"antimony spots." Cardiovascular mortality and morbidity and electrocardiographic changes have been attributed to inhalation of the trisulphide. Acute inhalation of the volatile hydride stibine (for which an occupational exposure limit of 0.1 ppm (0.5 mg/m³) has been defined¹³) may lead to haemolytic anaemia and acute renal failure. Unlike trivalent arsenic, trivalent antimony has not been convincingly shown to be carcinogenic.⁹

Although the hypothesis that stibine formed by fungal transformation of fire retardants containing antimony in cot mattresses might be a cause of the sudden infant death syndrome is interesting,⁴ it receives insufficient toxicological support. Experiments do not substantiate the suggested anticholinesterase action for stibine. Using blood concentrations of antimony in the assessment of stibine poisoning is risky. The toxic effects of stibine differ considerably from those of the oxides, sulphides, or organic antimonials. In the assay of antimony in blood the total element is measured instead of the toxic entity. This means that antimony blood concentrations resulting from stibine exposure may never be compared with those resulting from other sources.

To evaluate the hypothesis, environmental and biological monitoring should go hand in hand. Sampling of the air inspired by babies on polyvinylchloride mattresses would give information on actual exposure, which could then be compared with occupational data on exposure to stibine. It is important to realise that the minute volume and the sensitivity to the toxic insult in infants may differ from those in adults; infants are usually exposed to ambient air considerably longer than an adult's 40 hour working week.

The sudden infant death syndrome long predates the invention of plastics containing antimony. A recent epidemio-

logical study supports the scepticism towards the hypothesis of antimony trihydride being the cause of cot death.¹⁴ It is therefore most unlikely that, even after thorough toxicological evaluation, stibine will ever be convicted as the only cause of the syndrome.

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Use of chloramphenicol as topical eye medication: time to cry halt?

Bone marrow aplasia also occurs with ocular use

Chloramphenicol accounts for over half the general medical services prescriptions for ocular antibiotics in the Republic of Ireland, while in the United Kingdom 55% of patients presenting to general practitioners with "red eyes" are treated with chloramphenicol eye ointment.¹ The *British National Formulary* currently recommends chloramphenicol as the drug of choice for superficial eye infections. It has the advantage that it has a broad spectrum of activity and rarely causes local irritation or hypersensitivity, which may be a problem with other antibiotics. Yet on our wards we no longer prescribe topical ocular chloramphenicol. Why?

Since 1950, when Rich *et al* highlighted the relation between oral chloramphenicol and bone marrow aplasia,² doctors have been well aware of this side effect. The first death resulting from bone marrow aplasia induced by chloramphenicol eye drops was described by Rosenthal and Blackman in 1955.³ Numerous subsequent articles directly implicated chloramphenicol eye drops in causing bone marrow aplasia,^{4,7} and after the publication of Fraunfelder *et al*'s paper⁶ in 1982 the sale of chloramphenicol eye drops in the United States fell by 80% in two years.⁸ By 1993 the national register of drug induced ocular side effects (in Oregon) had received reports of 23 patients with blood dyscrasias that might have been related to topical ocular administration of chloramphenicol.⁸

This caution over the association is important since there are several problems in directly implicating ocular

chloramphenicol as a cause of blood dyscrasias. Firstly, clinicians do not usually ask about eye drops or ointment when taking a drug history; secondly, many patients do not realise that they have used ocular chloramphenicol; thirdly, blood dyscrasias may develop weeks to months after treatment has been stopped⁹; and, finally, some of the reactions are idiosyncratic. All these difficulties underline the importance of an extensive drug history.

Oral chloramphenicol causes two types of bone marrow toxicity.⁶ The first is a dose related reversible depression generally affecting erythroid cells, which is thought to be mediated by mitochondrial injury; the second is an idiosyncratic reaction, which affects all three cell lines and is generally fatal. In the second type a nitroreduction derivative of chloramphenicol produced by a predisposed patient is thought to induce damage to DNA in stem cells, leading to blood dyscrasias. The ultimate toxic derivative of chloramphenicol may be produced in the marrow in situ, thus making the marrow both the site of metabolic conversion and the target of injury. Genotoxicity in stem cells may make them non-proliferative or, alternatively, may initiate marrow damage mediated by the immune system. The occurrence of aplastic anaemia with the small doses characteristic of topical chloramphenicol is thus consistent with the hypothesis of an individual metabolic predisposition.⁸ Ocular chloramphenicol may therefore cause this idiosyncratic reaction only in genetically predisposed people, and a personal or

family history of blood dyscrasias may be very important.

At present there are no accurate figures to estimate the precise risk of marrow aplasia after the ocular administration of chloramphenicol. We do, however, know that the overall risk of developing aplastic anaemia after oral administration of chloramphenicol is 1 in 30 000 to 1 in 50 000,⁶ which is 13 times greater than the risk of idiopathic aplastic anaemia in the population as a whole. Since topical administration achieves systemic effects by absorption through the conjunctival membrane¹⁰ or through drainage down the lacrimal duct with eventual absorption from the gastrointestinal tract, we can postulate that the risk may be similar to that after oral administration of the antibiotic.

Although the numbers of documented cases of aplastic anaemia associated with topical chloramphenicol are few, the tragic consequences in previously healthy patients cannot be ignored.¹¹ From our review of published reports we find it difficult to justify subjecting patients to this potential risk—except when the ocular infection is resistant to all other available antibiotics. The prescribing habits of doctors on the other side of the Atlantic support this approach. In the United States the *Physician Desk Reference* emphasises with repeated boxed warnings the importance of not using ocular chloramphenicol unless there is no alternative. Framycetin and fusidic acid are but two of many safer and equally effective

preparations in the treatment of most superficial eye infections. All doctors should follow the example of their American colleagues in restricting their use of ocular chloramphenicol.

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Neuromuscular blockers during general anaesthesia

Less may be better

The recall of events occurring during surgery, including the suffering of pain, remains a problem experienced by at least one in 3000 patients.¹ In about half of these cases the problem is due to failure of equipment or an error in anaesthetic technique. In many cases, however, no cause other than individual "resistance" to anaesthetics can be found. Being "awake" during general anaesthesia without the knowledge of the anaesthetist was almost unheard of until the middle of this century, and its possibility is a direct consequence of modern techniques of anaesthesia. It may be time to re-examine these techniques.

In 1942, in Montreal, Griffith and Johnson introduced the use of small amounts of curare to enhance abdominal muscle relaxation during laparotomy, still relying on the diaphragm to ventilate the lungs.² Patients were made merely weak and not paralysed while receiving a full inhalation anaesthetic. A few years later, in Liverpool, Gray and others introduced a technique whereby much less anaesthetic and much more curare were used, effectively paralysing all skeletal muscles, including the diaphragm.³ Intubation of the trachea and mechanical ventilation of the lungs were therefore essential. This led to a reduction in mortality due to anaesthesia. Previously mortality had been mostly due to the severe cardiac depressant effects of general anaesthetics, a side effect absent from curare. The enormous advantages of this new technique gave it considerable popularity, which has lasted to the present day. But it also led to the possibility of carrying out surgery on paralysed, unanaesthetised patients, unable to communicate with the outside world.

Before curare was used the depth of anaesthesia was reliably judged by close observation of the patient, mostly of movement of skeletal muscle, including the breathing pattern and the reflex response to surgery. With total paralysis of skeletal muscle there is no reliable method of assessing depth of

anaesthesia and therefore guaranteeing unconsciousness during surgery. Great efforts have recently been made to develop methods of measuring depth of anaesthesia in paralysed patients. So far, these methods are still experimental, and the goal may well prove to be elusive.¹ The potency of anaesthetics continues to be defined in terms of loss of a motor response to a standard stimulus. It is noteworthy that recent reviews of cases of awareness during surgery show that neuromuscular blockers were used in all the reported cases; after awareness of sounds, the sensation of paralysis with inability to communicate was the most common recollection (85%) suffered by patients complaining of awareness.⁴

A close examination of the indications for muscle relaxation during surgery leaves only a small minority of procedures for which a short period of paralysis is absolutely necessary. Modern anaesthetics and analgesics allow good operating conditions to be maintained without paralysis for most major surgery, including cardiac operations. Why then is the use of paralysing agents so widespread in anaesthesia? If neuromuscular blockers were used only when there was a clear indication for them the incidence of awareness during surgery might be drastically reduced. But are our trainee anaesthetists being taught the right techniques?

Finding a clearly stated policy for the administration of neuromuscular blockers in standard textbooks is hard, although much emphasis is placed on the pharmacology of these drugs. In one popular British textbook indications for paralysis include: "to abolish skeletal muscle contractions which occur as reflex responses to painful stimuli or to tracheal intubation."⁵ In an equally popular North American textbook, however, the author states: "two philosophies govern the use of muscle relaxants. One end of the scale has been popularized by Gray and co-workers in Liverpool, England. In this approach nitrous oxide, oxygen, and large