death, both the defenders and the critics have, in fact, failed to allay the fears of the vast majority of people in the country on this matter of great importance. In the debate cases were mentioned both by Professor J Hughes and Dr R Paul in which patients declared dead by the British criteria had "life" left in them and were claimed to have recovered later. Similarly, a renal transplant surgeon has admitted that on a very few occasions he had been asked to go to see a potential cadaver kidney donor only to find that these criteria had not been met.¹

This clearly shows that the practice followed at present is not entirely satisfactory and at least the two following changes should be made soon: (1) One of the two doctors certifying such cases for organ transplantation should be a consultant neurologist and the other doctor should have qualified at least five years. (2) The tests for clinical signs of brain-stem death should be compulsorily repeated at least twice at an interval of 12 hours each. These simple additional changes should prove to be of great value in assuring the next of kin that the patient has been given every chance and has been thoroughly examined by doctors including a "nerve specialist."

The introduction of electroencephalography cannot be justified as it is too cumbersome and inconclusive and both teams in the debate seemed to agree that a "flat" EEG could not completely rule out cortical activity and that the deeper cells of the cortex could still be "alive" in many cases with a flat EEG. In fact it may complicate matters and may even be positively misleading.²

Until a long-term follow up study to analyse the survival rate of "brain-dead" patients is carried out in this country, the above two additional conditions for certifying brain death should be practical and inexpensive—and would not call for invasive tests—and should satisfy the majority of critics.

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¹ Sells R. *Br Med J* 1980; **281**:1212.

² Pallis C. *Br Med J* 1980; **281**:1140.

Epidemic of fractures during period of ice and snow

SIR,—The publication of the paper by Dr Z A Ráliš on an epidemic of fractures during a period of ice and snow (21 February, p 603) coincided fortuitously with a brief spell of ice and snow in the West Midlands. I have long wanted to have accurate information to be able to present to the local councils to convince them that it is a false economy nationally to neglect the pavements during an icy spell. The health authority may carry the bill initially but the taxpayer pays the bill in the long run.

The proposal for owners or occupiers of a building to be made responsible for cleaning slippery pavements is an admirable one but fraught with many dangers. It would have to be made quite clear that the occupier was not held responsible if, after clearing, a thin film of ice turned the pavement into a skating rink. Arrangements would have to be made by local communities to clear the pavements of the many people like the elderly and handicapped who could not do it themselves. Is it too idealistic to ask, for example, that

the large body of able-bodied men sadly flooding our employment exchanges be asked to turn out to carry out this important task?

In passing, it occurs to me that a similar study might profitably be carried out in accident and emergency departments relating road traffic accident cases to periods of ice and snow. This would be particularly relevant during the periods of non-gritting of the roads that we now experience from time to time. As a preliminary contribution to such a study we saw in Warwick Hospital a total of 27 road traffic casualties (10 requiring admission) during two days of "black ice" with no gritting on 10 and 17 December 1980. This was well in excess of our daily average of around four road traffic casualties and one admission per day.

Perhaps if local authorities were directly billed for all the road and pavement casualties resulting from periods of ice and snow there would be a greater stimulus to them to take the necessary action.

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How dangerous are falls in old people at home?

SIR,—In his letter on the subject of falls in residential homes for the elderly Dr J M Morfitt (21 February, p 649) compared the mortality of residents with English life tables. In doing this he did not compare similar things, for—as recent correspondence has shown—residents in homes for the elderly are extremely frail. Their life expectancy is, therefore, different from that of the general population.

The number of vacancies arising in the seven residential homes for the elderly in the London Borough of Merton can be predicted each year by dividing the total number of places by a factor of three. This means that the average life expectancy of all residents is three years. This would seem to indicate the fact that falling is not an indication of impending dissolution but more an indication of the frailty of the residents.

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Congenital rubella affecting an infant whose mother had rubella antibodies before conception

SIR,—Dr J W Partridge and others (17 January, p 187) report the occurrence of "congenital rubella affecting an infant whose mother had rubella antibodies before conception." The evidence that the mother had rubella antibody prior to conception is convincing. Detection of high levels of haemagglutination inhibition (HI) and complement-fixing (CF) antibodies in three serial samples of serum obtained before conception indicates immunity to rubella.

On the other hand, the evidence that her infant had congenital rubella is less convincing. The clinical manifestations are compatible with a diagnosis of so-called TORCH syndrome. In addition to rubella virus, the infection could have been caused by cytomegalovirus, herpes simplex virus, and *Toxoplasma gondii*. Therefore it would be important to

rule out these potential agents by performing appropriate virus isolation and serological tests.

The authors' laboratory confirmation of congenital rubella is not convincing because: (1) rubella-specific IgM antibody was not detectable; (2) the HI titre of 400 units at 3½ months of age, declining to 50 units at age 6 months, could represent waning passively acquired antibody of maternal origin; and (3) evidence of persistence of rubella antibody beyond 6 months of age is not presented. The report of a single isolate of rubella virus from the baby's nose and throat at 4 months of age would be more impressive if it were supported by serological confirmation of congenital rubella infection. It is unfortunate that follow-up serum specimens were not obtained from mother and baby.

In the absence of more definitive data I believe that the most appropriate title for this paper should be "Possible congenital rubella affecting an infant whose mother had rubella antibodies before conception."

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Factors contributing to mortality in paracetamol-induced hepatic failure

SIR,—We fully agree with Dr J Canalese and his colleagues (17 January, p 199) that emergency plasma paracetamol assays have little relevance to the management of adult patients who present with a clear history of paracetamol overdose within the previous 12 hours. Therapy with an appropriate antidote should be instituted without delay and the only benefit of a plasma paracetamol measurement may lie in curtailing the infusion of *N*-acetylcysteine into a patient not at risk. In cases where paracetamol poisoning is a possibility, such as in the two patients cited by Dr Canalese and others who denied drug overdosage, or in unconscious patients where a preparation containing paracetamol may have been taken, an emergency test is of value. In fact, it could be argued that a test for this drug should be carried out in all patients presenting with coma of unknown aetiology.

The simple test kit¹ is adequate for this purpose since the test may be performed in the accident and emergency department or the side ward by medical staff given adequate training by laboratory personnel. We are aware that the accuracy of the test kit can be criticised² and that in particular it may give false-positive results. However, this gives no cause for concern since this can only lead to the administration of an antidote which, although unnecessary, carries no serious risk. In the five years during which the kit has been in routine operation in our own hospital and elsewhere, we know of no incident where it has failed to detect serious paracetamol poisoning in patients admitted within 12 hours of ingestion.

Emergency plasma paracetamol assays are important when the patient is admitted (or paracetamol poisoning is diagnosed) at a time when antidotes are unlikely to be effective. There is some evidence that charcoal haemoperfusion may be beneficial in the presence of high plasma paracetamol concentrations.³ In these cases accurate analytical data should be

provided rapidly and in this context it is important to consider the limitations of the laboratory methods available. The test kit is based on the widely used colorimetric assay of Glyn and Kendal,⁴ which has a limit of accurate measurement of 50 mg/l. Both methods are susceptible to interference from salicylates⁵ and cresol BP, which is used as a preservative in certain heparin preparations.⁶ Ultraviolet spectrophotometric methods are also prone to interference from other drugs.⁷ We believe, therefore, that when active management of late paracetamol cases is contemplated selective chromatographic techniques (Buchanan *et al*;⁸ A Huggett *et al*, to be published) are obligatory at the present time, although the recently reported enzyme-based assay⁹ might well prove an acceptable substitute.

These considerations of selectivity and sensitivity are also relevant when patients present, or paracetamol poisoning is suspected, many hours after ingestion of the drug. Here the diagnosis may rest on the accurate measurement of a small residual plasma paracetamol concentration. In such cases it is advisable not only to ensure that an appropriate assay is applied, but also that qualitative confirmation of paracetamol ingestion is obtained by use of the highly sensitive urine spot test.¹⁰

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¹ Kendal SE, Lloyd-Jones G, Smith CF. *J Int Med Res* 1976;4, suppl. 4:83-8.

² Stewart MJ, Barclay JE. *Lancet* 1976;ii:362-3.

³ Helliwell M, Prior J, Volans GN. *Br Med J* 1981; 282:473.

⁴ Glyn JP, Kendal SE. *Lancet* 1975;ii:1147-8.

⁵ Mace PFK, Walker G. *Lancet* 1976;ii:1362.

⁶ Pitts J. *Lancet* 1979;ii:213-4.

⁷ Wiener K. *Ann Clin Biochem* 1978;15:187-96.

⁸ Buchanan T, Adriaenssens P, Stewart MJ. *Clin Chim Acta* 1979;99:161-5.

⁹ Hammond PM, Scowen MD, Price CP. *Lancet* 1981; i:391-2.

¹⁰ Higgins G, Leach H. In: Clarke EGC, ed. *Isolation and identification of drugs*. Vol 2. London: Pharmaceutical Press, 1975:873.

Chlorosis, anaemia, and anorexia nervosa

SIR,—I have enjoyed reading Dr I S L Loudon's interesting and well researched paper on chlorosis, anaemia, and anorexia nervosa (20-27 December, p 1669). However, in describing chlorosis as an organic disease, "an anaemia characteristic of the oppressed working classes in the nineteenth century," and in discussing the aetiology of this affection known in more recent time as "idiopathic hypochromic anaemia,"¹ the author might have mentioned the fact that many cases of "chlorosis" among low-income groups of people were, in fact due, to ancylostomiasis. This hookworm infection was known in the United States as "malarial chlorosis," while in Egypt the diagnosis of "Egyptian chlorosis" was common.

Nearly all clinical features of "chlorosis" quoted by Dr Loudon can be seen in long-standing hookworm infections, including anaemia, breathlessness, digestive disturbances, mental apathy, lassitude, and perversion of taste with pica or craving for eating earth, mortar, cinders, etc. The extraordinary history of ancylostomiasis, including its impact on the building of St Gothard tunnel

and subsequent spread of *Ancylostoma duodenale* to rural and mining areas of several European countries, has been given a masterly description by Scott.²

A less-than-successful attempt at eradication of hookworm from the rural areas of the southern states of the United States was made by the Rockefeller Foundation in 1913.³ Today ancylostomiasis has become relatively rare in advanced countries of Europe and the Americas, but not less than 300 million people in the developing tropical areas of the world are suffering from this affection.

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¹ Price FW. *A textbook of the practice of medicine*. 7th ed. London: Oxford Medical Publications, 1947: 803.

² Scott HH. *A history of tropical medicine*. London: Edward Arnold, 1939:840-54.

³ Hinman EH. *World eradication of infectious diseases*. Springfield, Illinois: Charles Thomas, 1966.

SIR,—Dr I S L Loudon's very interesting article on chlorosis, anaemia, and anorexia nervosa (20-27 December, p 1669) has provoked a fascinating correspondence but little support for his hypothesis that anorexia nervosa and chlorosis are two different names for exactly the same disorder. But an incident in my practice seven years ago led me to adopt the same hypothesis.

At that time our grammar school lower-sixth form girls were a closely knit group with the academic ambition of proceeding on to university in a year's time. One evening one of them said to her mother in alarm, "We were changing after games today when I saw that Alison has got dreadfully thin, and her skin has gone green." This observation was reported privately to me, and when I arranged for Alison to come and see me, she gave a clear history and showed the signs of anorexia nervosa. To my disappointment I could find no green colour in her skin, although it was sallow. Blood tests showed that she was not anaemic. Her anorexia nervosa responded to treatment at home, her menses returned, and she duly went on to her university and profession. Her anorexia nervosa has not recurred.

This incident shows that in some lighting the skin of a patient with anorexia nervosa may look green to an intelligent lay person who has never heard of chlorosis.

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* * * This correspondence is now closed.—ED.
BMJ.

Radiosensitisers

SIR,—I was glad to see the firm defence of your leading article on radiosensitisers (25 October, p 1089) in your reply to the mildly critical letter of Dr I C M Paterson (3 January, p 69). The favourable result of the Cardiff trial of hyperbaric oxygen in the radiotherapy of head and neck cancer does not disqualify the general statement of your editorial that the results of hyperbaric oxygen trials are disappointing; and completion of current trials of misonidazole is hardly required to justify your very modest prediction that this

drug is unlikely to have great clinical efficacy.

Clinical trials of putative new treatments for cancer are expensive in terms of manpower and money and not without risk to patients. Yet they are commonly instituted before an impeccable case has been made for them by relevant preliminary studies using a broad range of valid animal tumour models. Trials of hyperbaric oxygen therapy were begun in about 1953 on the basis of a very narrow range of animal studies; and the several hundred trials of immunotherapy currently in progress derive scarcely any foundation or rationale either from relevant studies of animal cancer¹ or from general clinical experience of the disease.² A preliminary trial of misonidazole done at the Mount Vernon Hospital some years ago resulted in neurotoxic damage in over half of the treated patients, which though always reversible was usually slow to resolve. Even when allowance is made for the more favourable pharmacokinetics of the drug in man than in the mouse, the clinical limitation of dose now imposed by toxicity has seriously dimmed the prospects of clinical value projected from the spectacular results of animal tumour studies which instigated the trials. It may be added that laboratory workers in this field are now intimating that they have already evolved sensitizers of significantly improved therapeutic ratio. The question arises whether it is ethical to continue trials of misonidazole if its potential is now known to have been excelled.

The regret of Dr Paterson is that the enthusiasm of participants in current trials of misonidazole may be abated by modestly discouraging interim prognostications about their success. But it should be realised that this clinical enthusiasm is only got by contagion from the enthusiasm generated by laboratory workers; and they are often over-anxious to encourage clinical application of their projects and so sustain favour with research-funding bodies.

Having myself been asked to defer publication of actual experimental data (or been criticised for publishing data³) on the grounds that it may discourage enthusiasts, I am specially aware that enthusiasm may well be too fragile which seeks protection against free communication—which may include the expression of plausible presentiments. Finally, we should not overlook Gibbon's advice that one of the manifestations of decadence is "enthusiasm masquerading as originality."

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¹ Hewitt HB. *Adv Cancer Res* 1978;27:149.

² Hewitt HB. *Clin Radiol* 1979;30:361.

³ Rapp HJ. *Cancer Res* 1978;38:4285.

SIR,—I have read with interest your leading article on radiosensitisers (25 October, p 1089) and the subsequent correspondence together with editorial comment which appeared in the issue of 3 January (p 69). I would like to make some comment on the statements concerning current views on the efficacy of misonidazole as a radiosensitizer.

None of the major clinical studies testing the value of this drug have yet been concluded. Indeed, in the three multicentre studies conducted by the Medical Research Council involving adult gliomas, head and neck tumours, and carcinoma of the cervix, no results are available. While a large number of