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.

Regional Immunology Department;
Public Health Laboratory Service,
and Regional Blood Transfusion Service,
Newcastle General Hospital,
Newcastle upon Tyne NE4 6BE

A. G. BIRD
A. A. CODD
A. COLLINS

1. McCluskey RT, Miller R, Benacerraf B. Sensitisation to denatured autologous gammaglobulin. *J Exp Med* 1962; **115:** 253–73.
2. Benacerraf B. The antigenicity of altered autologous proteins, a mechanism of autoimmune reactions *Ann NY Acad Sci* 1965; **124:** 126–32.
3. Dresser DW, Mitchison NA. The mechanism of immunological paralysis. *Adv Immunol* 1968; **8:** 129–81.

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.

Section of Infectious Diseases,
Lenox Hill Hospital,
New York, NY 10021, USA

EVAN T. BELL
MICHAEL L. TAPPER
ALAN A. POLLOCK

1. Jaffe HS, Abrams DI, Ammann AJ, Lewis BJ, Golden JA. Complications of co-trimoxazole in treatment of AIDS-associated *Pneumocystis carinii* pneumonia in homosexual men. *Lancet* 1983; ii: 1109–11.
2. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immune deficiency syndrome. *Ann Intern Med* 1984; **100:** 495–99
3 Holdsworth CD. Sulphasalazine desensitisation. *Br Med J* 1981; **282:** 110.
4. Taffet SL, Das KM Desensitization of patients with inflammatory bowel disease to sulfasalazine *Am J Med* 1982; **73:** 520–24.
5 Korelitz BI, Present DH, Rubin PH, Fochios SE. Desensitization to sulfasalazine after hypersensitivity reactions in patients with inflammatory bowel disease. *J Clin Gastroenterol* 1984; **6:** 27–31.
6. Purdy BH, Philips DM, Summers RW. Desensitization for sulfasalazine skin rash. *Ann Intern Med* 1984; **100:** 512–14.
7. Centers for Disease Control. Update on acquired immune deficiency syndrome (AIDS): United States. *MMWR* 1982; **31:** 507–08, 513–14.
8. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA* 1984; **252:** 913–17.

RESPONSE OF MOYAMOYA DISEASE TO VERAPAMIL

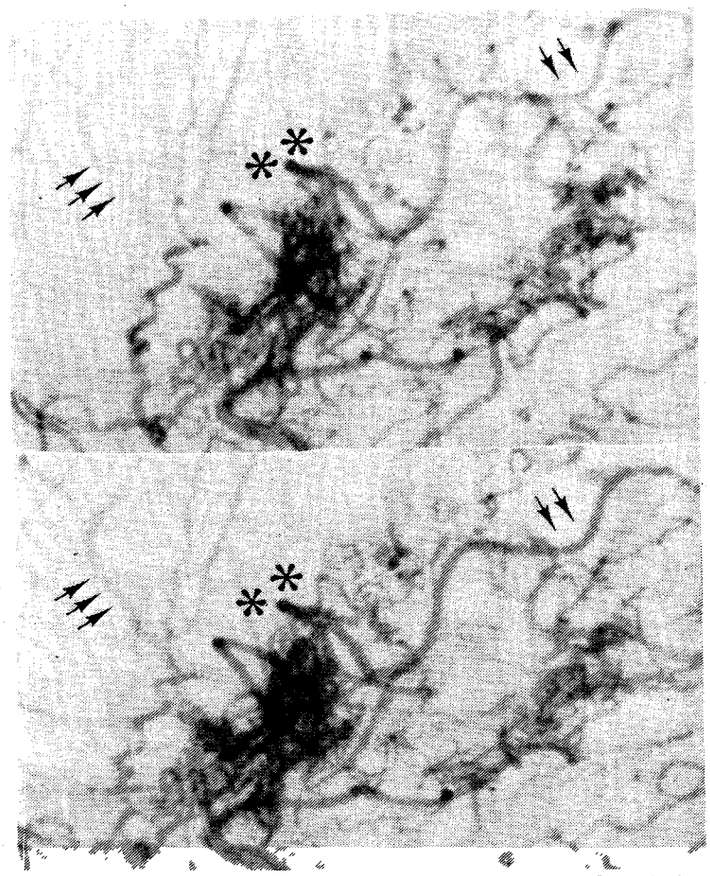
SIR,—Moyamoya disease is a vaso-occlusive disease of the intracranial circulation that is seldom seen in Western countries. The cause is unknown. The disease is characterised by occlusion of the intracranial internal carotid arteries and cerebral arteries, and it gets its name from the anastomotic networks 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



Effect of intravenous verapamil on cerebral vasculature of child with moyamoya disease.

Upper: lateral subtraction angiogram (left common carotid injection) before verapamil, at high resolution to emphasise transbasal collaterals.

Lower: after verapamil, phase being matched with that of upper picture. Note augmented filling of the transbasal collaterals and the increased dimensions of anastomotic network (double asterisks), suggesting opacification of "new vessels". Calibre of posterior branch of middle cerebral artery is increased (double arrows), suggesting vasodilatation. Filling of left anterior cerebral artery through transbasal anastomoses appears to be enhanced (triple arrows).

common carotid injection of 5 ml of 60% meglumine iothalamate before and 10 min after intravenous administration of 10 mg verapamil. Some vessels in the region of the left basal ganglia and a posterior cerebral vessel appeared to be increased in calibre (figure) after verapamil. There were no complications and subsequently oral verapamil was started. The child did not improve beyond her condition before the most recent episode. During 18 months of oral therapy with verapamil (20 mg three times daily) no further neurological deficits have developed.

Case 2

This 3-year-old white boy had a history of focal seizures at age 11 months after which he uttered only grunts and switched to using his left hand. He had then been seizure-free for a year while taking phenobarbitone, and language improved. At the age of 2 he had an episode of lethargy and vomiting followed by focal right facial seizures. 16 months later he became fatigued over several weeks, vomited, and had tonic-clonic seizures followed by mutism and difficulty in swallowing. He switched back to right-handedness. A slight left facial and arm paresis persisted.

Computerised tomography revealed right hemispheric loss of substance. The posterior cerebral and internal carotid arteries were occluded (with redirected flow) and transdural and transmeningeal anastomoses were noted. 3 months after bypass surgery (as in case 1) his vocabulary had increased but a mild left hemiparesis persisted and he reverted to left-handedness.

At age 6¾ he was admitted with a severe headache and left facial paresis. Shortly after intravenous administration of verapamil (10 mg over 5 min) the headache diminished, and by 60 min the facial paresis had resolved. 5 months later resolution of the acute deficit has persisted.

These two cases suggest that acute neurological deficits due to moyamoya disease may be improved by treatment with the calcium antagonist verapamil. In case 1 the deficits, progressive over one week and preceded by seizures, were consistent with a slow vaso-occlusive process. The increased perfusion through transbasal anastomoses (figure) suggested that verapamil acted by reversal of vasospasm. In case 2 the headache and facial paresis mimicked complicated migraine and could also be explained by vasospasm. Controlled studies, bearing in mind the possibility of adverse effects such as systemic hypotension with decreased cerebral perfusion and over-distension of abnormally fragile moyamoya blood vessels with resultant haemorrhage, are now needed. Clinicians in countries where moyamoya disease is more prevalent will be better placed to do these.

We thank Dr Dale Singer for her assistance with case 2, and Ms Debbra L. Neuvirth for secretarial help.

Departments of Neurology, Radiology (Division of Neuroradiology), Anesthesiology, and Pediatrics, and Communicable Disease (Division of Pediatric Neurology), University of Michigan Medical Center, Ann Arbor, Michigan 48109, USA

MICHAEL J. MCLEAN
STEPHEN S. GEBARSKI
ABRAHAM F. L. VAN DER SPEK
GARY W. GOLDSTEIN

1. Suzuki J, Takaku A. Cerebrovascular "moya-moya" disease. *Arch Neurol* 1969; **20:** 299.
2. Maki Y, Nakada Y, Nose T, Yoshii Y. Clinical and radioisotopic follow-up study of "moya-moya". *Child's Brain* 1976; **2:** 257–71.
3. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm: a controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med* 1983; **308:** 619–24.
4. Solomon GD. Calcium channel blockers in migraine. *Lancet* 1982; ii: 162.
5. Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. *Headache* 1983; **23:** 266–77.
6. Markley HG, Cheranis JCD, Piephe RW. Verapamil in prophylactic therapy of migraine. *Neurology* 1984; **34:** 973–76.
7. Cesaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; ii: 579.

CSF CONCENTRATIONS OF RANITIDINE

SIR,—Cimetidine but not oxmetidine can be detected in the cerebrospinal fluid (CSF) in small amounts after a single intravenous dose[1] and after one week of oral medication at therapeutic doses.[2] Case-reports of mental confusion after treatment with ranitidine have been published[3–6] so measurement of CSF ranitidine concentrations may be valuable.

Ten patients scheduled for diagnostic lumbar puncture volunteered to take 150 mg ranitidine twice daily for six days. On the morning of the seventh day 150 mg was given and lumbar puncture was done 2 h, 4 h, or 6 h later. Blood samples were taken before the morning dose on day 7 and at the same time as the lumbar puncture. Venous blood and CSF were analysed for ranitidine by an assay detecting 4 ng/ml or more.

Ranitidine was detected in the CSF in all ten patients (table). The CSF/plasma ratio was 0·08, 0·06, and 0·17 at 2, 4, or 6 h. The higher ratio in the 6 h samples can be ascribed to the lower plasma concentrations at that time. CSF/blood albumin ratios were used to define the status of the blood-brain barrier in each patient. One patient (a 75-year-old woman) had a defective blood-brain barrier but her ranitidine CSF/plasma ratio was 0·08, only slightly above the mean (0·06). No patient showed signs of mental confusion while taking ranitidine.

Although the CSF concentration of ranitidine is lower than the corresponding CSF concentration of cimetidine (mean 0·10 μg/ml plus 0·07 μg/ml for cimetidine's sulphoxide metabolite),[2] the CSF/plasma ratios of the drugs are almost equal—namely, 0·06 for ranitidine and 0·07 for cimetidine.

The mental confusion seen in the occasional patient treated with cimetidine or ranitidine is unexplained. In two cases mental confusion developing in a patient on cimetidine did not recur when the patient took ranitidine.[7,8] However, in one case[7] ranitidine was given at a pharmacologically lower dose than cimetidine, though both drugs were given at doses higher than normally recommended. In the other case[8] cimetidine was given in a high intravenous dose despite depressed renal function. When mental confusion appeared