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## MELATONIN/CORTISOL RATIO IN PSYCHIATRIC ILLNESS

SIR,—Hypersecretion of cortisol has been reported in a significant proportion of depressed patients[1,2] and is held to be a specific and sensitive marker of that illness.[1,2] Reduced nocturnal secretion of the pineal methoxyindole melatonin has also been found in depressed patients[3–5] and is held by some workers to be a marker of depressive illness.[4,5] Wetterberg et al.[6,7] have suggested that the ratio of melatonin secretion to cortisol secretion (M/C ratio) in samples taken at midnight relates closely to clinical state and is a more sensitive index of depressive illness than either of the above indices separately. We have investigated the secretion of these hormones in schizophrenic patients to assess these claims of diagnostic specificity.

Venepuncture was performed at midnight under the illumination of a dim night light in fifteen male chronic schizophrenics (who conformed to criteria of Feighner et al.[8] for the diagnosis of schizophrenia) and nine age and sex matched controls (two normal volunteers and seven patients in an orthopaedic ward awaiting minor elective surgery). No subject was taking psychotropic drugs at the time of study (the schizophrenics had had neuroleptic medication discontinued 1–12 years previously). All subjects had been in bed for 1–2 h before blood sampling and the same proportion of each group was awakened from sleep. Cortisol and melatonin were assayed blind from coded serum samples by radioimmunoassay[9,10] and results are shown in the table. Log transformed data were analysed by Student's t-test. Five chronic schizophrenics (33%) had undetectable midnight melatonin levels, which were considered for these calculations to be at the detection limit (7 pg/ml).

The schizophrenics had higher midnight cortisol values than did the controls (though only one schizophrenic patient was outside the normal range [>400 nmol/l]), lower midnight melatonin levels, and a highly significant reduction in the M/C ratio.

Thus a low M/C ratio has been demonstrated not only in depression[6,7] but also in chronic schizophrenia.

A reduced M/C ratio therefore has no diagnostic selectivity and may represent a non-specific sequela of psychiatric illness. For example a reduced M/C ratio may be related to phenomena associated with psychiatric illness such as low body weight (which is associated with low melatonin secretion[11,12]), weight loss (which has been implicated in the hypersecretion of cortisol in other psychiatric conditions[13]), "stress", or a history of previous psychoactive drug administration. Alternatively, changes in either melatonin or cortisol secretion may be more directly related to the disease process in schizophrenia or depression but even if this is the case the M/C ratio cannot be used to discriminate these psychiatric illnesses.

CORTISOL AND MELATONIN LEVELS AND M/C RATIOS IN MIDNIGHT BLOOD SAMPLES IN SCHIZOPHRENICS AND CONTROLS· MEAN±SEM

| | Chronic schizophrenics (n=15) | Controls (n=9) | p |
|---|---|---|---|
| Age | 59±5·1 | 52±3·0 | |
| Cortisol (nmol/l) | 185±32 | 72±17 | <0·01 |
| Melatonin (pg/ml) | 17±3 | 29±5 | <0·05 |
| M/C ratio (ng/nmol) | 0·15±0·04 | 0·69±0·23 | <0·005 |

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## NEONATAL ROTAVIRUS INFECTION

SIR,—Rotavirus is the most common cause of diarrhoea in children beyond the neonatal period in many parts of the world.[1] However, rotavirus infection in the newborn is frequently symptomless. There has been increasing interest in the epidemiology of neonatal rotavirus infections because of possible roles of such infections in the transmission of disease to susceptible household contacts and in the acquisition of immunity to the disease during infancy (in infants colonised in the neonatal period). The frequency of neonatal rotavirus infection varies from zero to 52%, and there are wide geographical and seasonal variations in incidence.[2,7] We report here on experience at a neonatal nursery in Baltimore.

Patients admitted to the full-term or preterm nursery at the Baltimore City Hospitals from Aug. 1, 1980, to July 31, 1981, were enrolled in the study, and these included inborn and transferred infants. Stool specimens were obtained on term infants on the first day of life and, when possible, a second sample was obtained before discharge (at age 2–5 days). In the preterm infants, stool specimens were obtained on the day of admission (day 1 or 2 of age) and then weekly until discharge. Stools were tested for rotavirus antigen by enzyme linked immunosorbent assay.[8]

1025 (87%) of the 1175 infants (902 term and 273 preterm) admitted to the nursery during the study period were studied. 200 (83%) of the preterm infants had two or more stool samples tested and 405 (52%) of the term infants had more than one stool sample tested. Rotavirus antigen was detected in 13 infants (1·3%). The incidence of rotavirus colonisation was 1·7% in preterm and 1·3% in term infants, but this difference was not significant. All infants colonised with rotavirus were symptomless.

Of 9 term infants colonised with rotavirus follow-up stool samples were available in 7. In 5 the stool sample at age 1 day was positive but stools were negative on the second day; in 1 stools were positive on the first day and on discharge at age 4 days; and in 1 the stool

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specimen was negative on the first day but positive on the next day.

Among the 4 preterm infants colonised 3 had rotavirus antigen detected in the stool specimen on the first day. All 3 were not colonised during the rest of their hospital stay (1, 2, and 4 weeks). 1 preterm infant's stool was negative on the first day, positive the next day, and negative at age 8 days.

In contrast to previous studies,[2-4] we found that most infants infected had acquired neonatal rotavirus within 24 h. In two studies[3,4] stool samples were collected after the age of 4 days and in the third study,[2] of the 22 babies studied within the age of 24 h, none was positive for rotavirus. In our study, of the 13 infants with stools positive for rotavirus, 10 were less than 24 h old. Similar to the findings of Crewe and Murphy,[9] the presence of rotavirus in stools of our infants was transient.

We conclude that rotavirus infection during the first 5 days of life was rare in the Baltimore City Hospitals, at least during the 1 year study period. However, we cannot exclude the possibility that the incidence may have been higher in other years or in term newborns older than 5 days of age.

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## BENEFICIAL EFFECT OF D-RIBOSE IN PATIENT WITH MYOADENYLATE DEAMINASE DEFICIENCY

SIR,—Myoadenylate deaminase (MAD) deficiency, a newly described metabolic disease of muscle, can present with muscle weakness, fatigue, aches, and cramps, often worsened by exercise; sometimes creatine phosphokinase (CPK) levels are moderately raised but muscle is histologically normal. The diagnosis is established by histochemical and biochemical demonstration of the enzyme deficiency in skeletal muscle, erythrocyte adenylate deaminase being normal[10] MAD probably plays a role in the maintenance of a high level of ATP during muscular activity, ensuring that a large energy charge is available for contraction.[11] Because of a finding of low ATP levels in skeletal muscle and a slow repletion of ATP in a patient with MAD deficiency investigated by me and my colleagues[12] I have attempted to prevent this depletion by giving D-ribose. The rationale is that adenine nucleotide biosynthesis is limited by the flow through the hexose monophosphate shunt, and that this limitation can be overcome by ribose or other pentoses or pentilols. Ribose, which bypasses the hexose monophosphate shunt, is immediately converted to ribose-5-phosphate thus enlarging the available pool of 5-phosphoribosyl-1-pyrophosphate, an essential precursor for the biosynthesis of adenine nucleotides. As a result, adenine nucleotide synthesis is enhanced. D-ribose increases the synthesis of and prevents, in rats, the diminution of adenine nucleotides which is characteristic of the action of high doses of isoproterenol.[13] This institute's committee on human experimentation approved the administration of ribose.

After several open trials had indicated remarkable improvement in the patient's strength, endurance, and sense of wellbeing while she was taking ribose and relapses to baseline strength within 2 days of stopping ribose, I undertook a double-blind study of ribose versus sucrose (placebo). Serial observations were made before the trial (baseline), during the administration of placebo, and during the administration of D-ribose. The ribose, on optical rotation and paper chromatographic criteria, was authentic D-ribose. Gelatin capsules containing 470 mg D-ribose or sucrose were given four times daily for four days. Neither I nor the patient knew when ribose was being given. Clinical data and conclusions were written up and sent to a physician at another university before the code was broken.

When the code was broken, we learned that ribose was associated with an average improvement of 29% in static muscle strength in the fourteen muscles tested, by opposition, and graded 0–5 on the Medical Research Council scale. Ribose administration was especially associated with improvement in proximal muscle strength in arms and legs. The patient felt better while taking the ribose and had been able to defrost her refrigerator and clean her home during ribose administration, something she had not been able to do for 2 years. Daily photographs showed some improvement in facial tone and general appearance while the patient was on ribose. She felt no benefit or worsening of her condition during sucrose therapy. Despite the improvement in static strength, there was no significant alteration in grip, or in leg or head holding times in the ribose period. No side-effects were noted.

I have been caring for this patient for over 5 years. Despite trials many different drugs and several placebos, she has reported a significant improvement only with ribose. This improvement was so impressive that a double-blind study in one patient seemed warranted. MAD deficiency is rare, and a conventional controlled clinical trial does not seem practicable. D-ribose deserves further trials in patients with MAD deficiency.

The use of D-ribose was based on an idea by Dr Edward Holmes of Duke University who also received the clinical data and conclusions before the code was broken. I thank Mr George Lindler of Houston, Texas, for his gift that helped to finance this study.

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## BETA BLOCKERS CAN OBSCURE DIAGNOSIS OF DELIRIUM TREMENS

SIR,—Alcohol withdrawal is associated with adrenergic hyperactivity such as tachycardia, hypertension, and sweating. Propranolol and related drugs have been used to treat alcohol withdrawal, but the possibility that beta-blockers might obscure the correct diagnosis and delay treatment has not been reported.

A 32-year-old male with a long history of severe alcohol abuse (a pint of vodka per day, some of it "moonshine") came to the emergency department complaining of dizziness. He had a blood pressure of 180/120 mm Hg and was given hydrochlorthiazide. His father had died suddenly after drinking while taking a medication prescribed in the emergency department, so his mother removed all alcohol in the hope of preventing a similar occurrence. The patient was re-examined the following day. As his blood pressure was still 180/120 mm Hg, propranolol was prescribed. 4 days later he returned, giving a 1 day history of "seeing things" (e.g., a head growing out of his wife's hand and one of her fingers cut off). His mother stated that he had had delirium tremens at least once before, and he had been admitted to a psychiatric hospital 3 years previously with a diagnosis of psychosis.

Because of the history of psychosis, absence of tachycardia (88/min), and normal temperature, his problem was regarded as functional. Haloperidol was given. His blood pressure remained at 180/120 mm Hg. There was no mydriasis, diaphoresis, or tremor. The visual hallucinations/illusions persisted. Short term memory was very poor, and concrete thinking was noted.

At this point, after 14 h of observation in the emergency department, the diagnoses being considered were delirium tremens, direct CNS effects of propranolol, functional psychosis, phaeochromocytoma, or toxicity from a contaminant in the moonshine liquor. Hallucinations in a patient who had suddenly

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