a similar process is involved in the development of NE.

Lawrence and Walker suggested that EN was initiated by the B toxin of *Clostridium welchii* type C in the intestinal lumen and noted that it almost always followed a meal including meat. Normally the toxin is extremely susceptible to proteolysis, but in the presence of low protein levels resulting from a low-protein diet and the presence of heat-stable trypsin inhibitors the toxin is undestroyed.

Your leading article states that NE occurs only in a bowel that has been colonised by bacteria, that it is less common if the food is human rather than cows' milk, and that it is commoner in preterm babies. Preterm babies have lower levels of digestive enzymes and of immunoglobulin than full-term babies. Cows' milk provides a larger protein substrate than human milk,² does not provide the immunoglobulins of human milk, and may be contaminated with bacteria. Considering these factors it is possible that NE of small babies is caused by a toxin liberated by gas-forming organisms entering the lumen in contaminated milk which is undestroyed because of a deficiency of proteolytic enzymes.

Further investigation may demonstrate an abnormally low level of proteolytic activity in the stools of affected babies. If the hypothesis proves correct active immunisation with a toxoid prepared from the toxin and given to susceptible babies may prevent NE.

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¹ Lawrence, G, and Walker, P D, *Lancet*, 1976, **1**, 125.
² Hutchison, J H, in *Practical Paediatric Problems*, 4th edn. London, Lloyd Luke, 1975.

Management of severe acute asthma

SIR,—I have read with interest your leading article (8 April, p 873) on the management of severe acute asthma and would like to record our experience of death in bronchial asthma. We have had no deaths in hospital during the past ten years.

The patients receive 200 mg hydrocortisone four hourly intravenously together with intravenous salbutamol 5 or 10 µg per minute or aminophylline 1 g per 24 hours. Oxygen and antibiotics are given if required. We do lose one or two patients per year from our asthma population through death at home. The patients are mostly young, between the ages of 15 and 40, and the clinical story is almost invariably the same: overwhelming asthma develops within a very short period of time, usually within one to two hours, often less, and the patient dies before medical help, including the family practitioner, arrives. As far as one can gather the patient seems unaware of the severity of the condition until he or she is beyond reach of help.

Our latest patient who died, some weeks ago, was a woman aged 31, who had had relatively mild asthma for many years, did not require continuous steroid therapy, and relied only on an occasional inhalation of salbutamol from a pressurised inhaler. On the morning of death she woke a little breathless. Within half an hour she was found accidentally on the kitchen floor by a neighbour, and she died before the family practitioner could be called. We have tried for many years to predict this

sort of occurrence and have been totally unable to do so.

If death in bronchial asthma, particularly in children, adolescents, and young adults, is to be reduced multicentre trials of therapy would seem to be needed and large numbers of asthmatic patients studied.

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SIR,—In your leading article on the management of severe acute asthma (8 April, p 873) you very rightly discuss tracheal intubation and mechanical ventilation. However, I am surprised that you do not also advocate bronchoscopy and either pulmonary lavage or, using the flexible fiberoptic bronchoscope, "syringing" of the bronchi in order to remove inspissated plugs of mucus. The effect of this procedure on desperately ill patients is most gratifying, with an immediate improvement in ventilation and a return of the blood gases towards normal. I would say that any unit responsible for treating severe acute asthma should have the facility to perform either pulmonary lavage or bronchial syringing, via the appropriate bronchoscope.

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Stricture of oesophagus associated with ankylosing spondylitis

SIR,—Readers of the paper by Mr V John and others (25 February, p 479) concerning a patient with rheumatoid stricture of the oesophagus may be interested in the following case history.

A 58-year-old housewife presented with progressive dysphagia of one month's duration. Fiberoptic oesophagoscopy revealed a 4-cm irregular stricture beginning at 22 cm from the incisor teeth. Repeated cytological and histological studies indicated a benign cause, the consistent feature being that of a submucosal chronic inflammatory process. The patient did not have a hiatus hernia, nor was gastro-oesophageal reflux demonstrable. The possibility of a columnar-epithelium-lined oesophagus was excluded, as was local extrinsic disease, by means of chest x-ray and bronchoscopy.

This patient has suffered from ankylosing spondylitis for more than 30 years and thus, in the absence of any of the recognised causes of benign oesophageal stricture, one is led to conclude that her stricture is a rare manifestation of the joint disease. There do not appear to have been any other reports of an association of this kind. The only gut-linked association with ankylosing spondylitis is, of course, ulcerative colitis, a condition not present in this patient.

Management of the stricture entailed repeated dilatation with Eder-Puestow dilators. Limited dilatation, however, required an unusual degree of force and the benefits of each dilatation were transient—within three or four days the patient could swallow only liquids. Oesophageal resection was contemplated, but the presence of severe dorsal kyphosis made surgery of this magnitude impracticable. Thus the next step merely involved forcible dilatation under general

anaesthesia to 45 Charrière. Two months have since elapsed without the need for further dilatation. The patient is able to swallow normally and recent endoscopic assessment of the previously strictured zone has demonstrated an intact mucosal lining.

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Fluorouracil cardiotoxicity

SIR,—The paper by Dr A Pottage and others (4 March, p 547) lends some support to our suspicion that 5-fluorouracil (5-FU) cardiotoxicity occurs more commonly than is believed. The authors proposed to look for ECG changes in patients asymptomatic after 5-FU. It would also be interesting to monitor cardiac enzymes.

In an earlier article,¹ among the several mechanisms we suggested to account for 5-FU cardiotoxicity was the involvement of a vasoactive component in the reaction. Therefore if there were a vasoconstrictive phase and/or direct damage or inflammation involving blood vessels (promoting thrombus formation) one could predict that the added insult of radiotherapy to the heart, also inducing small vessel thrombosis, might increase the incidence of 5-FU toxicity. It is well known that the combination of doxorubicin and myocardial irradiation probably exerts a cumulative cardiotoxic effect.^{2,3} However, the mechanisms involved may be different. These facts may explain the relatively high incidence of cardiotoxicity observed by Dr Pottage and his colleagues in their series.

We would not lightly dismiss the likelihood of other mechanisms causing 5-FU cardiotoxicity. We still cannot fully account for the possible protective effect of corticosteroids which we reported¹ and which, unfortunately, was not assessed by Dr Pottage and his colleagues.

We would like to suggest that there may be a cumulative cardiotoxic effect when 5-FU is used with other cytotoxics and/or irradiation of the myocardium as in treatment with doxorubicin + 5-FU + radiotherapy.

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¹ Lang-Stevenson, D, Mikhailidis, D P, and Gillett, D S, *Lancet*, 1977, **2**, 406.

² Prout, M N, et al, *Cancer*, 1977, **39**, 62.

³ Gilladoga, A C, et al, *Cancer*, 1976, **37**, 1070.

Continued effects of black light treatment of psoriasis

SIR,—Both psoralen DNA-monoadducts and DNA-interstrand crosslinks produced by light (320-380 nm) contribute to the lethal and chromosomal effects associated with the photochemotherapy of psoriasis.¹⁻⁵ There is good biological evidence that psoralen DNA-monoadducts in bacterial and mammalian cells can be converted to the more lethal DNA cross-links, in the absence of psoralen not already covalently bound to DNA as

pyrimidine monoadducts, by subsequent light irradiation.^{1,3}

The conversion of psoralen DNA-monoadducts to DNA-crosslinks is not without potential problems. For some as yet unknown period of time photosensitised skin may continue to be further damaged by exposure to either direct or indirect sunlight as the conversion of monoadducts to crosslinks occur. Physicians would be well advised to realise that the cessation of black light irradiation is not the end of the treatment unless the lesions are kept in the dark, perhaps for several weeks.

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¹ Ashwood-Smith, M J, and Grant, E, *Experientia*, 1977, **33**, 384.

² Ashwood-Smith, M J, *et al*, *Mutation Research*, 1977, **43**, 377.

³ Ben-Hur, E, and Elkind, M M, *Mutation Research*, 1973, **18**, 315.

⁴ Cole, R S, *Biochimica et Biophysica Acta*, 1971, **254**, 30.

⁵ Scott, B R, Pathak, M A, and Mohn, G R, *Mutation Research*, 1976, **39**, 29.

Remission of psoriasis during haemodialysis

SIR,—We read with interest the short report by Drs H L Muston and S Conceicao (25 February, p 480). We too have had experience with clearing of psoriasis during haemodialysis¹; however, the reports of fairly severe recurrence in case 2 and only incomplete clearance in case 1 are of special interest. This information corroborates the findings of both McEvoy and Anderson (personal communication).

Also of interest are the type of dialyser, heparinisation technique, and, in general, the methodology of haemodialysis used. Specific information of this type may help determine the most efficient mode of application of haemodialysis. We used the Lundia Optima 17- μ m disposable dialyser and patients were dialysed three times each week for six-hour periods. Heparinisation was accomplished through constant regional infusion in uraemics without an initial loading dose.² Initial loading heparinisation in non-uraemics was 100 U/kg just before dialysis.

Twardowski *et al* have reported successful treatment of psoriatics with peritoneal dialysis.³ They postulate removal of some noxious substance which may be filtered by the normal kidney but not excreted owing to tubular reabsorption. We intend to explore similar and alternative hypotheses. They include the possibility that psoriatic clearing after dialysis may be induced by one or a number of the following: (1) removal of pathological or physiological substances; (2) a sponge-sink effect binding effector substances; (3) removal of an inhibitor to epidermal chalone; (4) stimulation of a change in intracellular cyclic nucleotides or their prostaglandin modulators; (5) immunological activation, inactivation of substances, or alteration of feedback systems; (6) depletion or alteration of essential amino- or fatty acids; (7) stress-induced hormone production; (8) the production of an "unphysiological state" (for example, variations in osmolality, trace metals, or pH).

Immunological mechanisms are attractive. It has already been established that chemotaxis is decreased in uraemic patients and is further decreased during chronic haemodialysis.⁴ The procedure appears to activate complement and thus affect neutrophils irreversibly so that these neutrophils are less responsive to further chemotactic stimuli.⁵ White cell aggregation in the lungs and both thrombocytopenia and leucocytopenia have been documented during dialysis.⁶ Furthermore, one would expect trace-metal alterations depending on water delivery systems, and the general "unphysiology" of the dialysis technique has been documented as well.⁷ Documentation of prostaglandin and cyclic nucleotide alterations await further analysis, as do membrane accumulation, infusion or effusion of diffusible substances, and other immunological effects.

Elucidation of the possible changes induced by dialysis relative to these hypotheses may help in determination of the pathogenesis of the disease as well as the specific aspect of dialysis therapy which is effective in psoriasis.

We would be interested in the dialysis techniques used and any observations the authors or other readers might have regarding these or other relevant hypotheses.

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¹ Buselmeier, T J, *et al*, *Journal of the American Medical Association*, in press.

² Kjellstrand, C M, and Buselmeier, T J, *Surgery*, 1972, **72**, 630.

³ Twardowski, Z J, *et al*, *Annals of Internal Medicine*, 1978, **88**, 349.

⁴ Greene, W H, *et al*, *Journal of Laboratory and Clinical Medicine*, 1976, **22**, 981.

⁵ Jacob, H S, *Archives of Internal Medicine*, 1978, **138**, 461.

⁶ Craddock, P R, *et al*, *Journal of Clinical Investigation*, 1977, **60**, 260.

⁷ Kjellstrand, C M, *et al*, *Kidney International*, 1975, **7**, suppl 2, p 30.

Intended place of delivery and perinatal outcome

SIR,—In a field where statistics are notably lacking, Jean Fedrick and Professor N R Butler's contribution (25 March, p 763) is to be welcomed, but it must be seriously doubted that their evidence justifies their uncompromising conclusion. May I give four of the reasons why?

(1) The highly significant difference in perinatal mortality rates in favour of NHS consultant hospitals depends entirely on attributing to the original place of booking the relatively great number of deaths associated with maternal transfers. The attribution of such deaths poses a very difficult methodological problem. All possible solutions are open to objection, but the one adopted here would be logical only if it were known for certain that the risk attaching to delivery in hospital was not greater than in other places, which is precisely the issue which is in question. The proof that a proposition is true cannot depend on the prior assumption that it is true.

(2) In the three low-risk groups identified consultant hospitals are shown to have consistently the lowest mortality rates for booked cases; the χ^2 significance test permits the conclusion at a very high level of confidence ($P < 0.001$) that the differences in rates between the four listed places are real, though by itself it can prove no more than that. These are useful findings. It is, however, pertinent that while the level of significance is as high as this for the aggregate of the three groups and for group A considered separately, it falls to about $P < 0.05$ for group B and far below $P < 0.05$ for group C. In other words, for this group which

is at lowest risk of all and makes up nearly half of the cases studied there is no significant difference in death rates between the different places of booking. It is pertinent also that the very high level of significance is the result of including "private wards and nursing homes" and residual places. Without these the level of significance falls to about $P < 0.02$ and, if only hospital and home are compared, to far below $P < 0.05$. In other words, for the aggregate of groups A, B, and C there is no significant difference in death rates between hospital and home bookings (χ^2 calculated approximately from data in the article).

(3) Various factors conducive to increased risk are measured in table III of the article, while table IV shows their distribution by place of booking for group A (which, as indicated above, may not be completely representative). It is, of course, obvious that the factors are not additive but overlap considerably—for example, mothers of light weight tend to be of low stature also. The death rate associated with mothers born light and short is likely to be little higher than if they had only one of these characteristics. The home-booked cases were not free of high-risk factors, but the hospital-booked cases had more, yet had the lower death rates nevertheless. In itself this is evidence to be respected, but can the evidence of this one group legitimately be taken as applying to all groups? I have drawn attention elsewhere¹⁻³ to the arithmetic principle that an average death rate is determined by the sum of the products of the proportion of cases in each subgroup multiplied by the death rate in that group. Further analysis of data is required to establish that hospitals have a proportion of cases at high predelivery risk sufficiently greater than at other places of delivery to account for the great excess of their overall death rate—the issue in question.

(4) As the authors accept, conclusions based on 1958 data have limited relevance in 1978. To meet this weakness they quote from the Registrar General's annual analyses of stillbirths and point to the rising trend in the home stillbirth rate since 1970. Those readers who were not thoroughly misled by the deceptive scales used in the graph will have noticed that, even so, the home rate remained far below the overall rate: the original statistics show that in 1973 it was, in fact, still less than half the rate in consultant hospitals.

The rising stillbirth rate at home does indeed appear an extraordinary deviation from the general downward trend. If domiciliary deliveries are becoming less safe than they used to be for mothers of the same predelivery risk this is a serious indictment of official policy in dismantling the once very efficient domiciliary maternity service. More likely, the mothers are not of the same predelivery risk: those of them at lowest risk, from choice or lack of choice rather than medical need, are increasingly being delivered in hospital, and it is this dilution with low-risk cases which is the main contributor to the decline in the hospital stillbirth rate.

This is clearly illustrated by the experience of the group at minimal risk—mothers aged 20-29 having their second or third legitimate baby. In 1969⁴ 66% of this group gave birth in consultant hospitals; their stillbirth rate was 11.7 per 1000 births, while the rate for the remaining 34% in all other places combined was 4.2. By 1975⁵ 83% gave birth in hospital; their stillbirth rate had fallen to 8.8 per 1000, while for the 17% remaining outside the rate fell to 3.4. If the 17% who moved over to hospital had the average experience of this group in hospital, then their stillbirth rate per 1000 births rose from 4.2 (1969) to 8.8 (1975)—a worrying deterioration. If, on the other hand, they fared no worse than the 17% remaining outside, their stillbirth rate in 1975 would have been 3.4 per 1000; but in that case, since the overall average in hospital was 8.8 the other mothers in the group must have