blood dyscrasias, including 12 of aplastic anaemia, possibly related to topical administration of chloramphenicol have been registered at the National Registry of Drug-Induced Ocular Side Effects in the United States.² The duration of treatment ranged from 18 to 1460 days (median 120 days).

Doona and Walsh affirm that framycetin and fusidic acid are equally effective. These agents do not cover the wide range of bacterial pathogens implicated in eye infections, and when used alone they promote rapid emergence of resistance. Fusidic acid is an antistaphylococcal agent, and framycetin lacks activity against anaerobes and streptococci. The treatment whose antibacterial spectrum approaches that of chloramphenicol, but with reduced anaerobic activity, is a combination of neomycin, polymyxin B, and gramicidin. This costs £5.36 for 5 ml, compared with 50p for 10 ml of chloramphenicol eye drops.

Although there is potential for topical chloramphenicol to produce aplastic anaemia, more hard data on the absolute risk are needed before such a hard judgment is passed on a product that is effective, cheap, and well tolerated. To minimise toxicity even further, treatment with chloramphenicol should be short and avoided in patients with a personal or family history of bone marrow abnormality.

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- 2 Fraunfelder FT, Morgan RL, Yunis AA. Blood dyscrasias and topical ophthalmic chloramphenicol. *Am J Ophthalmol* 1993; 115:812-3.

General practitioners would expect to see aplasia roughly once each century

EDITOR,—Although chloramphenicol eye drops may induce bone marrow aplasia, it might be helpful to put the risk in perspective.¹ In our practice of 4600 patients we use chloramphenicol eye drops as our first line treatment for conjunctivitis and after removal of foreign bodies. We also frequently prescribe chloramphenicol drops on the advice of local ophthalmologists. In total, we issue 360 prescriptions for chloramphenicol drops or ointment a year. Assuming that the risk of aplastic anaemia after topical administration is the same as that after oral administration, we would expect to see one case every 83-138 years in the practice as a whole, or one case every 240-400 years per general practitioner.

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Prospective study of aplastic anaemia should give definitive answer

EDITOR,—We disagree with Marie Doona and J Bernard Walsh's conclusions and recommendations relating to chloramphenicol eye drops and aplastic anaemia.¹ Many drugs have been implicated as causing aplastic anaemia, but for most the evidence is weak, and no in vitro tests are available to prove causation. Furthermore, an apparent association may not mean causality: the exposure may have been a response to the early features of aplastic anaemia itself.

An association between use of chloramphenicol and the development of aplastic anaemia was predicted because of the drug's structure, and many reports appeared in the literature during the 1950s and '60s. The risk of developing aplastic anaemia after exposure to oral or intravenous chloramphenicol has been estimated at somewhere between 1 in 25 000 and 1 in 800 000 exposures, with a figure of about 1 in 60 000 being the most acceptable.² This compares with the overall incidence of aplastic anaemia of two or three cases per million per year. Most patients have received prolonged courses of chloramphenicol, though one report recorded aplastic anaemia after a single day's exposure.

Since the introduction of chloramphenicol 45 years ago about 20 cases of aplastic anaemia possibly associated with the use of chloramphenicol eye drops have been reported in the world literature.³ Doona and Walsh give no indication of the number of patients exposed to chloramphenicol eye drops, but it must be high. In a study in the Netherlands, where 3% of the population was exposed to ophthalmic chloramphenicol, no association was found with blood dyscrasias.⁴ Many of the reported cases of aplastic anaemia after exposure to eye drops have a weak association between the use of the drops and the development of the anaemia, and the incidence after the use of eye drops seems extremely unlikely to be higher than the background incidence. A hypothetical risk of a low incidence of aplastic anaemia after use of the eye drops has to be weighed against the clinical usefulness and lack of other side effects of this particular preparation.

Case-control studies have failed to show any association between chloramphenicol eye drops and aplastic anaemia. The United Kingdom aplastic anaemia study, funded by the Health and Safety Executive and the Leukaemia Research Fund, is a national perspective case-control epidemiological study of aplastic anaemia that is registering all new cases of aplastic anaemia occurring in the United Kingdom over the next four years. All patients will be administered a detailed questionnaire concerning possible domestic medicinal exposure, including eye drops. This will be the largest prospective study of the epidemiology of aplastic anaemia, and we hope that it will clarify some of the controversies relating to drug exposure in aplastic anaemia. In the meantime it seems a pity to exaggerate the risk of aplastic anaemia associated with the widely used preparation of chloramphenicol eye drops.

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Authors' reply

EDITOR,—We take issue with several of the points raised in the letters in response to our editorial. R J Mulla and colleagues accept that after systemic use of chloramphenicol the risk of aplastic anaemia is 13 times higher than that in the general population. Yet we know that topical ophthalmic chloram-

phenicol is absorbed systemically⁵ and that the development of aplastic anaemia is an idiosyncratic response; therefore any exposure is a risk factor regardless of dose or route of administration.

R J Buckley and colleagues state that patients with a proved personal or family history of blood dyscrasias should probably not receive chloramphenicol. In many instances a patient will not be aware of familial blood dyscrasias, and how often are patients asked about blood dyscrasias before they start treatment with ocular chloramphenicol preparations?

We accept that chloramphenicol provides broad spectrum cover, as alluded to by A V Hall and colleagues, but we believe that it should be reserved for resistant eye infections rather than be used as a first line agent.

Jim Cox and Eleri M Roderick believe that the risk is low. While we accept this, the mortality associated with aplastic anaemia induced by chloramphenicol is so high that the risk is unacceptable when the initial condition requiring treatment with chloramphenicol is benign.

We welcome the United Kingdom aplastic anaemia study mentioned by E C Gordon-Smith and colleagues and hope that it will improve knowledge and understanding of aplastic anaemias induced by drugs. We cannot, however, ignore the well documented relation between chloramphenicol and aplastic anaemia regardless of the route of administration.^{2,5}

In contrast to the *British National Formulary*, the *Physician Desk Reference* used in the United States emphasises, in boxed warnings repeated throughout the text, that ocular chloramphenicol should not be used unless there is no alternative. We support the American view—that chloramphenicol does not have a role as routine eye treatment.

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Should herbal medicines be licensed?

EDITOR,—The editorial by Dr Peter A G M De Smet highlighted the need for regulation of herbal medicine-like products.¹ We are particularly concerned about imported herbal medicines that contain heavy metals; this has been well documented in medicines from the Indian subcontinent.² We recently investigated the potential hazards of some Chinese patent medicines with high concentrations of mercurial ingredients that are used for the treatment of AIDS.

The labels and instructions were available only in Chinese, making identification of the product and ingredients difficult. The medicines were Angong Niu Huang Wan and Zhusha Aushen Wan pills, both of which are listed in the *Pharmacopoeia of the People's Republic of China*.³ The ingredients were primarily herbal and mineral and included cinnabar and arsenic. On analysis Angong

Niuhuang Wan was found to contain 47 mg mercury and Zhusha Aushen 659 mg mercury (in the form of cinnabar). Arsenic and lead were also detected. When taken together as prescribed this would have resulted in a daily intake of 706 mg of cinnabar. We are concerned that the use of this amount of mercuric sulphide in long term treatment is potentially hazardous and could lead to mercury intoxication. Kew *et al* reported symptoms of mercury poisoning in a patient after daily exposure to 180-252 mg cinnabar for four weeks.²

Cinnabar has been used for a long time in traditional medicines. The toxic effects of inorganic mercury are well recognised, but because of its insolubility it has been assumed that this compound would not be significantly absorbed from the gastrointestinal tract. However, a study by Yeon *et al* of the oral absorption of cinnabar in mice found a significant increase in mercury concentrations in the liver and kidney. Concomitant use of cinnabar and drugs containing bromides, sulphates, sulphides, nitrates, and iodine may enhance its toxicity by increasing the gastrointestinal absorption.³

We wish to bring the availability and use of these preparations to the attention of medical professionals and to emphasise the importance of obtaining full information on all the medications used by their patients. We are carrying out a traditional remedies surveillance project and would be interested in receiving reports of adverse reactions to herbal remedies and food supplements.

This study is supported by the Ministry of Agriculture, Fisheries and Food.

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recommended as the drug of choice for sedation on the basis of pharmacokinetic and pharmacodynamic properties⁴ and lends itself to a careful titration technique. Combinations of opioids and benzodiazepines are best avoided owing to the additive and synergistic effects on the cardiovascular and respiratory systems. It must be remembered that the antagonist drug flumazenil has a shorter half life than the benzodiazepines in common clinical use.

Local anaesthetic sprays have been implicated in the development of pneumonia after gastroscopy.⁵ Their use may be unnecessary in most diagnostic endoscopic procedures. Formal training of junior endoscopists in sedation techniques together with adequate supervision should ensure the rational use of the available drugs.

When single operator sedationists practise endoscopy the British Society of Gastroenterology recommends at a minimum that a nurse trained in endoscopy techniques and dedicated to patient care is present throughout. Supplemental oxygen and monitoring should ideally be continued throughout the period of recovery, and premature discharge to maximise turnover must be resisted. The employment of qualified staff who are able to monitor patients, interpret changes in the monitored variables, and start cardiopulmonary resuscitation when necessary may have implications for general practice endoscopy services, where it may prove difficult to ensure both safety and cost effectiveness.

We may be able to influence these worrying statistics by centralising services, ensuring proficiency of endoscopists, providing skilled help, and adopting the excellent guidelines already available.

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valuable, and prior knowledge is needed to prevent misinterpretation. Many limitations of pulse oximetry have been described, including the fact that it is a "lag" monitor; that it measures oxygenation, not ventilation; and that the function of the oximeter is adversely affected by a variety of factors.⁴ Anaesthetists are required, as part of their training, to have detailed knowledge of all the monitoring devices they use on patients perioperatively, including pulse oximeters. A recent survey of junior doctors in specialties other than anaesthesia showed poor overall knowledge of the principles of pulse oximetry, its limitations, and its application to clinical practice.⁵ A failure to interpret oxygen saturation values correctly could be as dangerous as not having them available.

If monitoring techniques such as pulse oximetry are introduced widely this should be accompanied by an increase in training in the use of such devices for staff. Widening the remit of the national confidential inquiry into perioperative deaths to include endoscopy would certainly be a start in auditing the safety of current endoscopic practice, but perhaps the safest method of all would be to add endoscopy under sedation to the list of procedures that are monitored by anaesthetists.

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Gastric lavage poses risks to patient

EDITOR.—J E Charlton comments on the safety of diagnostic and therapeutic endoscopy.¹ Gastric lavage is a procedure akin to upper gastrointestinal endoscopy that is invariably performed on an already sedated patient. It is likewise associated with cardiovascular and respiratory compromise² and should perhaps be undertaken with a similar degree of care and monitoring.

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Paediatric endoscopy should be carried out under general anaesthesia

EDITOR.—J E Charlton highlights the hazards of gastrointestinal endoscopy carried out under sedation.¹ These dangers are not confined to adults.

In a prospective study of 32 children undergoing gastrointestinal endoscopy under sedation, desaturation (oxygen saturation of 90% or less) occurred in 37.5%; this desaturation was unpredictable and failed to correlate with the patient's weight, age, or tolerance of the procedure.² In another prospective analysis, of 57 small children, 10% of the examinations had to be interrupted by removal of the endoscope because the child developed stridor and a low oxygen saturation.³

Monitoring during endoscopy

Attention to sedation techniques may reduce mortality

EDITOR.—J E Charlton draws attention to the estimated overall death rate of 1 in 2000 from upper gastrointestinal endoscopy, which is usually performed under sedation or local anaesthesia, or both.¹ When compared with the overall mortality solely attributable to anaesthesia, which is 1 in 185 000,² this mortality seems unacceptably high.

Recommendations for standards of sedation and for monitoring patients during gastrointestinal endoscopy were published by the British Society of Gastroenterology in 1991,³ and guidelines for sedation by non-anaesthetists were published by a working party of the Royal College of Surgeons in 1993.⁴ Despite this, practice across Britain seems to vary widely.

We were surprised to find that in some regions the preferred benzodiazepine for sedation during endoscopy is diazepam,⁵ which has an active principal metabolite (desmethyldiazepam) with a half life of 48-96 hours. Midazolam has been

Pulse oximetry has limitations

EDITOR.—Most anaesthetists are already aware of the dual problems of oxygenation and monitoring during endoscopy on sedated patients.¹ The solution, however, may not be as simple as introducing supplemental oxygen and using pulse oximetry for all patients. There are crucial differences between a sedated patient undergoing endoscopy and an anaesthetised patient undergoing surgery.

Firstly, for patients undergoing endoscopy there is usually only one operator, who performs the endoscopy as well as giving sedation and cannot therefore give the patient's oxygenation and monitoring full attention during the procedure. The revised recommendations for standards of monitoring during anaesthesia and recovery issued by the Association of Anaesthetists of Great Britain and Ireland state that the anaesthetist should be present throughout the general anaesthesia and that this consideration applies to any technique or sedation carrying a risk of unconsciousness.

Secondly, and most importantly, pulse oximetry is not an infallible monitoring device, though it is