phosphodiesterase-inhibiting properties,¹ and more recently functional SRS-A antagonism.² The clinical relevance of these properties is the subject of further investigation.

Ketotifen was shown early in its development to inhibit antigen-induced bronchospasm in man when given orally.³ This encouraged further clinical development, leading to other controlled trials, now reported⁴⁻⁹ (also by Carrasco *et al* at 11th International Congress of Allergology, Jerusalem, 1979), as well as the one cited¹⁰ in the review. The majority of trials, particularly the long-term studies, demonstrate efficacy for ketotifen in comparison with placebo or other agents.⁴⁻¹⁰

WILLIAM P MACLAY
GRAHAM R KENNEDY

Sandoz Products Limited,
Feltham,
Middx TW13 4EP

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SIR,—Your leading article on mast-cell stabilisers (21 February, p 587) raises two interesting and important questions—should the term mast-cell stabiliser be discarded and does sodium cromoglycate have actions other than its ability to inhibit the release of mediators from mast cells?

It is now becoming clearer that the drug does have another activity in asthma unrelated to mast-cell stabilisation. This is shown by its ability to prevent asthma induced by cold air¹ and by sulphur dioxide² and by the fact that in the latter effect sodium cromoglycate has a different dose-response curve to that observed in allergen-induced asthma.³ Although the details of this mode of action have still to be elucidated it would appear likely that the drug influences at some point the neurological reflexes involved.⁴

While this effect may be important in the day-to-day control of asthmatic symptoms it is the capability of the drug to reduce bronchial hyperactivity over the short⁵ and the long term⁶ that is most important in the management of asthma. This effect is related to its ability to block both type I and type III allergic reactions.⁷ It may be, however, that long-term modification of the neurological mechanisms is also important in reducing bronchial hyperactivity. However, there is no evidence to support this hypothesis at present, whereas evidence does exist for an effect on hyperactivity following a type III reaction.⁸

It is possible that newer drugs for asthma have failed to show the therapeutic promise indicated by challenge tests because they have only one of these two modes of action shown by sodium cromoglycate. Asthma is a multifactorial disease and a challenge test will indicate activity of a drug against only that particular challenge, and not show that it is an effective long-term therapeutic agent. In addition, no good animal model for asthma exists which can be used as a predictor in man.

At this stage, we would argue that both activities of sodium cromoglycate are important in a drug providing baseline therapy for asthma; but, of the two, the ability to stabilise mast cells in clinical situations in man⁹ is the more important. Thus the term mast-cell stabiliser remains relevant, although we should recognise that other therapeutic effects are also necessary in the management of asthma. Sodium cromoglycate with its dual activity and its ability to reduce bronchial hyperactivity remains unique as the only drug able to alter the fundamental causes of the disease.

A M EDWARDS
T S C ORR

Pharmaceutical Division,
Fisons Limited,
Loughborough, Leics LE11 0QY

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Overdose with ibuprofen causing unconsciousness and hypotension

SIR,—We read with interest the report from Drs Diana P Hunt and Richard J Leigh (29 November, p 1458) of a case of ibuprofen overdose. However, we were surprised that the results quoted from our laboratory omitted to mention that the antihistamine chlorpheniramine had also been detected in the patient's urine by our normal screening procedure (using both gas-liquid and thin-layer chromatography¹). This is of particular importance since it has been reported that the toxic effects of H₁-receptor antagonists, such as chlorpheniramine, include depression of the central nervous system and hypotension,² both of which were exhibited by this particular patient.

We are currently studying the toxicity of the non-steroid anti-inflammatory drugs, and at present we are aware of the outcome in 55 cases of alleged overdose with ibuprofen. Of these, 37 patients (67%) remained symptomless. Only five patients exhibited serious symptoms and one subsequently died. The fatal case involved a mixed-drug overdose and is currently under investigation.

Cases of ibuprofen poisoning (all with recovery) for which plasma or serum ibuprofen concentrations are available

Age	Sex	Amount of ibuprofen ingested	Other drugs ingested	Symptoms	Plasma ibuprofen concentration (mg/l)	Hours after ingestion when concentration determined
1	M	? 1.2 g		Drowsiness, minimal rise in transaminase six days after ingestion	711	1½
17	M	14–16 g	Diazepam ("few tablets") alcohol ("moderate" quantity)	Coma grade IV, pulse 150 beats/min, blood pressure 140/100 mm Hg; conscious after 8½ hours	400	1½ after admission
70*	M	12 g	Chlorpheniramine	Coma grade III, hypotension	840 220	1 4

*Case referred to by Drs Hunt and Leigh.

The table summarises three cases for which serum ibuprofen levels are available.

It is necessary to acquire more information on cases where large single overdoses of ibuprofen have been confirmed by laboratory analysis before we can draw firm conclusions about the toxicity of this drug. For the present, our experience suggests that ibuprofen is relatively non-toxic in acute poisoning compared with some drugs prescribed for the same clinical indications. We would be pleased to provide laboratory analyses (blood and urine samples) in any further cases of suspected ibuprofen overdose.

HENRIETTA COURT
P J STREETE
GLYN N VOLANS

National Poisons Information Service,
New Cross Hospital,
London SE14 5ER

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Pulmonary oedema after transfusion with fresh frozen plasma

SIR,—The recent report by Dr P C O'Connor and others (31 January, p 379) of pulmonary oedema after transfusion with fresh frozen plasma and the authors' failure to demonstrate clearly a cause for the complication suggests that consideration be given to the possible role of the granulocyte in the development of pulmonary oedema in this situation.

We have recently seen a 19-year-old boy who, while undergoing second-remission induction for acute lymphoblastic leukaemia, developed pseudomonas septicæmia. He was severely neutropenic (total neutrophils $<0.2 \times 10^9/l$) and was treated initially with tobramycin and carbenicillin, and after 36 hours with daily granulocyte transfusions from related donors. On the fifth day of transfusion he became apyrexial and peripheral blood and bone marrow examination suggested marrow recovery. The following day he became confused and this was associated with severe hypoxia. Physical signs and a chest radiograph were compatible with pulmonary oedema. He had polyuric renal failure and there was no evidence of gross fluid overload. Ventilation with high levels of oxygen and positive end-expiratory pressure was instituted. Severe persistent thrombocytopenia precluded pulmonary artery pressure measurement. There was a gradual return to normal oxygenation over the following 10 days. He spontaneously recovered from his renal failure, though he required regular haemodialysis throughout this period. Repeated culture of blood and endotracheal aspirate showed no evidence of continued infection. He recovered completely from this episode and went into bone marrow remission. We were unable to demonstrate the presence of antileucocyte antibodies in either the patient or any granulocyte donors.

Pulmonary oedema is described as a complication of granulocyte transfusion and several mechanisms have been proposed.¹ Leucocyte agglutinating antibodies have been implicated in the development of non-cardiac pulmonary oedema following the infusion of whole blood²⁻⁴ or plasma.^{5,6} Non-cardiac pulmonary oedema develops in other situations where aggregation of leucocytes and their sequestration in the lungs have been observed. Complement activation seems to be important in some instances and in particular the C5a fragment acts as the trigger for leucocyte aggregation and adherence. Granulocytes adherent to endothelial cells may release toxic oxygen species.⁷ A recent report suggests that other release products from granulocytes, such as neutral proteases, may be important in the causation of endothelial damage in the lungs and the resultant oedema.⁸ This damage can be reduced by the administration of corticosteroids.⁷

Artificial ventilation with positive end-expiratory pressure should be considered when ventilation defects indicate in this potentially reversible condition.

PETER J WYLD
B E WOODCOCK

Department of Haematology,
Hallamshire Hospital,
Sheffield S10 2JF

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Air pollution: the "classical" pollutants

SIR,—Readers of Daphne Gloag's article (28 February, p 723) might be excused for gaining the impression that Britain's Clean Air Act has been the overriding factor contributing to today's vastly improved air quality, but this is a view which should be tempered with a degree of caution.

Certainly the Act represented a major breakthrough in that it at last enabled local authorities to get on with the job of smoke control—a job which many had fought to be able to do for decades¹—and striking improvements were achieved in many of the leading cities, where smoke control programmes were vigorously pursued. But it should also be noted that significant changes were also occurring simultaneously in the types of combustion equipment and fuel available, and that these too are likely to have been factors, the importance of which may be gleaned from the fact that a number of cities without major smoke control programmes experienced substantial declines in mean winter smoke concentrations during the 1960s.² This no doubt has contributed to the admission that "it is impossible to decide from the data to what extent the Clean Air Act of 1956 has been responsible [for the decrease in smoke] or to what extent it has been due to modernisation of habits of living," to quote S R Craxford *et al* (Clean Air Conference, Folkestone, 1971).

With reference to the discussion of the usefulness of air quality standards, and Britain's reliance on the method of "best practicable means," the position, in practice, has already

moved on. In July 1980 a European Directive,³ specifying "limit" and "guide" values for smoke and sulphur dioxide for the protection of health and the environment, was signed. From the pollution control viewpoint the burning question is now how the mandatory "limit" values can best be attained. Analysis of monitoring data for Britain shows that a fair number of areas fail to meet these limit values, in the main because of high smoke concentrations; and it is intended that smoke control zones be further extended to meet this exigency. In a few areas, notably central London, sulphur dioxide concentrations exceed the limit values,⁴ and a new and more complex abatement strategy may be necessary. Information on the sources of sulphur dioxide in London^{5,6} suggests that, if further control is to be enacted, this will have to focus on the use of fuel oil by commercial and institutional premises.

Another point of current concern centres on smoke emissions from motor vehicles. Though for centuries coal burning has been the main source of dark smoke in our cities this situation is changing too, emissions especially from diesel-engined vehicles becoming increasingly significant. In fact, estimates for London show emissions from motor vehicles now to be dominant.⁷ While the debate over possible associated health effects remains unresolved, there is no doubt that the soiling effect of these emissions is of widespread annoyance to the British public,⁸ and warrants closer attention. They may also be found to conflict with the limit values specified by the European Directive.

D J BALL

Environmental Sciences Division,
Greater London Council,
London SE1 7PB

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Haemorrhage from gastric artery aneurysms

SIR,—We would like to comment on the article by Drs M Helliwell and J D Irving (7 February, p 460). They suggest that submucosal vascular malformations of the stomach causing haemorrhage may be impossible to diagnose unless coeliac axis angiography is performed. In the last nine months we have diagnosed single-vessel haemorrhage without ulceration in the stomach at endoscopy in four patients, the appearances being similar to those described initially by Goldman in 1964.¹

One of the patients was submitted to emergency surgery because of profuse haemorrhage; the single vessel was identified and undersewn, with complete recovery. In the most recent case an elderly lady who had had a cerebrovascular accident had a major haemorrhage from a single gastric vessel, which was

successfully treated by endoscopic laser photocoagulation. We feel that these lesions are probably underdiagnosed at endoscopy, particularly in those patients who are admitted with major acute upper gastrointestinal haemorrhage and in whom no source of blood loss is identified. At endoscopy, if the vessel is not actively spurting, the lesion looks like a small nipple protruding through the mucosa.

We are currently conducting a randomised controlled trial with a neodymium YAG (yttrium aluminium garnet) laser in patients with acute upper gastrointestinal haemorrhage. Endoscopic laser photocoagulation of single-vessel gastric haemorrhage may well be the treatment of choice in these patients in the future and constitutes one of our trial categories.

I A MACLEOD

Department of Surgery

J FRASER MCKENZIE
PETER R MILLS
R I RUSSELL

Department of Gastroenterology,
Royal Infirmary,
Glasgow G4 0SF

¹ Goldman RL. *Gastroenterology* 1964;46:589-94.

"Hazards and Errors in Anaesthesia"

SIR,—While I appreciate Dr Michael Rosen's review of my recent book (28 February, p 727), attention must be drawn to a misprint and an answer given to allegations of inaccuracy.

Dr Rosen writes, "Some statements are incorrect. It would be foolish to believe (p 172) that 'Vomiting is a reflex arc'" (this is a misprint—the text says "act," which is something quite different) "of considerable complexity ... not possible in anaesthetised subjects."

Borison and Wang¹ using direct stimulation of the medulla in cats, reported that "Vomiting was not at all elicitable in cats during the surgical state of anaesthesia." I myself have never known a patient in the first plane third stage of anaesthesia to vomit.

D A BUXTON HOPKIN

London WS3 4LE

¹ Borison HL, Wang SC. *J Neurophysiol* 1949;2:306.

Endoscopic assessment of oesophageal disease

SIR,—We are concerned that some of your readers may misinterpret Mr K S Mullard's statement (14 February, p 569) that "any patient suffering from a mishap following oesophagoscopy without preliminary radiology will have an almost irresistible claim for damages for negligence."

He writes from experience of a long and distinguished career in thoracic and oesophageal surgery, during which oesophagoscopy was usually performed with rigid instruments, often under general anaesthesia. This procedure certainly carried substantial risks, even in the most expert hands. The situation has changed with the recent widespread introduction of flexible endoscopes. Oesophagoscopy is now mainly performed on lightly sedated outpatients by physicians with specialist training in gastroenterology. Far larger numbers of oesophagoscopies are performed than in earlier days, since the procedure is usually only part