instability; they can take part in all physical education programmes and sports[3] and their parents can be reassured. With the other 13% or so who have instability but no symptoms, special precautions can be taken with regular check-ups to identify children at high risk before spinal cord damage ensues. The 1–2% of individuals with Down syndrome and symptoms of atlantoaxial instability will usually require surgical stabilisation of the upper cervical spine.

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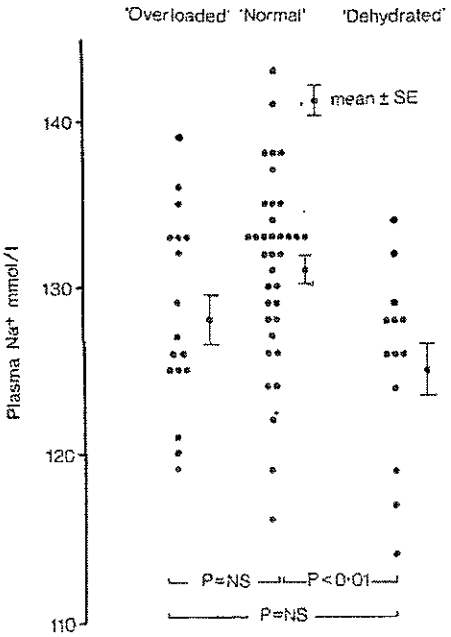
HYPONATRAEMIA AND HAEMOLYTIC URAEMIC SYNDROME

SIR,—Hyponatraemia is a common feature of the haemolytic uraemic syndrome (HUS),[1,2] reflecting enteric electrolyte losses and renal impairment. In a national survey the British Association for Paediatric Nephrology, the British Paediatric Surveillance Unit, and the division of enteric pathogens, Central Public Health Laboratory, collected clinical and laboratory data on HUS from admission and for the duration of the illness. Of the 290 children notified 220 (76%) had a plasma sodium below 130 mmol/l during the acute illness, the lowest recorded plasma sodium being on the day of admission in 67 (23%). 55 patients had seizures. Although seizures in children with HUS are multifactorial, hyponatraemia was recorded in 84% of those with seizures but in only 50% of those without seizures ($p < 0.001$) and convulsions occurred within 24 h of the lowest sodium in 35 of the 55 children.

In individual cases the state of hydration, as assessed by the admitting paediatrician, did not correlate with hyponatraemia (figure). No difference was found between the three groups of children (overloaded, normal, dehydrated) in the duration or severity of prodrome or the incidence of vomiting, and prodromal features could not be used to identify hyponatraemic cases. Worryingly, 84 (29%) of the children with HUS reached the nadir of their hyponatraemia 4 or more days after admission. This must have been due to an incorrect assessment of hydration at presentation, and/or inappropriate fluid and electrolyte prescription.



Plasma sodium and clinician's assessment of hydration.

There are no physical signs to warn physicians of hyponatraemia, and we recommend that any child presenting with bloody diarrhoea (the typical prodrome of HUS) should have close monitoring of plasma sodium from presentation. Moreover, since sodium and water requirements in these children with renal impairment are often complicated by continued losses through vomiting or diarrhoea, sodium and water requirements must be estimated independently.

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PROGUANIL

SIR,—Dr Hanson and colleagues (Jan 28, p 225) do not qualify their claim to report two novel side-effects of proguanil. Hair loss coincided with taking proguanil in 10 out of about 1750 Scandinavians in Tanzania; it was reversed in all 10 cases when proguanil was stopped and recurred in 2 on rechallenge. The scaling of palms and soles was a less frequent and less distressing complaint. I have prescribed proguanil for several thousands of patients of both sexes in Nigeria and Zambia, both long term (eg, to about 5000 patients with sickle-cell disease and to patients with the hyperreactive malarial splenomegaly syndrome, lymphomas, or leukaemias) and short term to pregnant women and patients receiving blood transfusions or total dose iron infusions. I do not recollect a single African patient complaining of loss of hair or scaling of the skin. A racial susceptibility in northern Europeans might be postulated; however, although there have been anecdotal reports of mouth ulcers and loss of memory blamed on proguanil, I never heard, in 22 years, of complaints of hair loss or scaling of the skin amongst the European expatriate communities, many of whom were taking proguanil, often for years.

That all those who lost their hair were women, except for 1 girl, does suggest that other factors were involved, which could include some related to hairdressing, for example. Hanson and his colleagues should look for other factors common to these women and related causally to their loss of hair, either alone or in conjunction with co-factors, which might include proguanil.

Proguanil is the safest and most effective single antimalarial prophylactic for use in tropical Africa. It could be disastrous if anyone in need of protection against malaria were persuaded to discontinue prophylaxis or to change to some less effective regimen out of an unsubstantiated fear of loss of hair.

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INFECTIVITY OF UNCONVENTIONAL VIRUSES IN DURA MATER

SIR,—Unconventional viruses cause several fatal spongiform encephalopathies, including Creutzfeldt-Jakob disease (CJD) and scrapie. Victims harbour the virus in body fluids and tissues, the highest level being in the brain. These viruses are resistant to chemical and physical methods that are generally used to inactivate conventional viruses, and inactivation can be achieved only by autoclaving at 132°C for 1 h or by strong alkali.[1,2] Contamination of tissue with such viruses can be demonstrated only by tedious and expensive transmission studies to animals. Iatrogenic transmission of CJD (eg, at brain surgery, electroencephalography with deep electrodes, or corneal transplantation) has been reported,[3] and in 1987 a case of CJD in a 28-year-old woman was thought to have

TABLE I—TYPICAL INFECTIVITY LEVELS IN EXPERIMENTS* ON DURA MATER AND BRAINS OF SCRAPIE-INFECTED HAMSTERS

Material and treatment	Diseased/total infected	Incubation (days)	Estimated LD_{50} (/g wet tissue)†
Brain homogenate	4/4‡	72 (1)	10^9–10^{10}
Dura mater			
Untreated	10/10	81 (3)	10^6–10^8
Standard + irradiation	10/10	93 (5)	10^5–10^7
Standard + irradiation + 0·1 mol/l NaOH	0/10	350§	$<10^1$
Standard + irradiation + 1 mol/l NaOH	0/10	350§	$<10^2$

*Scrapie hamster brain at clinical stage containing 10^9–10^{10} LD_{50}/g used as reference. 50 µl of 1% suspension inoculated intracerebrally. Dura mater was prepared from skulls of 10–20 clinical stage hamsters, freed of muscle and brain, kept in distilled water at 4°C and then carefully peeled from bone. Material rolled with forceps on filterpaper and weighed. Material was sonicated twice for 15 s. "Standard treatment" refers to cycles of incubation with water, salt solutions, dilute hydrogen peroxide, and acetone for about 3 weeks.
†LD_{50} estimates are from brain (two), dura mater, standard (four), and dura mater non-standard (two) experiments; of these thirteen experiments only five are shown here.
‡Detection limit <10 LD_{50}/g.
§Experiment terminated.

been caused by transmission via a transplant of cadaveric dura mater.[4] We have done experiments in hamsters to see if dura mater does carry the risk of possible contamination with unconventional viruses and to find out whether such contamination can be avoided (for methods see table 1).

Brain from scrapie-infected hamsters at the clinical stage contains 10^9–10^{10} LD_{50}/g. Dura mater contains 10^7–10^8 LD_{50}/g tissue (table) but this is over 1000 times more than is found in muscle fascia.

Commercially available human dura mater is treated with salt solutions, hydrogen peroxide, and acetone for several weeks and is then irradiated with cobalt-60 (25 kGy) but treatment of hamster dura mater in this way lowers infectivity only 10–100 fold. If incubation for 1 h with strong alkali at room temperature was included in the procedure, infectivity was almost completely destroyed (table 1). Scrapie developed in only 1 of 40 hamsters infected intracerebrally with such material and the incubation time **was 260 days.**

Intraperitoneal scrapie infection is followed by up to 50 days of no apparent virus replication in the brain followed by virus replication (days 50–85), and then amyloidosis at 80–100 days, towards the end of which symptoms first appear.[5] During these "preclinical" stages we assayed the infectivity of brain and dura mater material from donor hamsters (infected intraperitoneally) in recipient hamsters (infected intracerebrally). Up to 42 days no infectivity was detected in dura mater (and during this period infecivity in the brain is borderline[5]) (table II). From day 47 to day 78 in only 4 of 17 animals was infectivity detected in the dura mater; in 3 this was at a very very low level and in 1 the infectivity was more than 10^3 LD_{50}/g.

TABLE II—INFECTIVITY TITRES IN DURA AND BRAIN DURING *PRECLINICAL STAGE*

Day*	Diseased/total *infected*†		LD_{50}‡	
	Dura	Brain	Dura	Brain
4	0/5	ND	<10	..
38	0/15	ND	<10	..
42	0/15	ND	<10	..
47	2/20	ND	<10 to $\sim10^2$	..
50	1/9	2/10	<10 to $\sim10^2$	10^4–10^5
57	0/12	9/11	<10	10^4–10^5
64	0/9	4/5	<10	10^3–10^6
71	3/10	12/13	<10 to 10^3	10^3–10^5
78	0/8	8/8	<10	10^3–10^5

*Hamsters were infected i.p. with about 10^9 LD_{50} of scrapie. The i.p.-infected animals (donors, 5 for a given day) were all free of clinical symptoms on the day they were killed for infectivity assay by i.c.-inoculation in the recipient hamsters. Titres were estimated in individual 10%-brain homogenates and in individual dura mater suspensions of material from 1 animal per ml (5–10 mg wet weight). Detection limit <10 LD_{50}/dura mater. Numbers refer to total recipient hamsters.
†Titres refer to the observed range of infectivity determined in 3 individual animals.

These data from the hamster scrapie model demonstrate that **unconventional viruses may contaminate dura mater and confirm the suspicion that CJD may have been transmitted via a commercially available dura mater graft in one case.[4] As shown here the procedure generally used to treat dura mater material reduces infectivity by 90–99% but not completely. Strong alkali destroys scrapie infectivity in the dura mater of hamsters and such treatment would seem to be a very efficient method of inactivating any CJD** agent in human dura mater.

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CARDIAC ARRHYTHMIAS AND HAEMODIALYSIS, BICARBONATE OR ACETATE?

SIR,—In 1988 a multicentre Italian group described cardiac arrhythmias in patients on haemodialysis.[1] All the patients in that study were on dialysis with acetate buffer. Bicarbonate haemodialysis is a well-established alternative for patients with cardiovascular instability during haemodialysis.[2]

We have studied ten patients (seven male) by Holter monitoring through four serial haemodialysis sessions—two with acetate and two with bicarbonate as buffer (4 h each). The mean age was 64 **years and the patients had been on maintenance haemodialysis for an average of 7·4 years. Four had ischaemic heart disease in an asymptomatic phase. The frequency of ventricular arrhythmia was 93 (SD 66)/h during acetate haemodialyses and 32 (26)/h during bicarbonate haemodialyses ($p<0·005$). More class III and IV Lown arrhythmias were recorded in acetate haemodialysis than in bicarbonate; moreover no patient on bicarbonate haemodialysis was in class IVB. The increased frequency of ventricular arrhythmia in** acetate dialyses was prominent during the first hour. Patients with ischaemic heart disease had more frequent and dangerous **arrhythmias than the others.**

Changes in body weight, haematocrit, osmolarity, serum potassium, and ionised calcium during acetate and bicarbonate haemodialysis were similar. Correction of acidosis was quicker and more regular over time with bicarbonate haemodialysis; the consequent difference in ionic flow between the intracellular and extracellular spaces might explain the less arrhythmogenic effect of bicarbonate over acetate haemodialysis.

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