- All letters must be typed with double spacing and signed by all authors.
- No letter should be more than 400 words.
- For letters on scientific subjects we normally reserve our correspondence columns for those relating to issues discussed recently (within six weeks) in the *BMJ*.
- We do not routinely acknowledge letters. Please send a stamped addressed envelope if you would like an acknowledgment.
- Because we receive many more letters than we can publish we may shorten those we do print, particularly when we receive several on the same subject.

Interleukin 2

SIR,—Professor T J Hamblin argues in his editorial that interleukin 2 has emerged as a treatment capable of inducing complete responses in patients with cancers that were previously thought to be unresponsive to treatment.¹ He cites as examples malignant melanoma and renal cell cancer. The assertion that malignant melanoma is unresponsive to conventional chemotherapy is unfounded and misleading. Data were presented last year on response to treatment according to the International Union against Cancer criteria and survival of patients with surgically incurable metastatic melanoma who were treated between June 1977 and June 1989 at Westminster Hospital with four consecutive chemotherapy protocols that were developed in this unit (S Retsas, second international conference on melanoma, Venice, 1989). The table summarises the updated information on 350 patients in this study.

Response of patients with metastatic melanoma to four consecutive chemotherapy protocols

Regimen	No of patients	No (%) with complete response	No (%) with partial response	% True response rate
Vindesine	65	3 (5)	10 (15)	20
Vindesine plus dacarbazine	75	7 (9)	8 (11)	20
(B)DPV3*	100	7 (7)	22 (22)	29
DJV3†	110	6 (5)	17 (16)	21
Total	350	23 (6)	57 (16)	22

*Vinblastine, cisplatin, and vindesine (with or without bleomycin) alternating every two weeks with dacarbazine plus vincristine.

†Same as DPV3 but with carboplatin instead of cisplatin.

The median duration of response with these treatments ranged between six and nine months and response rates were not significantly better with the combinations than with monotherapy. Large tumours of multiple lesions in multiple organ sites were, however, more susceptible to polychemotherapy. Up to date data on survival are available for all of the regimens except DJV3. At the last analysis, of the 240 patients treated with these three regimens, 36 (15%) had survived longer than two years from the start of treatment. Included among these survivors were patients with hepatic and cerebral metastases. Such survival seems to depend on response to treatment.² Survivors in complete remission beyond two years are rare but by no means unknown to this unit.

Comparison of these results with those of interleukin 2 protocols for which up to date data are now available from the National Cancer Institute group in Washington³ show that interleukin 2 has not achieved responses superior to conventional

chemotherapy in terms of quality, duration, or rates. What makes interleukin 2 inferior as a treatment is its considerable toxicity (as described by Professor Hamblin) compared with the chemotherapy protocols described above, which can be given as outpatient treatments. The major toxicity of chemotherapy—vomiting—has now virtually been conquered with the recent introduction of 5-HT₃ antagonists (for example, ondansetron), which have revolutionised the tolerance of these drugs.

Interleukin 2 has not come of age in the treatment of melanoma or any other tumour. It has enjoyed, like interferon before it, the favour of the lay media, which have the power to shape the opinions of vulnerable patients and impatient clinicians alike. It should remain an investigational drug, carefully monitored by ethical committees, before it is released from Pandora's box. Chemotherapy remains the treatment of preference for metastatic malignant melanoma.

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1 Hamblin TJ. Interleukin 2. *Br Med J* 1990;300:275-6. (3 February.)

2 Retsas S, Gershuny A. Central nervous system involvement in malignant melanoma. *Cancer* 1988;61:1926-34.

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AUTHOR'S REPLY.—Dr Spyros Retsas misses the point of my article,¹ which was not to talk about the efficacy of interleukin 2 but its toxicity. Although I went into great detail on the possible toxicities of the drug, the main thrust of my argument was that these have been overemphasised in the minds of oncologists. Dr Retsas is a perfect example of this mindset. Without any personal experience of the drug he tells us of "its considerable toxicity" and quotes only the National Cancer Institute data,² which refer to the use of interleukin 2 in a way that enhances toxicity without improving response rates. The point that I was making is that as for other drugs the toxicities of interleukin 2 depend on the doses and schedules used. When the continuous infusion protocols are used³ then, as my article was subtitled, "side effects are acceptable." Furthermore, an effective low dose subcutaneous schedule has been developed that may be administered to outpatients.⁴

It should also be recognised that the side effects of interleukin 2 are transient—they disappear when the drug is stopped. This is in contrast with the permanent neuropathy associated with the vinca alkaloids of which Dr Retsas seems so fond and the permanent pulmonary damage associated with bleomycin, the permanent cardiac damage

associated with anthracyclines, the permanent renal damage caused by cis-platinum, and the permanent haemopoietic damage due to alkylating agents.

There is no doubt that chemotherapy has some effect in patients with metastatic melanoma, but Dr Retsas's own figures attest to the fact that response rates are unsatisfactory and the duration of responses short. The best response rate reported for interleukin 2 is 40% (proceedings of the American Society of Clinical Oncology, 1989). Similarly, for renal cell cancer—a tumour for which no one claims high response rates with chemotherapy—response rates of 33% have been reported with interleukin 2.⁵

Although it is too soon to be sure that the duration of interleukin 2 induced responses will be longer than those induced by chemotherapy, it is clear that one or two courses of the drug have a profound and persisting effect on the immune system⁶ and that in some cases partial responses improve to complete responses with time but no further treatment.⁷

All treatment for all metastatic cancer remains experimental. No one can be satisfied with the current results with either chemotherapy or immunotherapy. Interleukin 2, however, is now established as an active drug in several tumours and one that may be given safely. It is a prime candidate for inclusion in phase III studies of the treatment of metastatic melanoma, renal cell cancer, and possibly colonic cancer. A strong claim may be made for it being the most effective agent available for the treatment of patients with metastatic renal cell cancer.

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2 Rosenberg SA, Packard BS, Aebersold PM, et al. Use of tumour-infiltrating lymphocytes in the immunotherapy of patients with metastatic melanoma. *N Engl J Med* 1988;319:1676-80.

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SIR,—There are widely differing philosophies on the management of patients with incurable cancer. In his editorial Professor T J Hamblin draws

attention to the tremendous advances, including the development of curative treatments, that have arisen as a result of having previously subjected patients to toxic experimental treatments.¹ But we should not forget that clinical oncology has seen many false dawns. Professor Hamblin documents the toxicity of interleukin 2 in considerable detail and draws attention to the views of some that such treatment would not seem to merit further application in the compassionate management of patients with cancer.

It is thus a little surprising to see the unqualified statements that "side effects are acceptable" and that patients should not be "deprived of effective treatment." Such phrases can be misleading without comment as to whom the side effects are acceptable and when they might be acceptable and on what is meant by "effective." To non-oncologists the phrase "complete response" can also be misleading as in most cases in which it is used, especially in the treatment of solid tumours, it merely indicates substantial but incomplete and temporary tumour regression, and what is often our inability to detect a thousand million or more residual drug resistant cancer cells.

Even if a third of patients have their lives prolonged by several months the therapeutic ratio in some will be low. The remaining two thirds of patients will experience toxicity and no benefit and might have found the "arms of alternative practitioners" more comfortable.

In an editorial on an experimental (and expensive) treatment it would have been worth while saying that no patients should at present be treated with interleukin 2 outside a clinical trial, preferably a randomised controlled trial with evaluation of quality of life.

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SIR,—In his editorial concerning the treatment of some cancers with interleukin 2 Professor T J Hamblin describes some of the physical side effects that are suffered by most patients who are given the drug. These symptoms of malaise, fatigue, anorexia, and myalgia are identical with some of the physical symptoms experienced by most patients suffering from myalgic encephalomyelitis (the postviral fatigue syndrome).¹ Neuropsychiatric symptoms commonly encountered in patients with myalgic encephalomyelitis¹ have also been described in patients being treated with interleukin 2.²

Interestingly a study from Charlotte, North Carolina,³ reported mean concentrations of interleukin 2 in 104 patients diagnosed as having myalgic encephalomyelitis⁴ that were about 40 times greater than those in 22 sex and age matched controls. Could the side effects of this newly emerging treatment for certain malignancies be providing a clue to the mystifying range of symptoms experienced by patients with myalgic encephalomyelitis at a time when there is much debate and argument as to the aetiology and pathogenesis of this disease?

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5 Cheney PR, Dorman SE, Bell DS. Interleukin 2 and the chronic fatigue syndrome. *Ann Intern Med* 1989;110:321.

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SIR,—We would like to make a comment about a point brought up in Professor T J Hamblin's excellent editorial on interleukin 2.¹ When treatment with continuous infusion of interleukin 2 is given hypotension responds quickly to stopping the infusion and the administration of fluid and dopamine are best avoided. Hypotension associated with treatment with interleukin 2 in bolus form is, however, more problematic; colloid and pressor agents should be used with extreme caution, and in the absence of pending cardiac or renal damage an expectant policy may be sufficient.

The large doses of intravenous interleukin 2 that are required to produce an antitumour effect are associated with systemic side effects. By administering interleukin 2 by other routes such side effects can be reduced even at high doses. Thus interleukin 2 has been administered locally to neoplastic deposits, intraperitoneally, and also through the splenic vein. In this hospital we have given interleukin 2 through the ileal lymphatic system and observed some partial responses in patients with end stage metastatic melanoma but no change in patients with non-Hodgkin's and Hodgkin's lymphoma. We observed symptoms of fatigue at doses of 4-5 × 10⁶ units per day, but there was no capillary leak or hypotension. This treatment produced the lymphopenia associated with intravenous interleukin 2 and rebound lymphocytosis that occurs on stopping interleukin 2. During and after endolymphatic administration of interleukin 2 lymphokine activated killer cell activity was increased and lymphocytes were particularly sensitive to the effects of interleukin 2 in vitro. We therefore suggest that this novel administration of interleukin 2 can produce antitumour effects without major side effects.

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Advanced rectal cancer

SIR,—In his leading article Professor J Alexander-Williams suggests two methods for the palliation of advanced rectal cancer.¹ As he points out, effective palliation can be achieved by transanal diathermy loop excision or neodymium-yttrium aluminium garnet (Nd-YAG) laser ablation. Based on our experience with palliating oesophagogastric carcinoma we suggest that there may be an equally effective but much cheaper option.

Several treatments have been considered for advanced rectal cancer,^{2,3} each having disadvantages in terms of results or morbidity or cost. The ideal palliative technique should be quick, safe, and painless; need only a short inpatient stay; and have a low complication rate.¹ One way by which good palliation may be achieved in a district hospital without the need for expensive equipment or extensively trained staff is by endoscopic injection of ethanol directly into tumour, thereby causing tumour necrosis.⁴ This technique is successful in the palliation of oesophageal tumours, giving results equivalent to those of laser ablation. Use of ethanol to induce tumour necrosis may also be appropriate for the palliation of advanced rectal carcinoma, particularly in patients with luminal obstruction, continuous mucous discharge, or bleeding.

In this technique the tumour is visualised by using a fiberoptic endoscope, and aliquots of 0.5 ml of dehydrated alcohol are injected through a vari-

cal injector needle directly into the growth. Injections are continued until all visible (or accessible) tumour has been treated. This technique would also be suitable for small tumours in patients who are unfit for surgery because of concurrent disease and in elderly patients. The procedure can be repeated as required.

One example of a case in which we used the technique is that of a 78 year old woman with a large rectal carcinoma and liver metastases who had undergone a defunctioning colostomy. She had a continuous offensive mucous discharge per rectum. At endoscopy as an outpatient 15 ml of dehydrated alcohol was injected into all of the visible tumour. The mucous discharge stopped within 48 hours, giving complete relief of symptoms, which was maintained until her death three weeks later.

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Doctors and medical negligence

SIR,—Writing with careful moderation, Dr J D J Havard¹ has been the first person seriously to address the subject of the difficulties likely to arise from the imposition of crown indemnity. He correctly names the likelihood of settlement without just cause, the effects on the funding of health districts, and the lack of legal experience in district and regional management, and he points to the fragility of the safeguards for the interests of doctors. He makes long overdue proposals for reducing risk and improving the quality of communication between patients and doctors.

Writing with far less moderation but perhaps with longer and deeper experience of the subject than that of Dr Havard, I wish to warn the public and the profession about the dangers inherent in the arrangements set out in the Department of Health's new circular² and its annex.

Patients confronted by the state's limitless capacity for obfuscation and prevarication are likely to find it harder than ever to pursue claims—large claims at any rate—to a satisfactory conclusion. Doctors are likely to have their views disregarded or not sought at all. They have certainly lost any right to independent representation. My own experience confirms that health authorities have hardly waited for the publication of the circular to take the conduct of affairs in current cases out of the hands of the defence organisations. Consultants have lost their ultimate deterrent in their dealings with health authorities in matters concerning the safety of patients. Nowhere in the circular or its annex is there any mention of the principle of consultant responsibility: it is likely that health authorities will deal with cases concerning juniors without any reference to the professionally responsible consultants. Some doctors, freed from the fear of financial penalty for malpractice, may adopt standards of care and responsibility that are less than acceptable. Health authorities, and in particular the governing bodies of newly independent hospitals, confronted by the intermittent necessity to find large, unbudgeted capital sums, are likely to delay and prevaricate or to impose cuts on services to patients. The position of the junior doctor who