Author's reply

Sir-O M Kon and D S Robinson reference a meta-analysis on methotrexate treatment.1 This study showed that methotrexate treatment resulted in modest steroid-sparing effects, similar to that observed with cyclosporin. However, Marin concluded that longterm studies of both steroid and methotrexate toxicities were necessary before methotrexate could be recommended for routine clinical use. I do not disagree with Kon and Robinson that these alternative anti-inflammatory agents could be considered in certain patients with severe steroid toxicity. In these instances, the risk-benefit ratio would need to be assessed for each individual: this is different from a general recommendation for their use in all patients with severe asthma

A B Kay and N C Barnes draw attention to their study showing the steroid-sparing effects of cyclosporin in steroid-dependent asthmatics.² The study referred to in the table was their earlier investigation showing improvement in lung function with cyclosporin.³ The aim of this table was to comment on steroid-sparing effects only, and this fact was signalled in the original title for the figure. Unfortunately, "steroid-sparing" was omitted from the title in the published versions.

S H Lock and co-workers' study² shows variable steroid-sparing effects in people with chronic asthma. The difference between the mean daily use of prednisolone in the cyclosporin and placebo treated groups was modest (4.4 mg). Although greater reductions in steroid use were achieved during the later weeks of the study, it was not clear that these reductions could be maintained with continued use. Whether the reduction in steroid toxicity could justify the additional toxicity incurred with cyclosporin is conjectural. Although the renal impairment incurred with cyclosporin was said to be reversible, longer treatment with low-dose cyclosporin has resulted in permanent morphological renal damage.4 Aside from issues of drug toxicity, the use of cyclosporin does not lend itself to routine management. Careful monitoring is essential and rigorous attempts at steroid reduction are necessary to achieve the steroid-sparing Sec. 12. effects cited. ·· . .

R Madhok and colleagues' remarks about terminology in describing these agents is appreciated. I did originally refer to these agents as alternative antiinflammatory drugs, but this was changed for the published version. Although the designation alternative

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anti-inflammatory agents is commonly used in pulmonary research and published work, its meaning is not obvious to a general audience. The terms disease-modifying and steroidsparing agents seem more appropriate.

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Malarone-donation programme in Africa

Sir—We welcome the addition of atovaquone to the short list of antimalarial drugs that are effective against multidrug-resistant falciparum malaria. However, the possible negative effects of Glaxo's planned donation programme of Malarone (atovaquoneproguanil combination) are a cause for concern. We agree with Peter Bloland and colleagues (Nov 29, p 1624)¹ that the disadvantages associated with the introduction of this drug in Africa may outweigh potential benefits.

Do African countries really need one million "free" doses of Malarone each year? Despite the spread of drug resistance, chloroquine is still a useful drug in everyday life. Currently available second-line and third-line drugs are also cost-effective for the management of uncomplicated (amodiaquine, sulfadoxine-pyrimethamine) and severe and complicated (quinine) malaria. Other new antimalarial drugs (mefloquine, halofantrine, artemether, artesunate) are not only expensive but do not have any clear indication for the treatment of indigenous patients, since multidrug resistance has not been fully documented in Africa. Why then add another new drug when there is no well-defined role for Malarone in ្រូវវិទ្ទាដ $c_{\rm Neg}$ Africa today?

Rare but severe and potentially fatal adverse effects of mefloquine and halofantrine have been documented in Europe, North America, and Thailand, countries where the health-care system allows pharmacovigilance. If Malarone

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is distributed in Africa, a country where health-care facilities, follow-up of patients, and compliance are generally poor, who would guarantee the continued safety of the drug?

Furthermore, crossresistance between sulfadoxine-pyrimethamine and Malarone is possible. Our studies show that in-vitro responses of Plasmodium falciparum isolates to two dihydrofolatereductase inhibitors-pyrimethamine and cycloguanil (a biologically active metabolite of proguanil)-are highly correlated, which suggests a real potential for in-vivo crossresistance if the proportion and degree of resistance to one of these two drugs increase in Africa.² In addition, the same singlepoint mutation within the dihydrofolate reductase gene has been associated with resistance to pyrimethamine and cycloguanil.3,4 The epidemiology of drug resistance in southeast Asia strongly suggests that the widespread use of pyrimethamine led to the development of resistance to pyrimethamine and cycloguanil.5 Thus, if Malarone is widely used in Africa, its proguanil component will exert drug pressure and may select pyrimethamine-resistant mutants, leading to the spread of resistance to sulfadoxine-pyrimethamine. Such a scenario will be disastrous since sulfadoxine-pyrimethamine has so far been, and still is, a reliable, cheap, and safe alternative to chloroquine throughout Africa.

Another potential difficulty is the selection of correctly diagnosed, eligible patients. It is not clear who would benefit from free medication. Furthermore, as occurred in the Mectizan-donation programme, a limited supply of "free" drugs in areas where demand is high may encourage unauthorised sale, which obviously defeats the humanitarian goal of the donor company. Malarone is a precious new drug that should be used with rationality, for example, in endemic areas where multidrug resistance is prevalent.

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Poliovirus vaccination in an infant with hypogammaglobulinaemia

Sir—W L Yeung and colleagues (Nov 29, p 1594)¹ report an unusual case of a 6-month-old infant who presented with high fever, convulsions, and encephalitis. They believe that the poliovirus isolated in the infant's brain after death was the cause of the encephalitis, because of the underlying hypogammaglobulinaemia.

A boy aged 5 months was transferred from an Albanian hospital to our department in March, 1996. He had had cephalosporin, aminoglycoside, and prednisolone for respiratory infection without improvement. On admission he had cyanosis and tachypnoea (90 breaths per min) with bilateral pneumothorax, but no other clinical abnormalities. He was put on mechanical respiratory support for 2 weeks. Tracheal culture revealed coagulase-negative staphylococcus sensitive to vancomycin and he was given cephalosporin and vancomycin. Differential white cell count, C-reactive protein, and chest radiography suggested an infection in the lungs. B and T lymphocytes were normal, but immunoglobulin concentrations were abnormally low for his age (IgG 0.61 g/L, IgM 0.84 g/L and IgA 0.066 g/L).² 6 weeks after admission he was clinically and haematologically normal; no signs of infection were present, but immunoglobulin values remained abnormally low.

The infant had been vaccinated at the age of 2 months with Sabin oral vaccine in Albania with no adverse reaction. We regarded his hypogammaglobulinaemia either as transient or secondary to severe infection, since B and T cells were functionally normal.³ Therefore Bruton's disease was excluded. We decided to give intramuscular diphtheria/pertussis/tetanus and oral Sabin vaccine at age 9 months, which was uneventful. He was discharged home to Albania in June, 1996, on trimethoprim 2 mg/kg daily for 3 weeks

and returned at age 10 months. Because his aunt was pregnant and she lived close to the patient, it was decided that the third dose of vaccination for poliomyelitis should be given as killed vaccine, to avoid spread of the virus in his environment. At this time his serum immunoglobulin was increased (IgG 5.95 g/L, IgM 0.056 g/L, IgA 0.066 g/L, and CD₄/CD₈ lymphocyte ratio 2.9 [normal 1.2-1.6]) and the child was given all the regular vaccines. The patient was examined clinically in January, 1998, and his development and growth was normal.

From this report is seems that if hypogammaglobulinaemia is transient, it is probably secondary to infection.

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Danaparoid sodium in diabetic retinopathy

Sir—The report by Johan W van der Pijl and co-workers (Dec 13, p 1743)¹ suggests that the heparin-like molecules and glycosaminoglycans (GAGs) may be systemic adjuvant for the treatment of diabetic retinopathy. This observation is also important because it supports the optical safety of GAGs therapy.

Experimental and clinical reports have shown that GAGs improve microalbuminuria and diabetic nephropathy. However, one major concern has been the risk of their anticoagulant activity, particularly in patients with retinal neoangiogenesis, due to the fragility of new vessels. Although this probably represented excessive caution with regard to the doses used, sufficient only in inhibit factor X, van der Pijl shows the therapy to be safe. . من المراجع المراجع المرجع المرجع المراجع المرجع المراجع المراجع المراجع المراجع المراجع المراجع المراجع المراجع 10 11 11 This report is also important because it indirectly gives insight into the pathogenesis of diabetic microangiopathy. In diabetic retinopathy (both , the proliferative form and maculopathy), overexpressed vascular endothelial growth factor (VEGF) has a pivotal role,² and various approaches

have been devised for blocking its action.³ In physiological conditions, some VEGF isoforms are sequestered, and modulated by extracellular-matrixsulphated glycosaminoglycans. Alterations of the sulphation of glycosaminoglycans in diabetes are well known, and exogenous GAGs revert these disorders.⁴ Thus, the effect of danaparoid on hard exudates could be related to the modulation of sequestered VEGF in the retina.

Finally, that a drug such as danaparoid works concurrently on diabetic retinopathy and nephropathy lends support to the idea that these have common pathogenic steps and genetic background.⁵

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Diabetic ketoacidosis and compliance

Sir—Andrew Morris and colleagues (Nov 22, p 1505)¹ find evidence of poor compliance with insulin-therapy in young patients with insulindependent diabetes mellitus (IDDM). They suggest that lack of adherence to insulin treatment was the major factor contributing to long-term poor glycaemic control and to diabetic ketoacidosis (DKA) in these young patients. We have reported a relation between level of education and the severity of diabetic ketoacidosis, with more severe acidosis seen among patients with less advanced education.²

We have conducted an 11-year retrospective case-note review of all episodes of diabetic ketoacidosis admitted to our department between January, 1987, and December, 1997, Only patients older than 15 years were included because younger patients were admitted to the department of paediatrics. We defined diabetic ketoacidosis as newly diagnosed or

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