1974). The syndrome is characterized by severe extrapyramidal symptoms of muscular rigidity and akinesia, with hyperpyrexia, fluctuation in the level of consciousness and autonomic dysfunction, which includes tachycardia, labile blood pressure, hyperventilation, profuse diaphoresis, sialorrhoea, dysarthria and dysphagia. The patient may be alert, but mute, with other catatonic symptoms, progressing to stupor and coma in severe cases.

The syndrome may develop within hours of initial drug exposure, or after months of drug use, and occurs at therapeutic rather than toxic dosage. Once started, the syndrome develops rapidly over the next 24–72 hours, and if neuroleptic medication is not stopped the outcome may be fatal. A mortality rate of 20 per cent has been reported (Cardoff, 1980). Cardio-respiratory collapse is the usual mode of death, and there is no specific treatment, apart from supportive measures.

There are no specific or diagnostic laboratory findings in the NMS, but there may be a polymorphonuclear leucocytosis, abnormal liver function tests, and elevated serum CPK, probably caused by myonecrosis after prolonged skeletal muscle contraction (Smego and Durack, 1982). The EEG is generally normal, but may show non-specific slow activity. Examination of CSF, isotope brain scans and CT scans where performed have been normal (Caroff, 1980), and post mortem findings have been negative.

The disorder may be mis-diagnosed as encephalitis or other infectious diseases of the CNS. The NMS has been compared to acute lethal catatonia described by Stauder (1934) many years before the advent of neuroleptics, and to the syndrome of malignant hyperthermia associated with general anaesthetics. Heat stroke which may occur in patients receiving phenothiazines and butyrophenones can be distinguished from the NMS by the lack of muscular rigidity.

Although the pathogenesis of the NMS is unknown, it has been suggested that features of the syndrome can be explained by dopamine-receptor blockade in the basal ganglia and hypothalamus. It is not known why some individuals are susceptible to the NMS, but there have been some case reports of pre-existing organic brain disease (Meltzer, 1973) or physical exhaustion and dehydration (Itoh *et al*, 1977). It is interesting that some patients have been safely re-exposed to the same neuroleptic without recurrence of the syndrome.

Having recently seen a case with fatal consequences (Cope and Gregg, 1983), I hope that this brief summary of the condition will lead to more widespread recognition.

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References

ALLEN, R. C. & WHITE, H. C. (1972) Side effects of long-acting phenothiazines. *British Medical Journal, i,* 807.

CAROFF, S. N. (1980) The neuroleptic malignant syndrome. *Journal of Clinical Psychiatry,* **41,** 79–83.

COHEN, W. J. & COHEN, N. H. (1974) Lithium carbonate, haloperidol and irreversible brain damage. *Journal of the American Medical Association,* **230,** 1283–7.

COPE, R. V. & GREGG, E. M. (1983) The neuroleptic malignant syndrome. *British Medical Journal,* **286,** 1938.

DELAY, J., PICHOT, P. & LEMPERIERE, T. (1960) Un neuroleptique majeur non phenothiazine et non reserpinique l'haloperidol dans le traitment des psychoses. *Annales Medico-Psychologiques,* **118,** 145–52.

ITOH, M., OHTSUKA, N. & OGITA, K. (1977) Malignant Neuroleptic Syndrome: its present status in Japan and clinical problems. *Folia Psychiatrica et Neurologica Japonica,* **31,** 565–76.

MELTZER, H. Y. (1973) Rigidity, hyperpyrexia and coma following fluphenazine enanthate. *Psychopharmacologia,* **29,** 337–46.

SMEGO, R. A. & DURACK, D. T. (1982) The Neuroleptic Malignant Syndrome. *Archives of Internal Medicine,* **142,** 1183–5.

STAUDER, K. H. (1934). Die tödliche katatonia. *Archiv für Psychiatrie und Nervenkrankheiten,* **102,** 614–34.

MACROCYTOSIS AND DOWN'S SYNDROME

DEAR SIR,

We reported macrocytosis in 92 adult Down's syndrome patients (MCV 102.5±7.87 fl), the MCV having been calculated from separate red cell counts (Model D Coulter counter) and microhaematocrit estimations (Eastham and Jancar, 1970). No significant sex difference was found. Using a Coulter-S-Plus electronic cell counter, we have now found the MCV in 16 male and 17 female adult Down's syndrome patients to be 96.3±3.79 fl (1 SD), again with no sex difference, and with an RDW of 10.68±1.67. (The normal RDW of about 10 indicates no abnormal anisocytosis). These patients were not being treated with anticonvulsants and were not anaemic.

This latest result is significantly smaller than our earlier result (t test, P 0.001), and almost certainly reflects the change in technological method, but the mean value for the MCV is still above the accepted upper limit of the normal range (95 fl). The earlier method included centrifugation of red cells with associated plasma trapping, while the current method measures the MCV directly and eliminates the effects of plasma trapping. The explanation for macrocytosis in Down's syndrome is still unknown, but it has been shown that the red cell envelope in trisomy Down's

syndrome undergoes accelerated aging (Kedziora *et al*, 1981).

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References

EASTHAM, R. D. & JANCAR, J. (1970) Macrocytosis in Down's syndrome and during long-term anticonvulsant therapy. *Journal of Clinical Pathology*, **23**, 296–8.

KEDZIORA, J., KOTER, M., BARTEL, H., BARTOSZ, G., LEYKO, W. & JESKE, J. (1981) *Acta Biologica et Medica Germanica*, **40**, 423–8.

PSYCHIATRIC MORBIDITY AND CIRCADIAN RHYTHMS

DEAR SIR,

In commenting on the paper by Jauher and Weller (*Journal*, March 1982, **140**, 231–5), Dr Gunnar Götestam (*Journal*, September 1982, 317–18) has confused certain matters. One of the confusions arises from the ambiguity of the references to what is 'advanced' when we refer to alterations in the circadian rhythm. He writes, 'Flying east also means a phase advance in the sleep-wake cycle', and cites Wehr *et al* (1979) in support of the observation that a flight eastwards tends to produce elevation of mood. What Wehr *et al* have written is, 'Sleep in depressed patients resembles sleep in normal subjects whose circadian rhythms of temperature and rapid-eye-movement sleep are phase-advanced (shifted earlier) relative to their sleep schedules' (*Ibid*, p. 710). Thus if the phase of the sleep-wake cycle is *advanced* the phase of the other circadian systems is *delayed*. But in writing of flights westwards Götestam states, 'Flying west prolongs the 24 hour day and delays the circadian cycle'. This is incorrect: it does not—it *advances* it (shifts it earlier) relative to the sleep-wake cycle, hence the depressive effect.

Neither is Götestam correct when he states that, 'It is now well known that sleep deprivation elevates mood (Pflug, 1978). A deprivation of a night's sleep may result in a slight increase in mood, as is often experienced by doctors after an entire night on duty'. But the study of Pflug to which he refers was concerned with endogenously depressed patients: in a previous study Pflug and Töller (1971) showed that normal subjects suffer some dysphoria after the loss of a night's sleep in contrast to the relative euphoria of depressed patients. There is little doubt about the validity of this finding for it has been confirmed independently by Cutler and Cohen (1970) and Gernet *et al* (1979). It seems hardly likely that Götestam's medical colleagues were endogenously depressed! Now that the therapeutic possibilities of using sleep deprivation are being further explored (see Lovett Doust and Christie, 1980) it is of great importance to get our basic facts right.

Finally, I must point out that Götestam is hardly correct in stating that, 'Tricyclic antidepressants (TCA) are not so far known to affect the circadian rhythm . . .' He cites Wehr *et al* (1979) but the latter state quite unequivocally that tricyclics do have this effect— '. . . tricyclic antidepressants and estrogen, all of which have profound effects on depressive illness, also alter the basic timekeeping function of the circadian clock'. (*Ibid*, p. 712).

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References

CUTLER, N. R. & COHEN, H. B. (1979) The effect of one night's sleep loss on mood and memory in normal subjects. *Comprehensive Psychiatry*, **20**, 61–6.

GERNER, R. H., POST, R. M., GILLIN, J. C. & BUNNEY, W. E. JR. (1979) Biological and behavioural effects of one night's sleep deprivation in depressed patients and normals. *Journal of Psychiatric Research*, **15**, 21–40.

GÖTESTAM, K. G. (1982) Psychiatric morbidity and circadian rhythms. *British Journal of Psychiatry*, **140**, 317–18.

JAUHER, P. & WELLER, P. I. (1982) Psychiatric morbidity and time zone changes: A study of patients from Heathrow Airport. *British Journal of Psychiatry*, **140**, 231–5.

LOVETT DOUST, J. W. & CHRISTIE, H. (1980) Repeated sleep deprivation as a therapeutic *Zeitgeber* for circular type manic depressive disturbance. *Chronobiologia*, **7**, 505–11.

PFLUG, B. (1978) The influence of sleep deprivation on the duration of endogenous depressive episodes. *Archiv für Psychiatrie und Nerven krankheiten*, **235**, 173–7.

—— & TÖLLER, R. (1971) Disturbance of the 24 hour rhythm in endogenous depression by sleep deprivation. *International Pharmacopsychiatry*, **6**, 187–96.

WEHR, T. A., WIRZ-JUSTICE, A., GOODWIN, F. K. & GILLIN, J. C. (1979) Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science*, **206**, 710–13.

MONTHLY VARIATION OF SUICIDAL AND ACCIDENTAL POISONING DEATHS

DEAR SIR,

Barraclough and White (1978a, 1978b) reported that the monthly distributions of accidental and undetermined deaths due to poisons were significantly