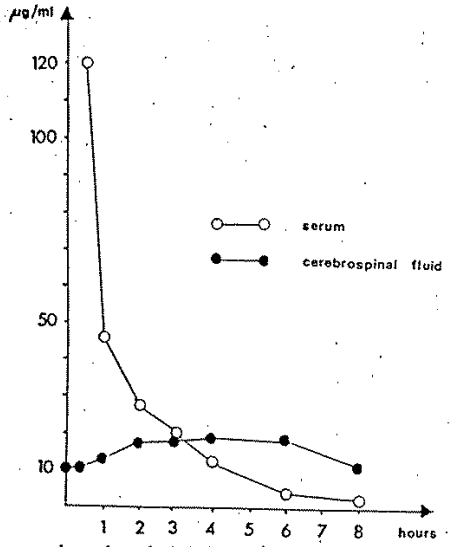


**Serum and cerebrospinal fluid concentrations after dose 15 of ceftazidime in a patient with pseudomonas meningitis treated with ceftazidime 2 g iv thrice daily.**

remaining focus ceftazidime 2 g three times a day intravenously was given for another 2 weeks. Later the defects in the meninges were repaired and a permanent ventriculoperitoneal shunt was installed. No further relapse of the pseudomonas infection occurred.

This case shows that when inflammation of the meninges is present high doses of ceftazidime as a single agent may give satisfactory CNS concentrations for eradication of a pseudomonas infection without the addition of other anti-pseudomonas drugs.

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## ATRIAL FIBRILLATION AND ALCOHOL

SIR,—Dr Thornton's paper (Nov 3, p 1013) on atrial fibrillation precipated by alcohol ingestion was of interest to me, as I have seen a similar case.

A 36-year-old college lecturer was admitted to another hospital in atrial fibrillation following a bout of heavy drinking over one weekend. He was a non-smoker. Viral titres, cardiac enzymes, and echocardiography were normal. Electrocardiogram showed no evidence of pre-excitation but inverted T waves were present in leads III and AVF. Clinical examination was normal. In view of the abnormal electrocardiogram in association with an arrhythmia, cardiac catheterisation including coronary arteriography was carried out, but no abnormality was found. This case seems to meet Thornton's criteria.

Many people ingest significant quantities of alcohol on an occasional or regular basis. However, in few of these is atrial fibrillation recognised. Therefore it is likely that there is a more specific predisposition in certain individuals to induction of atrial fibrillation by the mechanisms which Thornton cites. This predisposition may well be myocardial ischaemia, particularly in the middle-aged male. Thus, while it is useful to recognise that excess alcohol may precipitate atrial fibrillation in a "normal" heart, it remains important for the physician to take all reasonable steps to exclude occult myocardial ischaemia.

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## CYTOTOXIC CHEMOTHERAPY IN BREAST CANCER

SIR,—The overview of cytotoxic chemotherapy trials in early breast cancer reported in your issue of Nov 24 (p 1205) revealed a highly significant delay of death—and not, as Dr Price and Dr Hill (Dec 22/29, p 1461) indicate, merely of recurrence. Moreover, at least for premenopausal stage II disease, the size of the effect appeared large enough to be not only statistically but also medically significant.

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## HAEMOPHILIA AND AIDS

SIR,—Your Dec 22/29 editorial gave an up-to-date and generally balanced view of haemophilia and acquired immunodeficiency syndrome (AIDS). However, we do not agree with the advice to switch completely to heat-treated factor VIII for the treatment of haemophilia A. This decision would involve a probably irreversible change of policy and, as the editorial makes clear, would be based on inadequate evidence. Moreover, the policy would expose all haemophiliacs to a new series of risks and difficulties.

Our major concern stems from the very preliminary and mostly unpublished data on the heat sensitivity of the AIDS virus and the unknown but very real dangers of heat treatment of impure protein fractions. Even mild heat treatment will aggregate protein and the subsequent product will not only predispose to the phlogistic reactions seen with intravenous gammaglobulin but also enhance the immunogenicity of native factor VIII and thus the propensity to antibody formation.[1,2] Production of inhibitory factor VIII antibodies may appear late[3] and, even if uncommon, would further complicate the future management of haemophilia and further jeopardise limited supplies of factor VIII. There is, therefore, a considerable danger that the unproven benefits of heat treatment will be offset by potential risks—one of which, antibody (inhibitor) formation, would be irreversible.

A total change to heat-treated product would take no account of the serological status of the individual patient. It is very unlikely that seropositivity to human T-lymphotropic virus type III (HTLV-III) can occur without exposure to live replicating retrovirus. Experience with other viruses with similar modes of spread (eg, hepatitis B and Epstein-Barr virus) indicates that seroconversion only results from active virus infection.

Many haemophilia centres have been heavily dependent on imported factor VIII concentrates, and until recently little attempt has been made to reserve single batches for individual patients. Therefore, it is probable that over 50% of patients will be seropositive following exposure to live retrovirus in many regions. These patients are most unlikely to benefit from future attempts to prevent reinfection and would not be protected by the heat-treated product. Indeed, the increased protein load and aggregate content may hasten clinical expression of the retrovirus through immune stimulation.

We would, therefore, suggest a truly pragmatic policy based on current knowledge and the serological status of individual patients. Seronegative patients must be clearly and rapidly identified. Only in this group are future protective measures (eg, vaccines, cloned factor VIII) likely to be of benefit and all measures to prevent future HTLV or other interim infection should be taken. We suggest that this group should receive British heat-treated material as soon as it is available or in the meantime cryoprecipitate from seronegative donors. We are concerned that implementation of the policy advocated in the editorial will lead to some seronegative individuals receiving imported blood products of unknown safety for the first time before British heat-treated material becomes available. Seropositive individuals are unlikely to be at further risk on superinfection and they should receive non-heated British concentrate; if this is not available such patients would not be placed

at further risk from untreated imported material. We appreciate the possible risk to families or health-care attendants of exposure to these products but would regard these risks as very small when compared with the danger of concomitant blood exposure and would reinforce the need for extreme care during administration. The continued use of non-heated British concentrate will not compromise the aim of national self-sufficiency of factor VIII. All patients receiving heat-treated preparations must be thoroughly monitored for appearance of reactions and formation of factor VIII antibodies and results compared with those in the non-heat-treated cohort.

The urgency of the situation must not be allowed to obscure the need for a clearly defined policy for the future, formed on scientific evidence, and for management to be based on serological status. Hasty and ill-considered decisions may expose haemophiliacs to new and further risks and may foster complacency which could delay the implementation of measures required now to slow transmission of the virus and to protect the remaining vulnerable members of at-risk groups.

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## SULPHADIAZINE DESENSITISATION IN AIDS PATIENTS

SIR,—Adverse reactions to sulphonamides in AIDS patients[1,2] may become especially troublesome in the treatment of cerebral toxoplasmosis where regimens lacking sulphonamides are not effective. Successful desensitisation has been demonstrated in patients with inflammatory bowel disease[3-6] but not, to our knowledge, in AIDS patients. We describe here successful desensitisation to sulphadiazine in three AIDS patients with cerebral toxoplasmosis who had had severe sulphonamide reactions.

The patients, all male homosexuals, had AIDS diagnosed on the basis of biopsy-proven cerebral toxoplasmosis (one) and *Pneumocystis carinii* pneumonia (two).[7] The latter two patients later had cerebral abscesses compatible with toxoplasmosis on computerised tomographic scanning which regressed completely on anti-toxoplasma therapy. All three patients had fever (more than 39·4°C), leucopenia (below 1500/μl), and a diffuse maculopapular rash during sulphonamide therapy for toxoplasmosis; two patients were also on dexamethasone 16 mg daily for increased intracranial pressure. Two patients had similar reactions to co-trimoxazole for *P carinii* pneumonia.

Before desensitisation, each patient was maintained on dexamethasone (9–16 mg daily). Sulphadiazine was then started at a dose of 250 mg daily in conjunction with pyrimethamine 25 mg daily. The sulphadiazine dose was then increased by 250 mg every second or third day. At daily doses of 1·5–2·0 g larger increments of 0·5–1·0 g every 1–2 days were well tolerated. Maximum daily dosage achieved was 2 g in one patient and 4 g in two patients. Side-effects included transient fever (less than 37·8°C) in two patients, mild pruritus in one patient, and hyperglycaemia in two patients, presumably exacerbated by the steroids. Two patients noted a flare of their rash when dexamethasone was reduced below 4 mg daily; this was controlled by a brief increase in the dexamethasone dose in one patient and by a reduction of the sulphadiazine dose to 2 g daily in the other.

Cytomegalovirus retinitis was diagnosed in two patients 4 and 6 months after desensitisation. Whether this was promoted by the use of steroids is unclear, though no exacerbation of other opportunistic infections was noted. One patient remains alive 9 months after desensitisation with complete resolution of cerebral lesions and has tolerated a further reduction of dexamethasone to 1·5 mg daily. Two patients died, 1½ and 7 months after desensitisation, of unknown causes; the latter patient had resolution of cerebral abscesses documented by CT scan.

Sulphadiazine desensitisation seems feasible in AIDS patients experiencing severe sulphonamide reactions during therapy for toxoplasmosis. Although Luft et al[8] have suggested that pyrimethamine, alone or with clindamycin or spiramycin, might be used in these patients, we noted progression of cerebral lesions in one patient treated with pyrimethamine and clindamycin and believe that sulphadiazine desensitisation may offer a useful alternative.

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## RESPONSE OF MOYAMOYA DISEASE TO VERAPAMIL

SIR,—Moyamoya disease is a vaso-occlusive disease of the intracranial circulation that is seldom seen in Western countries. The cause is unknown. The disease is characterised by occlusion of the intracranial internal carotid arteries and cerebral arteries, and it gets its name from the anastomotic networks seen on the angiogram (the Japanese word *moyamoya* means "puff of smoke").[1] The clinical course in children varies but often results in a chronic dependency.[2] This gloomy outlook and the uncertain success of surgery justify the search for different treatments. Clinical reports in other conditions suggest that calcium antagonists might be useful in moyamoya disease. For example, morbidity and mortality in patients with subarachnoid haemorrhage may have been reduced by nimodipine,[3] calcium antagonists had prophylactic value in treatment of migraine,[4-6] and alternating hemiplegia in children has been reported to improve during therapy with flunarizine.[7]

*Case 1*

This 6-year-old white girl with a history of seizures (with postictal stupor and right arm weakness) controlled by carbamazepine was admitted with progressive right hemiparesis and mutism. Angiography revealed transbasal and transmeningeal anastomoses typical of moyamoya disease. After a left superficial temporal to middle cerebral artery graft and synangiosis with a patch of dura and muscle her right arm remained slightly weak. At the age of 6 years 8 months she had a mental age of 2 years 7 months and was severely aphasic.

Seizures recurred 11 months after surgery and she became mute with a right hemiparesis. She was brought to hospital with the right arm held flexed at the waist and the thumb in fist. She did not use the arm and walked clumsily. There was right hypotonia with hyperreflexia and ankle clonus, but no Babinski sign. She could not understand (or obey) simple commands. Verapamil 10 mg was administered intravenously over 5–10 min without adverse effect. 10 min later the child spoke several simple sentences, grasped the drip stand with her right hand, and walked with minimal circumduction on command.

Computerised tomography revealed loss of substance in the perisylvian region bilaterally and over the superior right frontal convexity, and enlargement of the ventricular system. With the informed consent of the parents, the effect of verapamil was investigated angiographically under general anaesthesia. Serial synchronised biplane cerebral angiograms were obtained after left