summers, 1974). This would explain all the symptoms assuming that overnight urine volumes *are* inversely proportional to prolactin

levels, that anosmia is due to low gonadotrophins and that failure of the temperature to fall at night is due to the absence of the hypothermic influence of dopamine.

GILLIAN M. SKUTSCH.

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GENETICS OF MANIC-DEPRESSIVE DISEASE: ICELAND REVISITED

DEAR SIR,

Winokur *et al.* (1967, 1970), in an elegant series of studies based on family history data, have proposed a genetic theory for the aetiology of the bipolar group of manic-depressive disorders. These authors have further suggested that the transmission is through an X-linked dominant gene (Winokur *et al.*, 1969). In support of this hypothesis, they cite the well-substantiated fact that manic-depressive disease is much more common in females than in males. Other family history data on manic-depressive disorders have supported a genetic theory of transmission, but not Winokur's specific X-linked dominant gene hypothesis (Perris, 1966).

While it is true that there is an increased incidence of females over males in manic-depressive disorder, this greater incidence is also seen in *all* affective disorders regardless of specific diagnosis, as Winokur himself notes (Winokur *et al.*, 1969). This is illustrated by the figures for patients admitted with diagnoses of depressive disorders to the in-patient services of state and county mental hospitals in the United States during 1969 (Department of Health, Education and Welfare, Publication #HSM 72-9048, 1971). These H.E.W. data would suggest that the explanation for the approximately 2 : 1 ratio of females to males would have to be broader than Winokur's specific X-linked genetic hypothesis for bipolar depressions. There is additional evidence from an epidemiological study in Iceland (Helgason, 1964) which appears to be incompatible with an X-linked dominant hypothesis for manic-depressive illness.

Helgason's data consisted of 5,395 probands who were born in the years 1895–1897 and who were followed until 1957. Within the category of manic-depressive psychosis Helgason included patients who had had periods of elation or depression, or both, which occurred without known external precipitants. He also included as part of this group patients with the diagnosis of involutional depression. A total of 81 probands received a diagnosis of manic-depressive psychosis: of these, 51 had had depressions only 7 had had mania only, and 23 had had both mania and depression. The overall expectancy rate for manic-depressive disorder was 1·80 for males and 2·46 for females, giving a ratio which is compatible with an X-linked dominant hypothesis. Helgason was also concerned with migratory patterns and their relationship to the prevalence of mental disorders. Consequently, he divided his probands according to their place of residence (rural/urban) at the beginning (1910) and the end (1957) of the observation period. He then reanalysed his expectancy rates according to the place-of-residency variable (Table I).

The female/male ratio of the expectancy rate for developing manic-depressive disease for probands living in rural areas in 1910 was approximately 2 : 1 (3·77 for females, 1·88 for males). The female/male ratio of expectancy rate for probands living in urban areas in 1910, however, was approximately 2 : 3 (2·09 for females, 2·98 for males). A chi-square analysis (computed by the present authors) on the absolute numbers of manic-depressive females and males in rural and urban areas, allowing for differences in numbers of probands at risk in each area, is significant at the $p < \cdot 01$ level ($\chi^2 = 5 \cdot 12$). Further, when the expected numbers of manic-depressive males and females were calculated for rural and urban areas, using the ratio derived from an X-linked dominant gene hypothesis (1 male : 2 female at the population incidence of manic-depressive disorder), and compared with Helgason's observed number of cases in each category (rural and urban), they differed significantly ($\chi^2 = 11 \cdot 3$, $p < \cdot 01$, see Table