chemotherapy, endocrine therapy, and immunotherapy. Again, support for any of these approaches can be marshalled as a result of clinical observations on patients suffering from advanced breast cancer, together with fundamental laboratory research. Early results from prospective trials of all of these new modalities of treatment look promising, although to date only premenopausal node-positive women have shown convincing evidence of prolongation of survival. There are still many questions to be answered and I cannot believe that any individual yet has all the answers.

I therefore find it a tragic irony that Dr L A Price (22 November, p 1422) and Dr Bridget T Hill (6 December, p 1565), representing a group of medical oncologists who have arrived late on the scene, should wish to impose their new dogma on the profession. They will find that British surgeons and radiotherapists are less naive than in the past and distrust those who claim to have the whole answer. This is perhaps illustrated by the fact that only a small minority of patients in the UK routinely have adjuvant chemotherapy following mastectomy.[1] Surely the ethical dilemma must be faced by Drs Price and Hill, who submit their patients to toxic therapy whose long-term sequelae (for example, the induction of new cancers[2]) are not known and before 10-year results of trials are available. I was generous enough to accept that their approach might in the long term turn out to be fruitful, but it is quite apparent from their letters that they are not sufficiently generous in return to consider that other people's ideas are worth pursuing as well. Incidentally, the new trial that our group has launched was not imposed "from above" but was a response to pressure from the participants themselves, who wish to resolve two areas of uncertainty.[1]

If a clinician knows with the certainty of divine inspiration that his treatment is correct, then I agree that it would be unethical to enter patients into trials; but if, like myself, the clinician honestly does not know the *best* way to treat breast cancer, then the only ethical way out of the impasse is to enter patients into such trials.

Ten years ago I was accused of unethical behaviour because of advocating less than a Halsted radical operation. Now I am accused of being unethical when offering less than the Price/Hill radical chemotherapy. One needs a sense of humour or else these beautiful ironies of life would be missed altogether.

I hope that Francis Bacon (1561-1626) will be allowed the last word on this subject: "If a man will begin with certainties, he shall end in doubts, but if he will be content to begin with doubts, he will end in certainties."

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[1] Baum M, Houghton J. *Lancet* 1980;i:929.
[2] Reimer RR, *et al. N Engl J Med* 1977;**297**:171-81.

Fulminant hepatic failure in childhood

SIR,—Your recent leading article on fulminant hepatic failure in childhood (27 September, p 823) focused on pathophysiological and therapeutic aspects of this perplexing problem. Mention was made that most of the 31 affected children at King's College Hospital in London[1] had acute hepatitis which was HBsAg negative.

Epstein-Barr virus infection in an immunodeficient child can cause acute fulminant hepatic failure in children. Our studies of males with the X-linked lymphoproliferative syndrome have revealed massive hepatic necrosis due to lymphoproliferation induced by the Epstein-Barr virus.[2] Pedigree analysis often reveals maternal male relatives with acquired agammaglobulinaemia or malignant lymphoma related to this virus. Our registries of the X-linked lymphoproliferative syndrome and fatal and chronic Epstein-Barr virus infections contain many cases wherein we have documented massive hepatic necrosis. Our studies,[3] including unpublished findings, show that these individuals often show dysgammaglobulinaemia or elevated IgM or polyclonal hyperimmunoglobulinaemia. Examination of the peripheral blood smear may reveal plasmacytoid lymphocytes. Tests of hepatic function reveal elevated enzyme concentrations and prolonged coagulation times. Thus the patients may succumb to haemorrhage or hepatic encephalopathy. The liver generally shows extensive periportal infiltration by cells showing plasmacytoid differentiation. Hepatic sinusoids may contain atypical or small lymphocytes. Heterophile determination and serological tests for Epstein-Barr virus, especially IgM against viral capsid antigen and early antigen, should be done.

Sir William Osler said, "There are three parts to therapy: diagnosis, Diagnosis, and DIAGNOSIS." Rational approaches to preventing and treating fulminant hepatic failure will come about after the aetiology of fulminant hepatic failure in childhood is clarified.

Our registries and laboratory are interested in evaluating cases of Epstein-Barr virus infection. Clinical history, microscopic slides, blood smears, bone marrow, liver biopsy specimens, and frozen tissues should be sent to me for evaluation for the virus.

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[1] Psarcharopouls HT, Mowat AP, Davies M, Portmann B, Silk DBA, Williams R. *Arch Dis Child* 1980;**55**:252-8.
[2] Purtilo DT. In: Sommers S, Rosen P, eds. *Pathology annual 1980*. New York: Appleton-Century Crofts, 1980:253-99.
[3] Purtilo DT, Paquin LA, DeFlorio D, Virzi F, Sahkuja R. *Sem Hematol* 1979;**16**:309-43.

Chasing the unknown primary

SIR,—Your leading article dealing with adenocarcinoma from an unknown primary site (ACUP) (8 November, p 1232) provides some comfort to pathologists like myself who must occasionally offer a clinical colleague a necropsy report which reads like a litany of excuses for professional incompetence rather than an account of definitive findings. The high incidence of ACUP which you quote should allay an individual's sense of embarrassment in such a situation as well as appeasing the clinician.

It is well known, of course, that normal tissues may be found in aberrant locations—for example, thyroid and melanocyte tissue in lymph nodes, ectopia of parathyroid glands, and heterotopic pancreas in stomach. It seems reasonable to assume that these ectopically sited tissues are under the same normal and pathological influences as their normally located counterparts. If this is so, it would not be surprising that these ectopic tissues would occasionally undergo malignant transformation. This possibility is also suggested in a recent paper describing hyperplastic but benign breast tissue in an axillary lymph node.[1] This intriguing possibility would explain, at least in part, the basis for ACUP.

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[1] Turner DR, Willis RR. *Histopathology* 1980;**4**:631-6.

Radiosensitisers

SIR,—In your leading article on radiosensitisers (25 October, p 1089) you state that there has been no major increase in tumour control rates with the use of hyperbaric oxygen in the treatment of malignant disease, and thus the results have proved disappointing. This is surely surprising in view of the results of the hyperbaric oxygen trial performed in advanced head and neck cancer in Cardiff showing a survival rate at four years of 56% for patients treated in hyperbaric oxygen, significantly greater than the 27% for patients treated in air.[1] Furthermore, there were improvements in recurrence-free rates which were not only of mathematical significance but also of clinical significance as well. Like the radiotherapy fraternity as a whole, you have chosen to ignore these results.

It is a pity that you have stated that misonidazole is unlikely to have great clinical efficacy since none of the randomised controlled trials being performed in this country are anywhere near to being completed. Such statements are likely to reduce the enthusiasm of participants to carry on, especially since the work generated in supporting these trials is quite out of proportion to the relatively small number of patients involved. Neurotoxicity is a considerable problem, and in addition to the studies involving phenytoin and phenobarbitone referenced in your leading article our own studies have shown that phenytoin can significantly reduce the half life and the total tissue exposure of misonidazole; yet phenytoin cannot be used in the context of the current clinical trials and is denied to those patients who are demonstrably at greatest risk of developing neurotoxicity. Consequently it is still not known whether this drug can significantly reduce the major dose-limiting toxicity of misonidazole.

I suggest that there is a danger that studies and trials in this area become pure academic exercises. It remains to be seen whether any new sensitisers will become rapidly available to any radiotherapist with declared interest and expertise in this field—if we are interested only in large differences of clinical significance these can be demonstrated in phase two studies without the necessity of prolonged controlled randomised trials.

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[1] Henk JM, Smith CW. *Lancet* 1977;ii:104-5.

***The overall results from the hyperbaric oxygen studies remain disappointing; the Cardiff head and neck results are an exception. Results similar to these are being claimed for combinations of chemotherapy and radiotherapy (with or without surgery), without the

complication of installing a hyperbaric oxygen facility. Trends in the results from the existing misonidazole studies do not suggest that this particular sensitiser will prove to be of great clinical efficacy. There is no risk that trials will become academic exercises. Radiotherapists and oncologists have an excellent record of willingness to consider and introduce new treatments, many of marginally greater efficacy than those that they replace. Surely it is inappropriate to draw such sweeping conclusions from a single example, particularly when simpler options exist that give similar results.—ED, *BMJ*.

Promoting the use of seat belts

SIR,—The article of the Wessex Positive Health Team on promoting the use of seat belts (29 November, p 1477) makes it crystal clear that voluntary persuasion is inadequate. Experience from Australia makes it equally clear that legislation is effective. It can hardly be thought that such a fiercely independent nation as the Australians is unaware that it is voluntarily restricting its freedom. The community appears to think that in this case the price is worth paying.

The article is timely with a new Bill in the offing in the United Kingdom. A private member's Bill in the Lords is to be introduced by Lord Nugent. Three years ago moves to introduce such legislation, firstly for Northern Ireland and then for the whole of the United Kingdom, came to nothing. It is sad to think of all those unnecessarily bereaved and maimed in the interval. It is to be hoped that all doctors involved in the care of road accidents will support the BMA in its backing for the new legislation. We should raise the issue in our professional associations and in the royal colleges, soliciting their support. And when the legislation is referred from the Lords to the Commons, we should all individually lobby our own MPs. Australian legislation was achieved because doctors alerted the community to the seriousness of the issue before it. We doctors in Britain can achieve the same result if we have the same dedication.

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Vaccination against smallpox

SIR,—With reference to the correspondence about vaccination against smallpox (11 October, p 1004; 25 October, p 1141-2), we would like to report a case of generalised vaccinia in a 15-year-old Asian schoolgirl, who is at present still in hospital. The vaccinia virus has been cultured from the skin lesions. She has not been abroad recently and has not been vaccinated since childhood, but she has suffered from eczema for many years.

Despite extensive inquiries it has not been possible to find a recently vaccinated contact of this girl. The search has included all people in the West Midlands vaccinated in NHS clinics or with NHS-supplied vaccine in the last few weeks. The likely source of this case, therefore, is a person vaccinated either outside the West Midlands or a vaccinated patient of a practitioner obtaining vaccine privately. The conclusion reached is that the girl acquired vaccinia from such an unknown vaccinee or from secondary contact. The present dried vaccine is known to be more potent than the previous glycerolated type and hence possibly more easily transmitted by passing contact. The dangers of unnecessary vaccination should again be stressed.

In view of the worldwide eradication of smallpox no travellers should be vaccinated. It is, however, clear that certain countries—for example, Madagascar—still require a valid certificate for entry despite World Health Organisation information. Should the DHSS now issue an unequivocal statement to the effect that the procedure is no longer necessary and should not be carried out? Waiver letters could be issued to prospective travellers still requiring a valid certificate.

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SIR,—The suggestion that smallpox vaccination be restricted to government centres such as those dealing with immunisations against yellow fever (25 October, p 1142) is both sensible and timely. Of the four countries (Madagascar, Djibouti, Chad, and Democratic Kampuchea) requesting vaccination certificates against smallpox from travellers in May 1980,[1] the only two expected to request such certificates by January 1981 are Chad and Democratic Kampuchea[2]—areas which could hardly be considered routine destinations for British residents.

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[1] Anonymous. *Weekly Epidemiological Record* 1980;55: 159.
[2] Anonymous. *Weekly Epidemiological Record* 1980;55: 378.

Drug prevention of malaria

SIR,—I was very perturbed to read recommendation (3) in the letter to the chairman of the Medical Committee of the London Hospital for Tropical Diseases and others (15 November, p 1347). I wrote to the only signatory who had had recent experience of medicine in the tropics, but he has not replied.

To recommend the use of Maloprim (pyrimethamine and dapsone) is, in my opinion, both useless and dangerous. Pyrimethamine is now useless in south-eastern Asia and resistance to dapsone occurs. In addition, dapsone used prophylactically for malaria is associated with agranulocytosis. This was first reported by Ognibene[1] in American troops and by Stickland and Hurdle[2] in Australian troops in Vietnam, and was subsequently reported by other authors.[3 4] In the forthcoming edition of *Chemotherapy of Malaria*,[5] it is stated that "the incidence of agranulocytosis is in the order of four per 1000 per year in people taking proguanil and dapsone."

I feel that practitioners following the recommendations of Professor A W Woodruff and others should be aware of this danger with Maloprim. Incidently, the recommended dosage of two tablets a week is twice that advocated by the Wellcome Foundation's Group Approved Circular Text of February 1980 and that recommended by Gilles,[6] professor of tropical medicine at the Liverpool School of Tropical Medicine.

I am surprised that Professor Woodruff and his colleagues have forgotten how effective mepacrine is at a daily dosage of 100 mg. It has at this dosage no side effects, unlike Fansidar (pyrimethamine and sulfadoxine), which cannot be recommended for pregnant women and like all sulphonamides can be associated with the Steven-Johnson syndrome. There are no reports of resistance of *Plasmodium falciparum* to mepacrine.

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[1] Ognibene AJ. *Ann Intern Med* 1970;72:521-4.
[2] Strickland JF, Hurdle RD. *Med J Aust* 1970;i:959-60.
[3] Smithurst BA, Robertson I, Naughton MA. *Med J Aust* 1971;i:537.
[4] Black RH. *Med J Aust* 1973;i:1265-70.
[5] Bruce-Chwatt LJ, ed. *Chemotherapy of malaria*. 2nd ed. Geneva: World Health Organisation, (in press).
[6] Gilles H. *Ann Soc Belg Med Trop* 1980;60:129-36.

Treatment of sciatica

SIR,—I refer to Dr Michael Snaith's letter (1 November, p 1217) and to the answer given to the question concerning the treatment of sciatica in "Any Questions" (30 August, p 606).

Dr James Cyriax has studied this problem for 50 years. His approach has been almost exclusively clinical, as he realised that *x*-ray examinations were of little help in the majority of cases. He confirmed his hypotheses by using local anaesthesia diagnostically. The results of this work are contained in his masterly book, *Textbook of Orthopaedic Medicine*.[1]

Sciatica is a symptom not a disease, and treatment depends on the cause. In 90% of cases the cause is a displacement of an intervertebral disc in the lumbar region. Other causes, such as sacroiliitis, metastatic deposits in the lumbar spine, and spondylolisthesis must, of course, be sorted out and treated accordingly.

If sciatica is due to a disc lesion, then treatment depends on what type of disc lesion. A careful history and examination will usually sort these out. One should answer the following questions. Is the lesion hard and cartilaginous, or soft and nuclear? Is the lesion posterocentral or posterolateral? If the latter, is it primary or secondary? Is the protrusion self-reducing or not? Is it reducible with no neurological signs, or irreducible with muscle weakness and cutaneous analgesia? It is only by answering these questions that rational treatment can be planned.

Treatment of sciatica caused by disc lesions falls broadly into three categories. These are: (1) Manipulation for the reducible, cartilaginous displacement; (2) traction for the reducible, nuclear lesion; (3) epidural local anaesthesia (using 50 ml of 0·5% procaine via the sacral hiatus) for the irreducible displacement. The majority will be relieved by these measures, but if not an injection of 2 ml of 2% procaine directly around the affected nerve root or a similar injection of steroid suspension may work. If not it is well to remember that sciatica usually gets well of itself within a year. Laminectomy should be reserved for patients with intractable pain