Lead in petrol: again

SIR,—Dr P S I Barry of Associated Octel Co Ltd, the company that manufactures lead additives for petrol, seeks to imply (19 June, p 1877) that the three-day CLEAR scientific symposium was “loaded” by the selection of chairmen and speakers. The opposite is the case. Firstly, we chose those speakers whose substantial research in recent years has been at the centre of the debate and who have no economic vested interest in the social policy repercussions of their research. Secondly, we advertised the symposium widely, and it was open to anyone to attend and cross-examine these contributors in detail. Personal invitations were sent to many known to have different views from CLEAR in order that they should have this opportunity. It is noticeable that many who have expressed firm views that low level lead exposure is not detrimental to health did not take the opportunity to fault or question the studies. Thirdly, Professor Michael Rutter, whose independence and integrity needs no underlining, was a member of the Lawther Committee often criticised by CLEAR, and when we invited him to be chairman we were well aware that in his final summary he could reach conclusions which were opposite to those held by CLEAR.

To sum up, we put the evidence on the line, invited a chairman we believed would be most acceptable to medical and scientific opinion, and offered the opportunity to anyone who wished to do so to examine that evidence.

It is, of course, Dr Barry's tragedy and that of Associated Octel that the evidence when it is presented speaks for itself—it may not be seen as conclusive evidence, for there are many to whom no evidence on this subject will be conclusive, but it satisfied Professor Rutter and many others of previously open mind that there exists a substantial risk to health that requires action.

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SIR,—As both Dr P S I Barry and I were at the symposium organised by the Campaign for Lead-free Air I think it is unfortunate that his account (19 June, p 1877) differs in several respects from the actual proceedings.¹

Dr Gerhard Winneke's more recent studies do not contradict his earlier findings² as he again shows statistically significant associations between blood lead concentrations and neuropsychological disorders. Dr Winneke used an unconventional assessment of socioeconomic status in his analysis which included the type of school attended, and this may have pre-selected children with higher lead concentrations. The interpretation of this data has been modified in that IQ differences are not shown, using a stepwise multiple regression analysis, but his other findings are less open to criticism. These reinforce his earlier work as they are statistically significant and show differences in attention-bound reactions and perceptual motor integration even when other variables are taken into account. Now that Winneke has used animals his statement that lead does cause this type of neurological dysfunction is fully justified.¹

Dr Barry also claims that no new evidence, apart from Winneke's finding, was presented at the CLEAR symposium. Details of the National Health and Nutrition Examination

Survey data, showing that the introduction of lead-free petrol in the United States was followed by a 37% reduction in the lead level of the American population, have not previously been available in this country.¹ This study relied on proper quality controls and is therefore of greater significance than the European data, mentioned by Barry, which may show a decline in blood lead levels over the past decade. The Frankfurt study^{3,4} has a follow-up period of only two years, and this is insufficient to make a proper assessment of lower petrol lead levels in the German population and is clearly superseded by the National Health and Nutrition Examination Survey data. The shortcomings of this data⁵ have already been identified in some detail.⁶

Dr Barry did not mention the remarkable parallels between Needleman's findings on classroom behaviour and a study of London school children using the same teachers' rating scale.¹ In the item of low overall function the attributable risk due to lead is 69% for Needleman's study and 63% for the London one, an amazing degree of similarity considering the two studies relied on different assessments of lead burden. (An assessment of risk attributable to lead can be calculated by the formula $(I_e - I_o)/I_o$, where I_e and I_o represent the incidence of non-adaptive behaviour of the highest and lowest lead groups respectively). Furthermore, the lead-related behavioural deficits in the London study were largely independent of social class.

In his concluding address to the symposium, Professor Michael Rutter observed that science proceeds by a series of experiments which fail to disprove a thesis. On this basis the last five years of epidemiological data is internally consistent and has incriminated lead as a major cause of neuropsychological damage to children. Although the magnitude of this damage is open to discussion I feel, like Professor Rutter, that we cannot wait any longer for it to be precisely quantified and that lead should not be used in petrol.

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¹ Rutter MA, Russell Jones R, eds. *Proceedings of an international symposium on low level lead exposure and its effects on human beings*. Chichester: John Wiley and Sons (in press).

² Winneke G. *Toxic effects of environmental lead*. London: The Conservation Society, 1979:33-52.

³ Sinn W. *Int Arch Occup Environ Health* 1980;**47**: 93-118.

⁴ Sinn W. *Int Arch Occup Environ Health* 1981;**48**: 1-23.

⁵ Barry PSI. *Lancet* 1981;ii:1264.

⁶ Russell Jones R. *Lancet* 1981;iii:100.

Elderly patients in a general surgical unit: do they block beds?

SIR,—While I found the paper by Dr D G Seymour and Mr R Pringle on elderly patients in a surgical unit (26 June, p 1921) extremely interesting and valuable, I feel I must amplify some of the comments made in reference to earlier work published by myself and my colleague, G H Davies.¹ It is not strictly true to say that our definition of “bed blockers” was those elderly patients no longer in need of inpatient medical or nursing care. In fact, the definition used in our own paper was much broader than this and included those elderly patients occupying a bed in an acute ward, who were “no longer in need of the type of medical and nursing care provided in that environment.” In other words, we included patients

who required care in a long-stay hospital bed in either a geriatric or psychogeriatric unit. In fact, almost half of the patients classified as “bed blockers” fell into that category, bearing in mind the type of local authority hostels at present available. Accordingly, although we did indeed conclude that increased residential and community services outside hospital would reduce bed blocking, an increase in the number of available long-stay beds would also appear to be required.

There does therefore seem to be some difference in classification between Seymour and Pringle compared with Davies and myself. Thus, since they appear to regard all patients who require some form of medical or nursing care to be appropriately placed even in a general surgical unit, our much more rigid interpretation or definition would obviously produce a higher percentage of patients who could be classified as “bed blockers.”

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¹ Rubin SG, Davies GH. *Age, Ageing* 1975;**4**:142-7.

Side effects of benoxaprofen

SIR,—In recent weeks extensive publicity has been given to the side effects of benoxaprofen. The majority of these have been dermatological^{1,2} (8 May, pp 1365 and 1368), although several fatal cases of cholestatic jaundice and renal failure have been recorded³ (8 May, p 1372). We report a case of toxic epidermal necrolysis which caused the death of a 72-year-old woman.

A few days after starting benoxaprofen 600 mg daily for osteoarthritis the patient developed an itchy erythematous maculopapular rash on both feet. She continued the medication, and the rash remained unchanged for six weeks. Two days before admission the rash rapidly spread to cover the entire body surface and began to peel. She had no previous history of any skin disorders, her only notable previous illnesses being chorea as a child, chronic bronchitis, and pneumonia. She had, however, had some facial swelling following sulphonamides. Examination on admission showed a maculopapular erythematous rash covering the entire body with at least 20% skin loss on back, arms, thighs, and feet. She also had a purulent conjunctivitis and swelling of the neck and face. Initial haemoglobin was 12.9 g/dl; white cell count $7.7 \times 10^{12}/l$ (normal differential count); plasma urea 9.5 mmol/l (57 mg/100 ml); electrolytes and liver function tests normal. A chest radiograph was normal. A diagnosis of toxic epidermal necrolysis was made, and treatment started with oral prednisolone 60 mg daily, amoxycillin, flucloxacillin, and intravenous plasma protein fraction. She was transferred to the plastic surgery unit for nursing on a ripple bed. Skin loss continued until over half of body surface area was lost, and she developed onycholysis. She developed a pneumococcal chest infection and septicaemia with coliform bacteria. Despite transfusion of three units of whole blood and 13 units of hyperimmune plasma protein fraction she became oliguric and developed extensive bronchopneumonia. Her condition deteriorated and she died nine days after admission.

Because of the unusual nature of the rash, absence of other possible precipitating causes (her only other medication was frusemide, which she had been taking for many years), and its association with the onycholysis characteristic of reactions to the drug, we believe that this patient's epidermal necrolysis was the result of benoxaprofen toxicity. Although the commonest side effects of benoxaprofen are photosensitivity rashes and

onycholysis, Stevens-Johnson syndrome and erythema multiforme have been reported (8 May, p 1368). Toxic epidermal necrolysis can be regarded as a severe variant of erythema multiforme and is associated with a high mortality rate. As far as we are aware this is the first reported case of fatal toxic epidermal necrolysis associated with benoxaprofen.

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Side effects of non-steroidal anti-inflammatory drugs

SIR,—In view of recent extensive reports on jaundice believed secondary to benoxaprofen we wish to report a case of probable flurbiprofen-induced cholestatic jaundice in a patient with mixed connective tissue disease. Seven cases of abnormal liver function tests believed due to, or associated with, use of flurbiprofen have been reported to the manufacturers.

A 36-year-old woman with a 17-year history of presumed rheumatoid disease presented with a new complaint of Raynaud's phenomenon. Subsequent tests revealed a positive antinuclear factor titre of 1/1280 with a speckled pattern, consistently negative DNA-binding, and a positive ribonuclear protein extractable nuclear antigen titre at 1/60. In view of the noted previous efficacy of flurbiprofen, as previously prescribed by her general practitioner, she was restarted on this drug at a dose of 100 mg twice daily in December 1981. This was continued until early March 1982, when she was admitted to hospital with a six-day history of epigastric tenderness, sore throat, facial rash, intermittent pyrexia, and also dark urine and clinical jaundice with increasing anorexia for four days before admission. Examination revealed an apyrexial jaundiced patient with a butterfly macular rash over the malar area, a petechial rash on the soft palate, and epigastric tenderness but no enlargement of liver or spleen. Blood tests on admission were: haemoglobin 14.4 g/dl; white cell count $4 \times 10^9/l$ g/dl with a normal film and differential count, reticulocytes 2.2%; and erythrocyte sedimentation rate 20 mm in the first hour. Other results were: alkaline phosphatase 150 IU (our normal range 30-115 IU); bilirubin 21.4 $\mu\text{mol/l}$ (1.3 mg/100 ml) (normal range below 17 $\mu\text{mol/l}$) (1 mg/100 ml); aspartate transaminase greater than 1200 (normal range 5-41) IU; total protein 68 g/l; albumin 40 g/l; urea, and electrolytes normal.

Flurbiprofen was discontinued, and subsequent investigations included a normal ultrasound scan of liver and gall bladder, negative tests for hepatitis antigens, and a normal coagulation screen. Liver biopsy performed one week after admission demonstrated a moderate infiltration of the portal tracts by lymphocytes, together with some polymorphs and eosinophils. Within the parenchyma some cells showed degenerative changes, and acidophilic bodies were present. There was also some increase of bile pigment within liver cells, but no bile plugging or ballooning cellular degeneration was noted. The absence of the latter feature, together with the presence of eosinophils suggested a drug-induced, rather than a viral, hepatitis.

Conservative treatment was continued with a fairly rapid resolution of jaundice over the next two or three weeks. Seven weeks later the liver function tests were within normal limits; alkaline phosphatase 76 IU; bilirubin 13.6 $\mu\text{mol/l}$ (0.8 mg/100 ml); aspartate transaminase 31 IU; and albumin 45 g/l.

The only other known patient in whom a liver biopsy was similarly performed had received flurbiprofen for one continuous period of six weeks in a similar dosage (Boots Company reference file), but one other case of

reported cholestatic jaundice was noted to redevelop jaundice on a subsequent occasion after only one trial of a 50-mg tablet. We therefore suggest flurbiprofen to be a potential cause of drug-induced hepatitis, and we re-emphasise that jaundice, while not necessarily occurring on initial challenge, may develop after a preceding or sensitising drug stimulus.

We wish to thank Dr K Jarvis, consultant in pathology at the North Middlesex Hospital, for kindly providing the pathology report.

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Severe bleeding disorders in children with normal coagulation screening tests

SIR,—The two case reports from Dr G P Taylor (19 June, p 1851) are salutary in reminding readers of the prime importance of the clinical history in the screening of bleeding and coagulation disorders. Furthermore, they re-emphasise the need for further investigation of patients with a positive clinical history even if initial laboratory screening appears unhelpful.

Where the report is radically wrong is in quoting old data that a normal partial thromboplastin time may be found with a 10% factor VIII level.¹ This in no way reflects the current practice in UK hospitals. A survey conducted from the National (UK) Reference Laboratory for Anticoagulant Reagents and Control in 1975, which included 320 hospitals, revealed that when challenged with a test sample with a comparable abnormality—that is, 11% factor VIII—94% of all hospitals in the exercise detected the abnormality with their own partial thromboplastin time reagent, and 99% of the same hospitals with the UK Reference Laboratory activated partial thromboplastin time method.² More recent studies performed on behalf of the UK External Quality Assessment Scheme in Blood Coagulation Testing have indicated considerable success in the detection of comparatively minor degrees of factor VIII: C defect by the activated partial thromboplastin time method. Thus, in the last two studies, the detection rate was 92.3% and 90.1% respectively with haemophilic plasma samples of 0.20 IU (20% factor VIII) and 0.24 IU (24% factor VIII). The small proportion of failures in the detection of mild haemophilia by the activated partial thromboplastin time method largely arise from the use of certain commercial reagents. This is indicated in the abbreviated table of data from 331 UK hospitals taken from the May 1982 External Quality Assessment Scheme report.

Success rate with various reagents in detecting a factor VIII concentration of 20%

Reagent	Abnormality detection rate
UK Reference laboratory	98.6
Boehringer	92.0
Thromboplastin Activated	70.0
Diagen (Bell and Alton)	90.0
Diagen (kaolin-platelet substitute)	93.1
Overall (all reagents)	92.3

The screening of severe haemophilia by the activated partial thromboplastin time method in UK hospitals is therefore much more dependable than Dr Taylor suggests, and with an appropriate activated partial thromboplastin

time technique is of considerable reliability even in mild haemophilia.

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¹ Biggs R. In: Biggs R, ed. *The treatment of haemophilia A and B and von Willebrand's disease*. Oxford: Blackwell, 1978.

² Poller L, Thomson JM, Palmer MK. *Lancet* 1976;iii: 842.

SIR,—We welcome the paper by Dr G P Taylor (19 June, p 1851) highlighting the difficulties in the diagnosis of bleeding disorders in children. In these cases it is our practice to assess them in a standard way by retaking the history ourselves. We never rely on a single set of tests—normal or abnormal; if the repeated tests are inconsistent, we then test a third or even a fourth time.

Over the last three years we have had 86 referrals of patients in whom bleeding disorders were suspected. In 44 cases the results were normal. Of the 42 cases with abnormal results, in eight cases (19%) the results were not the same on both visits. In four the initial sampling was normal with the second being abnormal, and in four the reverse occurred. In five patients a third sample was needed, and in three a fourth sample before a diagnosis could be made.

While the procedure we outline is not strictly logical in that it is difficult to be certain at what stage of repetition we have reached a satisfactory diagnosis we feel that it gives a greater likelihood of reaching a correct conclusion. Unfortunately it is not possible to test the correctness of our diagnosis except by prolonged follow up of the patients—perhaps even into a second generation. It seems therefore in haemostatic problems that the price of diagnosis is repeated testing.

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*.*This correspondence is now closed.—Ed, BMJ.

Zinc deficiency due to alcoholic cirrhosis mimicking acrodermatitis enteropathica

SIR,—We were interested to read the report by Drs A Ilchysyn and S Mendelsohn (5 June, p 1676) describing possible zinc deficiency due to alcoholic cirrhosis mimicking acrodermatitis enteropathica. While we agree with their statement "a single measurement of plasma or serum zinc concentration is not a good indicator of total body stores," we disagree with their implied support for the view that the best indicator of zinc deficiency is the response to treatment.

Work from our laboratory in patients with chronic liver disease,¹ pregnancy,² and Crohn's disease has confirmed the inadequacy of plasma zinc measurement, and shown that the zinc content of the peripheral blood leucocyte population is a good measure of tissue zinc status. This is supported by Prasad and Cossack.³ Although Ilchysyn and Mendelsohn correctly state that decreased hepatic zinc has been shown in patients with chronic liver disease we have shown that this measurement does not reflect extrahepatic zinc status either in health or disease.¹