similar haematoma could be very serious,[5] and failure to detect a haematoma in a patient being considered for carotid endarterectomy or antiplatelet therapy could be important too. In the USA endarterectomy is becoming an increasingly popular operation. Aspirin use may increase too. It may thus become even more important to know whether CT scans can reliably distinguish cerebral infarction from haemorrhage. Our case is a reminder that a CT scan, even within 48 h of onset, may occasionally miss a small but significant haematoma. Although the case emphasises the need for better methods of detecting small haematomas, CT scanning as soon as possible after onset remains the method of choice.

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## CHLORAMPHENICOL FOR MENINGITIS AND PNEUMONIA

SIR,—Dr Coulthard and Dr Lamb (Nov 2, p 1015) state that children describe intramuscular injections as "amongst the worst treatments that they ever receive". While intramuscular benzylpenicillin is certainly painful, chloramphenicol sodium succinate injections are much less so;[1-3] Ross et al commented that the succinate was "very readily tolerated with only a minimal amount of pain at the site of injection".[1] It may be sensible to use intramuscular injections of chloramphenicol in oil ('Tifomycin') as Coulthard and Lamb suggest; however, the study they refer to dealt with meningococcal meningitis, which may respond to treatment much more rapidly than pneumococcal or haemophilus meningitis do, and chloramphenicol in oil gave rather low serum concentrations in the 13 adults studied. Before chloramphenicol in oil is used routinely, it is important to show that this formulation gives adequate serum concentrations in children. Mixtures of long and short acting penicillins are indeed widely used, but the case against them is elegantly stated in the latest edition of "Goodman and Gilman":[4] "Bacteria eradicated by the repository penicillin are not more rapidly killed by the brief exposure to the higher concentration of drug afforded by the preparation; on the other hand, bacteria that can be eradicated only with a high concentration of penicillin G are not affected by the low persistent concentrations achieved with the repository preparation. These preparations are thus not recommended." Penicillin benethamine compound costs over three times as much as procaine penicillin to achieve comparable levels of penicillin.[5]

I agree with Dr Schlegel (Nov 9, p 1069) that chloramphenicol should be reserved for life-threatening infections, such as bacterial meningitis and severe pneumonia. The World Health Organisation protocols for the management of acute respiratory infections stipulate that chloramphenicol should only be given in referral-level health facilities to children who have pneumonia that is so severe that the child is cyanosed or too sick to feed.[6] It is important that the WHO protocols are widely promulgated so that abuse of chloramphenicol is avoided.

Dr Walterspiel (Nov 9, p 1069) is critical of our studies because we began treatment with parenteral chloramphenicol succinate 100 mg/kg and then changed to oral chloramphenicol palmitate without lowering the daily dose to 75 mg/kg. He cites evidence that the oral form has greater bioavailability than the parenteral form in North American children; however, malnourished children, who are often deficient in pancreatic lipase,[7] may have impaired absorption of the palmitate due to an inability to hydrolyse the drug.[8] We found a peak serum chloramphenicol concentration of 15 μg/ml or less in 7 of 15 Papua New Guinean children who had received 25 mg/kg of the palmitate every 6 h for at least three doses; 2 children had a peak of less than 10 μg/ml (unpublished). None of these children had severe malnutrition which, paradoxically, can cause high levels of chloramphenicol due to impaired clearance of the drug.[9] We have suggested that the daily dose of parenteral chloramphenicol succinate should be reduced to 75 mg/kg,[3] but, in areas where many children have mild malnutrition, it may be sensible to continue to give 100 mg/kg of the palmitate orally. Unfortunately, it is usually not possible to monitor chloramphenicol levels in developing countries, and third-generation cephalosporins are far too expensive for routine use. Walterspiel points out that meningitis is usually treated for less than 14 days in North America. Children in developing countries may need to be treated for longer because they often present with very advanced sepsis (for example, 26% of the 367 children in our meningitis study died despite treatment), and those who relapse are much less likely to return for further treatment than North American children are.

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## APOLIPOPROTEIN E ISOFORMS, SERUM CHOLESTEROL, AND CANCER

SIR,—It is unclear whether the relation between low serum cholesterol levels and cancer[1] is causal. In many studies occult tumour may have depressed cholesterol levels though in others the relation was found when serum cholesterol had been measured many years before the cancer was diagnosed. The relation is probably not explained by diet, because in the Seven Countries Study cohorts with widely different diets and corresponding differences in mean cholesterol levels experienced similar mean cancer rates.[2,3] On the other hand, within each region cancer incidence was higher in men with a serum cholesterol in the lowest part of the cholesterol distribution for that country.[3] Thus, naturally low cholesterol levels are sometimes associated with increased cancer risk.[1,3]

Differences in the aminoacid sequence of apolipoprotein E (apo E) are major determinants of differences in plasma cholesterol levels within a population. Apo E has a key role in the clearance of cholesterol from plasma.[4] The synthesis of apo E is under the control of three independent alleles, located at a single gene locus, coding for the major isoforms E-2, E-3, and E-4 with respective population frequencies of about 8, 77, and 15%.[5] The homozygous E-3/E-3 is the most common phenotype encountered and E-2/E-2 is the least common. From apo E-2 to apo E-3, one cysteine residue is replaced by arginine, and from apo E-3 to apo E-4 another cysteine residue is replaced. As a result the avidity of apo E containing lipoproteins for lipoprotein receptors increases from apo E-2 to apo E-3 to apo E-4. In several populations,[6-8] including the Finns and the Japanese (Dr G. Utermann, personal communication), the gradient in serum cholesterol levels in the population is associated with a gradient in apo E phenotype, E-2 being associated with lower serum low-density lipoprotein and total cholesterol levels than E-3 and E-4. Thus, if a naturally low cholesterol favours tumour

growth, then subjects with the E-2/E-2 or E-2/E-3 phenotype should have an increased risk of cancer.

Unlike most other indices of lipid metabolism, apolipoprotein aminoacid sequences are not disturbed by disease, and the apo E phenotype found in a patient will have been present since birth. A comparison of apo E phenotypes in cancer patients with those in matched controls might thus shed light on the relation between low cholesterol and cancer. If it is causal then the E-2 allele should be more common among patients and E-3 and E-4 more common among controls. On the other hand, equal distribution of apo E phenotypes among cases and controls would suggest that the association between low cholesterol and cancer is spurious. Measurement of apo E phenotype by isoelectric focusing of plasma is a routine determination in lipid laboratories; epidemiologists interested in cholesterol and cancer should include it in their studies.

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## TREATMENT OF OLIGOANURIC ANTI-GBM NEPHRITIS

SIR,—Dr Flores and colleagues (Jan 4, p 5) report the clinical outcome of not treating with plasma exchange eight oligoanuric patients with anti-GBM (glomerular basement membrane) nephritis.

Whilst accepting that total anuria carries a very grave prognosis in this condition, we have shown that patients with oliguria often show improvement and sometimes sustained recovery in renal function if plasma exchange and immunosuppression is instituted rapidly.[1] It is therefore not necessarily appropriate to consider oliguric and anuric patients as having identical clinical courses. In patients with glomerulonephritis[2,3] oliguria may occur as a result of a secondary acute tubular necrosis. Acute tubular necrosis can complicate anti-GBM nephritis.[1]

Flores and colleagues record that periods of oliguria and/or haematuria were present from 1 week to 3 weeks before presentation in seven cases and that in all eight more than 90% of glomeruli were involved with crescents by the time renal biopsy was done. The critical period when referral and institution of aggressive therapy is justified is during this period before total anuria is established and before nearly all the glomeruli are affected by crescent formation, a process which can happen in a few days.[1] In all forms of rapidly progressive nephritis, including anti-GBM nephritis, the presence of oliguria and/or haematuria should, in our view, be regarded as a medical emergency requiring immediate referral and therapy. In our experience, the most reliable indicators of both a poor response to therapy and a poor long-term renal outcome are the presence of total anuria and/or <90% crescent formation on renal biopsy. Oliguria and the need to institute dialysis do not predict long-term renal outcome.[1]

Flores et al draw some conclusions about the efficacy of treatment of anti-GBM nephritis without having treated the patients described. Not one of their patients had any recovery of renal function so it is not possible from this report to draw any conclusions about treatment. The eight patients followed up to end-stage renal failure had a median age of 64. Was this a factor in the decision not to treat them? Infective complications due to immunosuppression are generally regarded as being worse in the older age groups.

Although we agree that it is desirable to reduce the 20% mortality associated with anti-GBM disease,[4] including the reduction of infective complications due to combined immunosuppressive therapy and plasma exchange, we also regard end-stage renal failure as an undesirable endpoint of any rapidly progressive form of glomerulonephritis. The 1 year mortality (10%) and 3 year mortality (30%) for all non-diabetic patients receiving end-stage renal failure management (dialysis)[5] is at least comparable with current results in treated anti-GBM nephritis.

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## GENTAMICIN DOSAGE FOR THE NEWBORN

SIR,—We agree with Dr Davey (Sept 14, p 612) that there are insurmountable statistical difficulties in assessing the role of aminoglycosides in the genesis of neonatal ototoxity. However, clinicians caring for the newborn face the practical problems of dosage and monitoring of gentamicin therapy. A *Lancet* editorial[1] has suggested that correct dosage of aminoglycosides has reduced the risk of ototoxicity.

There is general agreement that gentamicin 2·5 mg/kg 12-hourly is adequate therapy during the first week of life in term babies, but various dosage intervals have been proposed for the pre-term. Szefler et al[2] have suggested 18 h intervals for babies less than 35 weeks' gestation, and Koren and colleagues[3] make similar recommendations for babies weighing less than 1 kg. However, three recent textbooks[4-6] still recommend 12 h intervals whatever the gestational age. Differing regimens reflect attempts to keep pre-dose (trough) levels below 2 mg/l whilst preserving peak gentamicin concentrations between 4 and 12 mg/l.

We have reviewed retrospectively 40 patients of birthweight 790–3600 g and gestational age 25–40 weeks receiving gentamicin therapy (mean dose 2·4±0·22 mg/kg). Thirty-two pairs of trough (immediately before) and peak (1 h after third dose) serum concentrations had been measured in 29 of these patients, 29 paired assays were made during the first week of life and 26 babies had received 12-hourly doses. 19 (66%) babies had trough levels greater than 2 mg/l, including 11 (38%) with more than 3 mg/l. Gestational age was significantly lower ($p<0·05$) in those babies with trough concentrations greater than 2 mg/l, whereas birthweight was not a significant factor. These data accord with those of Mulhall et al.[7]

Assuming a one-compartment model,[8] we have calculated dosage regimens which would produce trough concentrations less than 2 mg/l. We now suggest the following gentamicin dosage intervals for the first week of life:

| *Gestational age* | *Dose interval* | *Dose (mg/kg)* |
|---|---|---|
| ⩽28 wk | 24 h | 2·5 |
| 29–35 wk | 18 h | 2·5 |
| ⩾36 wk | 12 h | 2·5 |

If these intervals had been used in our sample only 9 (31%) of our babies would have had trough levels greater than 2 mg/l and 3 (10%) greater than 3 mg/l.

Would such attention to trough levels compromise the efficacy of gentamicin, as Rylance has suggested?[9] Provided distribution volumes remained within the normal range for the newborn, peak