Whether or not the peroxisomal disturbance in case 2 is inherited or induced by hereditary predisposition our message about a possible relation between benzodiazepine overconsumption in pregnancy and abnormalities in the offspring remains.

Czeizel and Lendvay[9] have commented on the effects of single intoxications by benzodiazepines. We agree that it is very unlikely that a single intoxication would lead to an effect detectable in the offspring. With alcohol, for example, we know that prolonged consumption during pregnancy is required to produce fetal damage.

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A POLICY ON BENZODIAZEPINES

SIR,—Professor Cohen (Nov 7, p 1080) expresses concern over the use of benzodiazepines. In North East Essex we share this concern and have adopted a formal policy on hypnotic and anxiolytic drugs. The objectives are to ensure that no new addicts are created during hospital treatment and that existing misusers are weaned off the drugs as safely and rapidly as possible. The policy is being passed on to general practitioners and pharmacists in the hope that they will adopt similar policies throughout the district. Monitoring the policy will initially rest with hospital pharmacists. Prescriptions that do not comply with the policy will be referred back to the prescriber; if he or she cannot be contacted the prescription will be dispensed only in accordance with the policy. The policy (full details of which can be supplied on request) is, in summary:

RECOMMENDATIONS TO LIMIT BENZODIAZEPINE ABUSE

(1) Treatment with benzodiazepines should be kept to a minimum, reviewed regularly, and discontinued as soon as possible. Withdrawal should always be gradual.

(2) Patients not previously prescribed benzodiazepines should not normally be given hypnotics in hospital for more than 5 days.

(3) Chronic users apart, no patient will be discharged with more than 3 days' supply of a benzodiazepine hypnotic.

(4) Lorazepam should not be prescribed unless patients are already chronic users.

(5) Benzodiazepines should not be routinely prescribed for elderly patients.

(6) Patients should be given more information on drugs prescribed.

(7) Benzodiazepine withdrawal over 6–8 weeks may only be possible in hospital. In general practice reduction at the rate of a quarter tablet every 2 weeks is recommended. Lorazepam should be changed to diazepam (up to 10 mg diazepam for 1 mg lorazepam).

(8) Alternatives to benzodiazepines may include: (a) a tricyclic antidepressent in the evening for insomnia and anxiety associated with depression; (b) non-pharmacological treatments such as relaxation or counselling; and (c) the avoidance of coffee, tea, and alcohol before going to bed, with reassurance to older patients that 5–6 hours' sleep a night is normal.

This policy was adopted for immediate action by the drug and therapeutics committee, North East Essex Health Authority, on Oct 6, 1987.

We would welcome comments from others with an interest in benzodiazepine related problems. We plan to monitor the efficacy of our strategy and report our findings.

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SIR,—We agree with Professor Cohen that there is no place for benzodiazepines in the treatment of anxiety. There may be a place for them in anaesthesia, the management of epilepsy, or parenterally in states of acute psychiatric disturbance—but that is all. What is to replace them in anxiety management? We suggest a personalised non-drug programme of anxiety management, using liberal amounts of physical exercise alternating with relaxation for which the patient has been trained.[1] Such programmes are already used in general practice and deserve to be better known in the hospital outpatient department.

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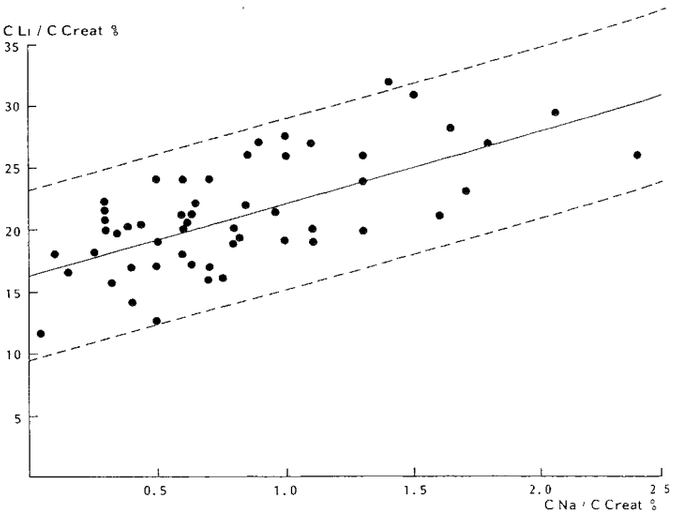
SIMPLIFIED METHOD FOR EVALUATING PROXIMAL TUBULAR FLUID REABSORPTION

SIR,—Lithium clearance can be used as an index of proximal tubular fluid handling. However, it has not become routine in research or clinical settings because two timed blood samples and quantitative urine collection over several hours are required.[1] Furthermore lithium clearance (C_{Li}) cannot be interpreted at face value because it varies with creatinine clearance (C_{Cr}) and fractional lithium clearance (C_{Li}/C_{Cr}) is influenced by sodium intake, which may be difficult to control. In an attempt to overcome these shortcomings, we studied 55 subjects to define the relation between the clearance of creatinine, lithium, and sodium. We then devised a short method for measuring fractional lithium clearance corrected for sodium.

We studied healthy volunteers and patients (other than those with fever, dehydration, fluid overload, glycosuria, and proteinuria and those on diuretics, xanthine derivatives, or non-steroidal anti-inflammatory drugs). Lithium carbonate 400 or 600 mg was ingested at 2200 h. Coffee was not allowed. Urine was collected



Linear regression analysis of fractonal lithium clearance as function of fractional sodium clearance.

Broken lines indicate 95% confidence interval.

from 0800 to 0930, and 0930 to 1100 h and blood samples were taken at 0800 h, 0900 h, and 1100 h next morning. We measured creatinine (Jaffé reaction) and sodium and lithium (flame spectrophotometry) and calculated clearances and fractional clearances. The relation between lithium and sodium excretion was studied by linear regression analysis of C_{Li}/C_{Cr} as a function of both absolute sodium excretion (Na_{exc}, μmol/min) and fractional clearance of sodium (C_{Na}/C_{Cr}).

The clearances found were: C_{Cr} 40–187 (median 129) ml/min, C_{Li} 5–47 (26) ml/min, and C_{Li}/C_{Cr} 12–38%. There was a linear correlation between C_{Li}/C_{Cr} and both absolute sodium excretion.

$$C_{Li}/C_{Cr} = 0{\cdot}17 + (0{\cdot}00027 \times Na_{exc}) \; (r = 0{\cdot}59) \; . \; . \; . \; (1)$$

and fractional sodium clearance:

$$C_{Li}/C_{Cr} = 0{\cdot}16 + (5{\cdot}9 \times C_{Na}/C_{Cr}) \; (r = 0{\cdot}72) \; \text{(figure)} \; . \; . \; . \; (2).$$

To correct for sodium, C_{Na}/C_{Cr} was substituted in equation (2) and the observed value of C_{Li}/C_{Cr} was expressed as a percentage of the predicted value. This correction reduced the variability of C_{Li}/C_{Cr}: the coefficient of variation of C_{Li} itself was 40%, that of C_{Li}/C_{Cr} 23%, and that of C_{Li}/C_{Cr} corrected for sodium 16%. In subjects whose creatinine clearance was below 90 ml/min or above 160 ml/min, the coefficients of variation were 80%, 29%, and 18%, respectively.

To judge the feasibility of using only one sample of urine and blood fractional clearances were also calculated using urine collected from 0930 to 1100 h and blood taken at 1100 h. Fractional lithium clearance averaged 20·8 (SD 6·4)%, both for two collections and for the short method. Fractional lithium clearance corrected for sodium was 100 (16)% of the predicted value for two collections and 101 (18)% for the short method.

Our results show that for lithium clearance to be interpreted correctly both creatinine clearance and sodium load must be taken into account. By correcting for fractional sodium clearance rather than sodium excretion we avoided the need for quantitative urine collection. In view of the long half-life of lithium in serum (18 h in our experience and 20 h as reported by others[2]) one blood sample can be taken to represent serum lithium throughout the period of urine collection. Obviously, our short method is more suitable for clinical use. Applications of this method include monitoring cyclosporin nephrotoxicity,[3] evaluating proximal tubular function in diabetics,[4] and researching essential hypertension.[5]

We thank Marja Belder for her assistance.

Part of this work was presented at the Dutch Nephrological Society in Nijmegen, on March 4, 1987.

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CYTOMEGALOVIRUS PNEUMONITIS

SIR,—Dr Grundy and colleagues (Oct 31, p 996) suggest that cytomegalovirus (CMV) pneumonitis is due to the host response against virally infected tissue rather than to uncontrolled viral replication in the immunocompromised host. They also refer to the contradictory data on CMV hyperimmune globulin, which is unlikely to neutralise virus in vivo and yet is effective in the treatment of CMV pneumonitis. They suggest that CMV hyperimmune globulin works by masking either HLA antigens or CMV-related antigens on infected cells and thereby inhibiting the T-cell recognition and attack of these cells. We would suggest a more probable mechanism based on the observation that infusion of non-specific immunoglobulin per se has an immunosuppressive effect.

Administration of high doses of non-specific immunoglobulins is useful in various autoimmune and immune-mediated diseases such as immune thrombocytopenic purpura,[1] autoimmune haemolytic anaemia,[2] and Crohn's disease.[3] The mechanism of this effect is thought to be immunosuppressive primarily via an induction of T-suppressor cell function[4] as well as reduced phagocytosis[5] and depressed natural killer cell activity.[6] Snydman et al[7] demonstrated a reduction in the severity of clinical CMV disease in renal transplant recipients who had received repeated CMV hyperimmune globulin infusions prophylactically but no significant changes in the rate of CMV virus infection. These results might be explained by reduced immunological host responsiveness, due to immunoglobulin infusions leading to increased suppressor cell activity. Unfortunately, this study did not include a control group receiving non-specific immunoglobulins. Studies on CMV hyperimmune globulin should include such controls to test whether the beneficial effect is due to non-specific immunosuppression.

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RIBAVIRIN

SIR,—Dr Wood and Professor Geddes (Nov 21, p 1189) classify ribavirin as "treatment still investigational". Ribavirin aerosol ('Virazid') was launched in the UK on Nov 23 for the treatment of severe respiratory syncytial virus bronchiolitis.

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TREATMENT OF MULTIRESISTANT SALMONELLA TYPHI WITH ORAL CIPROFLOXACIN

SIR,—Typhoid fever is uncommon in the UK and chloramphenicol is the recommended treatment. Ciprofloxacin has been used to treat typhoid fever, with encouraging results. Ramirez et al[1] treated 38 cases with ciprofloxacin 500 mg twice daily for 7–14 days with good results, although follow-up was limited; susceptibility to other antibiotics was not stated. Limson[2] achieved clinical and bacteriological cure in 18 of 20 patients given 500 mg ciprofloxacin three times daily for 14 days; 3 strains were resistant to chloramphenicol. We have used oral ciprofloxacin to treat a patient with typhoid fever caused by multiresistant *Salmonella typhi*. This 29-year-old man from Karachi came to the UK for a postgraduate course; he was admitted to hospital after 6 days of rigors, night sweats, and weight loss. *S typhi* phage O was isolated from blood cultures and stools taken on admission, and the strain was resistant to ampicillin, co-trimoxazole, tetracycline, streptomycin, and chloramphenicol, but sensitive to ciprofloxacin. He was treated with 500 mg ciprofloxacin twice daily for 10 days with rapid defervescence, clinical improvement, and eradication of the organism from the stool (five clear specimens so far).

Although only 1 of the 120 strains of *S typhi* reported to the Communicable Disease Surveillance Centre, London, in 1986 was