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Neutron treatment for squamous cell carcinoma

SIR,—Dr Mary Catterall's letter¹ cannot stand unchallenged. Firstly, it is quite possible to cure some advanced head and neck cancers without incurring great tissue damage to the degree which resulted from neutron treatment as described by Mr N Stafford and colleagues.^{2,3} Secondly, it is almost beyond belief that Dr Catterall seriously compares the advent of neutron treatment with the quantum leap that was made when effective chemotherapy for Hodgkin's disease was first used. This particular example represents one of the very few instances in modern cancer therapy where the magnitude of the advance was so great that no one could have countenanced a randomised controlled study in patients with advanced disease, for which no satisfactory alternative treatment then existed. The "complications" which Dr Catterall refers to consisted in the case of chemotherapy for Hodgkin's disease chiefly of short term and reversible problems such as nausea and myelosuppression, whereas the tragedy of side effects of neutron treatment lies in their long term and irreversible nature.

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- 1 Catterall M. Fast neutron treatment for squamous cell carcinoma. *BMJ* 1991;302:349. (9 February.)
- 2 Stafford N, Waldron J, Davies D, Smith R. Fast neutron treatment for squamous cell carcinoma. *BMJ* 1991;302:48-9. (5 January.)
- 3 SECCO participants. A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. *Eur J Surg Oncol* 1986;12:289-95.
- 4 Gupta NK, Pinton RCS, Wilkinson PM. A randomized clinical trial to contrast radiotherapy with radiotherapy and methotrexate given synchronously in head and neck cancer. *Clin Radiol* 1987;38:575-81.
- 5 Grant HR, Edwards WG, Tobias JS, Monson KM, Houghton J. Salvage surgery for advanced head and neck cancer in patients treated initially by a combination of chemotherapy and radiotherapy. *Semin Oncol* 1990;17 (suppl 2):351.

War and medicine

SIR,—As practising hospital and primary care doctors we are concerned that an excess of postwar euphoria is denying the British people adequate information on the true state of defeated Iraq. We cannot know the facts, but if the widely quoted figure of 100 000 dead in the Iraqi army is correct the allied forces have exterminated the equivalent of the entire population of a medium sized English town, probably—in view of the Iraqi soldiers' actual morale and degree of disaffection—gratuitously, even in military terms.

The eventual civilian death toll from wartime allied air bombardment, the probable epidemics of gastroenteritis and hepatitis, air pollution, food and fresh water shortages, and the destruction of hospitals in Baghdad and Basra may in a short time double this total. Many will have perished in a "turkey shoot" by unopposed allied air attack after Iraq had signalled its desire to comply and withdraw. Those wounded or suffering non-fatal illness will further increase the medical need, which will

also include the care of many children who will die prematurely. Rather than utilise resources to tackle famine and disease in Africa, the Western powers have chosen to expend enormous monies on a second killing field in the Arab world in aid of the restoration in Kuwait of a regime bereft of democracy and with a poor record on human rights. Some war, some victory.

This takes place against the continuing decline of the British NHS with which readers of this journal will all be familiar and for which we are repeatedly and inaccurately told there are no funds available. The monies pledged to the NHS for the care of Gulf casualties should now be retained to remedy the present bed shortages and waiting lists. Instead of gloating over the defeat of an ill officered, poorly equipped conscript army the Western powers would be better employed sending immediate unconditional humanitarian and medical relief to Iraq, regardless of the regime in power.

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Supply of blood products

SIR,—In October 1990 the Department of Health issued a statement entitled *Supply of blood products: the UK view*. It read:

"Since 1976 it has been government policy that the UK with its long tradition of voluntary blood donation should be self-sufficient in blood products. This position is entirely consistent with the more recent decision by the EC to promote a policy of community self-sufficiency based on voluntary blood donation.

"At the same time, Ministers accord great importance to the principle of clinical freedom. Where therefore a doctor decides, in the light of the available clinical information, that a particular product is indicated for a particular patient, we believe that this decision should be respected even if that product has to be imported from outside the EC. The principle of self-sufficiency therefore means that the supplies of domestically sourced blood products should be sufficient, both in range and quantity, to meet the needs of all patients whose clinicians prefer these to other available products."

For many in the blood transfusion services this statement will be profoundly disappointing. It fails to deal with the central issue that led to the recent European Commission directive—concern about the heightened potential hazard of virus transmission to patients when blood products are derived from paid donors.¹ The department's use of the word voluntary without including the word unpaid is both unhelpful and misleading. The promotion of national and European self-sufficiency in blood and blood products is linked by the EC with the promotion of safety: by inference those countries that have to resort to importing blood products derived from paid donors will have failed to meet EC standards.

The second paragraph of the department's statement seems to give greater importance to promoting clinical freedom than product safety, placing a substantial burden on to the shoulders of prescribing clinicians, health authorities, and the Medicines Control Authority. These burdens could have unwelcome legal and financial consequences.

The government has already committed capital to both British plasma fractionation centres. But if we must now link clinical freedom with the promotion of self-sufficiency based on the unpaid donor then the government needs to look beyond investment in property and equipment. The blood

transfusion services need more effective integration and management. Beyond this there is a need for enhanced investment in research directed towards developing blood based products that meet the needs of prescribers such as coagulation factor concentrates derived from unpaid British donors.

Finally, the government ought to persuade its Medicines Control Authority to restrict the licensing and importation of blood products derived from paid donors and take on board the pharmaceutical industry's guidelines concerned with the quality of information required in claims about superiority of products.² Exhortations on the sanctity of clinical freedom in the context of self-sufficiency of blood products are wholly inappropriate. They facilitate the continual movement of operational goalposts and frustrate those who are working—with public money and plasma from British donors—to secure national self-sufficiency in blood and blood products.

We (and, we suspect, the EC) would have much preferred the Department of Health's statement to have read: "The principle of self-sufficiency in the UK means that the supplies of domestically sourced blood products will be sufficient, both in range, quantity, and quality, to meet the needs of all patients. Where this is not possible, preference should be given to sources using unpaid donors, and audit arrangements put in place designed to ascertain why such external supply arrangements are necessary and whether they need to be sustained."

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- 1 Council Directive of 14 June 1989. *Official Journal of the European Communities* No L 1989 June 28:181/44-6. (89/381/EEC.)
- 2 Association of the British Pharmaceutical Industry. *Code of practice for the pharmaceutical industry*. 7th ed. 1st rev. London: ABPI, 1991:6-7.

Tobogganing injuries

SIR,—The rare/heavy snowfalls in England are associated not only with the hazards of snow shovelling¹ but more so with those of sledging. The public's benign view of amateur tobogganing is not always appropriate.²

From the evening of Friday 8 February to the evening of Sunday 10 February 1991, 62 patients presented to the accident service of the John Radcliffe Hospital, Oxford, with injuries caused by falls from, or collisions with on, sledges or toboggans. Of these, 10 required admission to hospital, seven needed minor operations under local anaesthesia to suture lacerations, and a further six needed operations requiring general anaesthesia. There were 36 male and 26 female patients, average age 23 (range 7-50) years.

The breakdown of injuries is shown in the table. Injuries of note were a displaced Salter-Harris type 3 distal tibial fracture in a 12 year old boy requiring open reduction and internal fixation, and a displaced Salter-Harris type 2 distal radial fracture in

Tobogganing injuries sustained 8-10 February 1991 and treated at John Radcliffe Hospital

Fractures:	
Upper limb	13
Spine	6
Lower limb	4
Soft tissue injuries:	
Upper limb	8
Spine	2
Lower limb	10
Head injuries	12
Pelvic injuries	2
Lacerations requiring suture	7
Total	62

CORRESPONDENCE

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Supply of blood products

SIR,—I am comforted to learn from Professor J D Cash's letter¹ that he is as confused and concerned as I am by the Department of Health's recent statement *Supply of blood products: the UK view*.

If the department is seriously committed to self sufficiency in blood derivatives it should refrain from actively promoting clinical freedom in this aspect of health care for it will give much encouragement to those who import blood products manufactured from paid donors of plasma. Such activity could seriously damage voluntary blood donations, would be contrary to the principles in the European Commission's directive 89/381, and would promote the use of products derived from plasma that may have an appreciably higher infectivity than that from unpaid donors.

Professor Cash did not point out that the recently introduced NHS marketplace, of purchasers and providers, has created substantial further potential for damage to the blood transfusion services in England and Wales. It is well known, in all parts of the world, that the cost of collecting plasma from unpaid donors is higher than the cost of collecting it from paid donors. This is due to higher standards of care for volunteer donors and the extra expense entailed in collecting plasma at the times when most donors are not at work. These facts are now acknowledged by the Department of Health or by the NHS Bio Products Laboratory; the government's imposed payments for plasma made by Bio Products Laboratory to transfusion centres is modelled on the international spot market price for commercial plasma and is thus unrealistically low. The magnitude of the difference (20-30%) between the procurement cost and the payment by Bio Products Laboratory is so great that grave financial problems are developing in most transfusion centres throughout England and Wales and efforts are being made to fend off a collapse by implementing cross subsidisation. This will entail purchasers of blood components such as red cells and platelets paying an extra amount to make up for the unrealistically low price of plasma.

Another serious problem is Bio Products Laboratory's loss of market share for factor VIII in favour of products from paid donors. As a consequence we have been advised to reduce our targets of input plasma to the laboratory—the British blood donor's gift is being turned away. Market forces, cloaked in eulogies about clinical freedom, are dictating that patients will receive the cheap and potentially less safe product options—products from paid donors.

Ministers must urgently decide whether they really wish to support the principles of a national blood transfusion service; a system of voluntary, unpaid blood and plasma donors; and self sufficiency. A decision in favour of this approach will require financing, but it will be a worthwhile

investment both as a long term strategic exercise and to ensure that we are really committed to "working for patients." Generations of voluntary, unpaid blood donors have served this country for over 50 years, and the deliberate attempt to convert their gift to the nation into marketable commodities might turn out to be a grave political error of judgment.

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¹ Cash JD. Supply of blood products. *BMJ* 1991;302:849. (6 April.)

SIR,—I challenge the conclusions of Professor J D Cash on two grounds that may not be evident from his letter on the supply of blood products.¹

Firstly, Professor Cash has totally ignored the potentially negative effects of self sufficiency in plasma from unpaid donors either in the United Kingdom or in Europe, with the exclusion of sources in the private sector. Many of the substantial advances in quality, safety, and clinical research in products derived from plasma have either resulted from the work of the private sector or been supported by it. The disappearance of this resource can scarcely be in the interest of patients or doctors.

Plasma products from commercial sources have always provided an invaluable buffer against shortages due either to technical problems or to fluctuations in demand. Without such a buffer adequate treatment of patients could be placed at risk. All plasma derivatives are not equivalent in purity, quality, or clinical efficacy, and self sufficiency through a few European public sector sources will inevitably lead to a restriction of clinicians' choice and thus not always provide the best treatment for patients.

My second point is that the European Commission's directive merely sets forward self sufficiency in plasma with unpaid donors as an objective to be worked towards and not a mandatory requirement. The reason for this approach is almost certainly an appreciation of the potential problems outlined above together with a growing realisation that self sufficiency is an elusive goal. Europe is currently only about 50% self sufficient, and requirements, particularly for coagulation factors, are increasing as such concepts as the prophylactic treatment of haemophilia become accepted.

The quality and safety of plasma are not functions of payment or non-payment. Areas of high risk for AIDS and hepatitis and the sophistication and intensity of donor screening are much more important than whether the donor receives payment or, as often occurs in the public sector, other benefits such as free meals, paid holidays from work, or "expenses." It would seem more relevant to concentrate effort on ensuring that the plasma collected from both paid and unpaid donors meets

the same high standards of screening and testing to provide the maximum safety of the finished products and to work towards achieving true self sufficiency—that is, adequate supplies of products from both private and public sectors to meet patients' needs for adequate treatment to give them the best possible quality of life. In this context, the Department of Health's statement is accurate.

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¹ Cash JD. Supply of blood products. *BMJ* 1991;302:849. (6 April.)

Suicide among men in the highlands of Scotland

SIR,—Dr Iain K Crombie reports high suicide rates in the highlands of Scotland.¹ Research in progress in Scotland shows that the mortality from suicide (ICD 950-959) in that area was inflated during 1986-8 by 13 deaths of people who were not resident in Scotland (out of a total of 91 deaths (of both men and women)). These 13 deaths constitute a high proportion of the total of 43 deaths of non-residents from suicide in Scotland as a whole.

When these deaths are taken into account the (crude) ratio for Highland Health Board falls from 136 to 119, which only just exceeds the value for the borders (118), with Dumfries and Galloway, Grampian, and Greater Glasgow Health Boards also having high ratios of 113, 113, and 111 (deaths of non-residents excluded).

Deaths of people not resident in Scotland may substantially influence published statistics, in particular those on deaths due to accidental and violent causes, and thus the interpretation of mortality differentials. The registrar general for Scotland could improve comparability by omitting the deaths of non-residents from area statistics, as is the procedure in England and Wales.

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¹ Crombie IK. Suicide among men in the highlands of Scotland. *BMJ* 1991;302:761-2. (30 March.)

SIR,—Dr Iain K Crombie's epidemiological review of suicide among men in the highlands of Scotland during 1974-86¹ raises some interesting questions about life in the highlands. Before accepting his conclusions, however, I require more explanation of his data on standardised mortality ratios.

As a police surgeon during the period of the study, on several occasions I visited remote beauty

tioners. Thus far Maynard and Scott's is but a voice "singing in the wilderness."¹

The alleged fall in the number of applicants to general practice training schemes has been attributed to the stresses incurred by general practitioners under the new contract. I think not. It is because most aspiring medical graduates want to practise medicine for most of their working week rather than deal with non-medical problems such as business management and medical trivia better dealt with by nurse practitioners.

With the inception of this ill conceived, untested contract general practice is dead. The trainee general practitioner could now profitably spend his or her time attached to a large firm of accountants rather than acting as a locum tenens for the partners for 12 months. The case for a salaried contract for general practitioners either full or part time must now be put to the vote.

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¹ Maynard A, Scott T. *Will the new GP contract lead to cost effective medical practice?* University of York: Centre for Health Economics, 1991.

SIR,—I am surprised that after one year of exposure to the new contract, which was unilaterally thrust on us, causing perhaps the biggest change in a general practitioner's working life, I and my partners, who are members of the BMA, have had no opportunity to give our point of view other than by writing a letter such as this.

As far as I am aware, there have been no local meetings in which BMA members have been able to vote in either a referendum or a ballot to ascertain general practitioners' views. I cannot think of any other profession or trade union that has been so moribund and wonder if other members feel similarly. I would also be interested to know whether our "leaders" have any plans to rectify this sad state of affairs.

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*The secretary of the BMA replies: BMA members who are general practitioners have been able to express views on the new contract at meetings of BMA divisions when the association's annual report has been considered and in motions submitted to both the BMA's annual representative meeting and its craft conferences. In addition, an extensive monitoring exercise undertaken last summer enabled every practice to give their views about the day to day working of the contract. We are sorry that these opportunities to express views may not have been sufficient, but we are not convinced that a referendum or a ballot would have served any useful purpose. It is widely known that many general practitioners are unhappy with the day to day working of the contract, and there is no need for a referendum or ballot to prove this. The GMSC is now engaged in a wide ranging consultative exercise to assess current policy and establish future policy. It is planning to involve all general practitioners in this exercise, which could take some two years to complete. This will enable all general practitioners to express detailed views on a wide range of specific subjects, many of which concern the working of the new contract.

Suicide among men in the highlands of Scotland

SIR,—Mrs Vera Carstairs¹ and Dr J D M Douglas² point out that suicide by visitors could artificially inflate the apparent mortality in the highlands.

This will apply only to people not normally resident in Scotland as deaths among visitors from other parts of Scotland are coded to their place of usual residence. None the less, there was an inflationary effect on the data that I used in my study,³ but it was much smaller than that predicted by Mrs Carstairs. The standardised mortality ratio for men in the highlands over the period 1974-86 was 161.3, which after exclusion of suicides by non-residents becomes 148.9.

The discrepancy between Mrs Carstairs's estimates and my own may have arisen because she used a limited period, 1986-8, and the resulting standardised mortality ratios may have been atypical owing to chance variation. Certainly, in a subsequent personal letter she reports an analysis of the period 1980-5 and concludes that, after exclusion of non-residents, "the mortality remains high in most of the highland districts." The conclusions from my study were not just about high rates in the highlands but also that the rates were unexpectedly low in the central belt of Scotland. Again, in her further analysis Mrs Carstairs confirms this finding.

Dr Douglas would be unwise to overemphasise the low standardised mortality ratio of the western isles (77) as the small number of deaths on which it is based means that the 95% confidence interval is very wide (46 to 120). The issue of regional variation in the incidence of mental illness is not one on which I expressed an opinion—I raised it only as a possibility that should be investigated further.

I am interested to learn from Dr P M Darragh⁴ that suicide in Northern Ireland seems to differ from that in Scotland in being less common in rural areas. This makes more puzzling the Scottish pattern of high rates in the rural highlands and low rates in the urban central belt.

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- 1 Carstairs V. Suicide among men in the highlands of Scotland. *BMJ* 1991;302:1019. (27 April.)
- 2 Douglas JDM. Suicide among men in the highlands of Scotland. *BMJ* 1991;302:1019-20. (27 April.)
- 3 Crombie IK. Suicide among men in the highlands of Scotland. *BMJ* 1991;302:761-2. (30 March.)
- 4 Darragh PM. Suicide among men in the highlands of Scotland. *BMJ* 1991;302:1020. (27 April.)

Supply of blood products

SIR,—We share Professor J D Cash's anxieties over the statement issued by the Department of Health entitled *Supply of Blood Products: The UK View*.¹

Five years ago the regional transfusion directors (England and Wales) asked the Department of Health to consider options available to achieve a nationally coordinated transfusion service. After reviewing the management consultancy report the department decided against creating a special health authority for the National Blood Transfusion Service; in October 1988, however, it established the national directorate to coordinate the activities of the 14 regional transfusion centres. The national directorate has been very successful, particularly with regard to quality assurance, management information services, assessing targets for self sufficiency in plasma, and interregional transfer of blood and fresh blood products.

One of the main problems that now faces the national directorate is that it can only advise the transfusion service on present and future policy as the 14 regional transfusion centres are independent of each other and are managed by their respective regional health authorities. The recent changes in the NHS have meant that the regional transfusion centres now have to price their products and services. One of our concerns is that if the situation

does not change in the near future this will eventually lead to competition among the centres, which can result only in fragmentation of the service, a possible waste of blood, and tarnishing of the service's image with the irrevocable loss of the good will and support of the voluntary unpaid blood donors. Without such good will and support the blood transfusion service as we know it cannot exist.

We believe that we must build on the sound foundation laid by the national directorate to collect sufficient blood for use in hospitals and produce sufficient fresh plasma for fractionation by the Bio Products Laboratory to achieve self sufficiency. We also need to attain uniform standards of quality now required of us by the European Community and, ultimately, by patients. Before this service, which underpins many modern hospital practices, is irretrievably damaged the Department of Health must seek to create a properly funded and fully integrated National Blood Transfusion Service.

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¹ Cash JD. Supply of blood products. *BMJ* 1991;302:848. (6 April.)

Creutzfeldt-Jakob disease and blood transfusion

SIR,—Currently, the general public are very aware of the potential of blood transfusion to transmit infection unless appropriate selection of donors and testing have been carried out. Thus we are concerned that the comment that "Transmission of Creutzfeldt-Jakob disease may occur through donor tissue, infected blood, and urine" should not be misinterpreted.¹ This comment was referenced to a review that stated, "There is no recorded case of CJD [Creutzfeldt-Jakob disease] transmission by blood in man, but transmission via human blood to mice has recently been reported (Tateishi, 1985)."² The report by Tateishi was of transmission by means of intracerebral inoculation of a crushed blood clot obtained at necropsy from a patient with the disease into mice.³ Mouse to mouse transmission through inoculation of blood was also successful. Manuelidis *et al* have also reported transmission of the disease from the buffy coats of affected subjects by intracerebral inoculation into guinea pigs.⁴

Despite the transmission of Creutzfeldt-Jakob disease from human sources by intracerebral inoculation of laboratory animals and the passage of infection in mice by inoculation of blood, it should be emphasised that there is no evidence of any association between transmission of the disease and blood transfusion in the many millions of patients who have received transfusions. Although viraemia can occur in patients with Creutzfeldt-Jakob disease, current criteria for selecting donors in the blood transfusion service ensure that demented subjects and (since 1986) people who have received pituitary extracts are excluded from donating blood as preventive measures. The differences between intracerebral inoculation of laboratory animals and transfusion of human blood must be clearly borne in mind, while maintaining awareness of the potential hazards of blood transfusion.

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¹ Buchanan CR, Preece MA, Milner RDG. Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human

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Avoidable blindness

SIR,—In his editorial Dr Andrew R Potter states that blindness in about 80% of the 30 million affected is avoidable.¹ This is a concept much favoured by those concerned with public health aspects of eye disease. It is a clever semantic device whereby cataract, which is curable but not yet preventable and is by far the largest cause of blindness, is added to such potentially preventable diseases as xerophthalmia, trachoma, and onchocerciasis to show that most blindness is avoidable. This has proved to be quite profitable for propaganda purposes for medical and relief agencies working to prevent blindness.

In other respects, however, how useful is it to talk of avoidable disease? Not at all, I suggest, and it can be misleading. The major killers are all avoidable to a considerable extent if people have a better lifestyle (coronary disease, cancer, stroke) or better living conditions (malnutrition, gastroenteritis). Labelling such diseases as avoidable would not help to bring about needed change.

As Dr Potter points out, "Unless things change the number of people who are blind will double by the year 2025." He is, of course, urging greater awareness and increased resources and personnel, but I suggest that the necessary change is conceptual rather than logistical.

From earliest times until only recently medicine has concerned itself with treating individual patients. With increasing complexity of knowledge and practice it was inevitable and fully justifiable that specialisation by systems should develop. This organ based approach so necessary for treating individual patients is, however, totally inappropriate for controlling disease in the community, where health interventions are broadly based. It is neither logical nor cost effective to hive off the relevant measures from the mainstream of primary health care just because these very dissimilar diseases have the same target organ. At the first international meeting on the prevention of blindness held by the World Health Organisation in 1976 xerophthalmia, trachoma, onchocerciasis, and cataract were officially identified as "the four giants," but unofficially they were described as "four uneasy bedfellows." They have very different aetiologies, risk groups, and global occurrences and require totally different approaches, as Dr Potter acknowledges.

This misconception has now become deeply institutionalised and will take some shifting. WHO as a prevention of blindness programme with numerous collaborating centres around the world; the International Association for the Prevention of Blindness has affiliated to it national prevention of blindness committees in 60 countries. Interestingly, non-governmental agencies supposedly dedicated to preventing blindness are increasingly supporting general health care—I suspect because

the penny has dropped among those with the most practical experience.

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1 Potter AR. Avoidable blindness. *BMJ* 1991;302:922-3.
(20 April.)

The Cook Report: assisted conception

SIR,—Mr Roger Neuberg's factually inaccurate letter carries innuendoes beneath comment.¹ However, I was in no way responsible for the treatment of Dr Jack Glatt or, indeed, anybody else mentioned in this programme. I neither wished for, nor had, any editorial input.

For the record, I made three short observations only. I gave the briefest history of a woman who had had 10 separate private attempts at embryo transfer unknowingly into a non-existent uterine cavity at a cost of nearly £30 000. I was put under great pressure to release her name, but this was refused, as was the identity of the clinic largely responsible for her mismanagement. Secondly, I said that "many private [in vitro fertilisation] clinics are, in the main, offering a single treatment for a multiplicity of causes." That this is true can be seen from last month at Hammersmith Hospital. Eleven patients in whom in vitro fertilisation had failed conceived after tuboplasty, correction of uterine disease, or induction of ovulation or simply spontaneously. All had previously had multiple private attempts at in vitro fertilisation without specific (and usually cheaper) treatment being offered first. Thirdly, I observed that "many [in vitro fertilisation doctors] have gone into the private sector because they have failed to make the grade sometimes in the NHS." This is substantiated by the numerous applicants from private clinics trying unsuccessfully to get back on to the career ladder. Mostly, they are not even shortlisted.

In our weekly clinics at Hammersmith Hospital we see perhaps six new patients who have been inexpertly or inadequately treated, mostly from various private in vitro fertilisation clinics. These patients in general are not dissatisfied customers, complaining about their previous doctor, but couples whose sad mismanagement would make sensitive doctors weep. We cannot encourage patients to sue their previous doctor, and most private communication simply induces a hostile response. These are not problems that could have been effectively policed by the excellent Interim Licensing Authority, and there are occasions when, despite Professor James Owen Drife's rather ill judged comments,² the medical profession needs to come clean. Often, we are reputed to close the

shutters against criticism. In the case of in vitro fertilisation and related treatments patients are too frequently getting a raw deal from the NHS and often from private clinics. Of course I have no "contempt of clinics in the private sector"—there are many good ones—but our profession should do much more to protect the interests of these particularly desperate and vulnerable patients.

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1 Neuberg R. The Cook Report: assisted conception. *BMJ* 1991;302:1078. (4 May.)
2 Drife JO. Overcooked. *BMJ* 1991;302:1028-9. (27 April.)

Supply of blood products

SIR,—In response to Mr R B Christie's recent letter,¹ I regret that I was unable to comment on the potential difficulties of national self sufficiency in my earlier letter,² but editorial considerations necessitated substantial reductions in the final text and, in any event, I have addressed this topic before.³ Mr Christie is right to emphasise that commercial sources of plasma products have in the past provided an important buffer against shortages, but European politicians have decided that this buffer has hitherto been too large and has brought with it needless devastation in the form of transmission of viral disease. There is nothing unique in the concept of self sufficiency: the European Commission has simply implemented recommendations made by the World Health Organisation in 1975.⁴

Mr Christie's statement that the safety of plasma is not a function of payment or non-payment of donors is frankly astonishing. Many scientific publications refute this statement, and I know of none in support of it. Publications on this topic started in the 1930s with syphilis and continued with hepatitis B virus, cytomegalovirus, HIV-1, HIV-2, human T cell leukaemia/lymphoma virus type 1, and hepatitis C virus. On the other hand, we should support Mr Christie's exhortations that we must concentrate more effort on ensuring that the plasma collected from both paid and unpaid donors meets high standards of safety. Doctors will be interested to note that those collecting plasma from paid donors in the United States have recently considered it necessary to propose that it should be assayed for contamination with heroin.

Mr Christie suggests that I proposed that the European Commission's directive on self sufficiency is legally binding (mandatory). This is not so, and I have specifically emphasised this point previously.³ But a definition of self sufficiency in the *Oxford English Dictionary* is "able to meet one's

need from one's own resources," and that is the goal that the European Commission has set. It follows that our government should now be striving to establish appropriate conditions that will enable those with this formidable task to respond appropriately. There can be no doubt that the United Kingdom can be self sufficient in providing the major blood products, provided that the blood transfusion services are allowed to develop appropriate management arrangements.

Mr Christie emphasises the desirability of maintaining clinical freedom of prescribing but omits to point out that the British prescribers of coagulation factor products have recently declared their desire to prescribe, exclusively, high quality products derived from plasma of unpaid donors.⁵

Finally, I share Mr Christie's concern about the propriety of some so called unpaid donors in Europe. I hope that this important issue will be tackled in future technical directives associated with directive 89/381.

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- 1 Christie RB. Supply of blood products. *BMJ* 1991;302:1019. (27 April.)
- 2 Cash JD. Supply of blood products. *BMJ* 1991;302:849. (6 April.)
- 3 Cash JD. Blood transfusion services and the European Community. *BMJ* 1990;300:481. (24 February.)
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- 5 L'Industrie du plasma renforce ses règles pour améliorer son image. *La Nouvelle Gazette de la Transfusion* 1990 October 2.

SIR,—I am dismayed, although not surprised, by the erroneous and misleading statements of Professor J D Cash¹ and Dr Marcela Contreras.²

Professor Cash indicates that the central issue leading to the European Community's recent council directive³ was concern over blood products derived from paid donors. This is quite wrong. In fact, the directive cited was only one of three extension directives issued at the same time, the purpose of which was to bring under the control of European Community directives a whole range of products including vaccines, sera, and radiopharmaceuticals. The issue of paid versus unpaid donors continues to be used as a rather poor weapon by those in the blood transfusion service seeking a monopoly of the supply of blood products. Perhaps they need reminding that HIV was transmitted via non-heat treated factor VIII derived from unpaid British donors in the early 1980s.⁴ It is unpaid donors who have been responsible for at least 30 cases of HIV infection in the United Kingdom,⁵ and it is unpaid donors who may well be transmitting hepatitis C virus in blood transfusions because of the failure of the British blood transfusion service to introduce even a surrogate screen for this virus. It cannot be claimed that unpaid donors are necessarily safe donors.

Crown immunity has, until 1 April this year, protected the Bio Products Laboratory from commercial competition and regulatory compliance, to the detriment of both doctors and patients. Under that system Bio Products Laboratory has been supplying to the United Kingdom market unlicensed blood products produced for many years in manufacturing facilities that fall far short of acceptable practice (Granada Television. *World in Action*, "The blood business," 22 December 1980). It was Bio Products Laboratory that introduced and then withdrew an intravenous immunoglobulin product which in one trial transmitted non-A, non-B hepatitis to all 12 patients receiving it.⁶ A similar product introduced by the Scottish Protein Fractionation Centre, and derived from unpaid donors, has also been shown to transmit non-A, non-B hepatitis.⁷ These facts, coupled with the appalling shortfalls in the supply

of products from Bio Products Laboratory until the late 1980s, make it imperative that the British public never has to rely totally on them in the future.

Industry produces a range of blood products that are required to comply not only with the United Kingdom's regulatory requirements but also as necessary with those of many other countries. I challenge Professor Cash and Dr Contreras to produce any evidence that currently licensed commercial products are, as they imply, less safe than those produced by Bio Products Laboratory or the Protein Fractionation Centre. Furthermore, I refute the suggestion that price somehow relates to safety. Rather, I suggest that the high cost of Bio Products Laboratory's products results mainly from its inefficient system of collecting plasma and high production overheads. Dr Contreras makes several unsupported claims concerning the standards of care for paid versus unpaid donors, the cost of collecting plasma, and the international spot market price for commercial plasma.¹ The price paid by Bio Products Laboratory for apheresed plasma in the United Kingdom is £60/kg whereas in the United States the market purchase price for its equivalent, source plasma, is currently only about \$60/litre. Thus the price that Bio Products Laboratory is paying for its plasma, far from being low, is in fact extremely high.

The interests of users of blood products in Britain are undoubtedly best served by allowing commercial competition to act as the stimulus for reasonable pricing and continuous product improvement rather than by relying on protected monopolies.

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- 1 Cash JD. Supply of blood products. *BMJ* 1991;302:849. (6 April.)
- 2 Contreras M. Supply of blood products. *BMJ* 1991;302:1019. (27 April.)
- 3 Council Directive of 14 June 1989. *Official Journal of the European Communities* No 1 1989 June 28:181/44-6. (89/381/EEC.)
- 4 Ludlam CA, Tucker J, Steel CM, et al. Human T lymphotropic virus type III (HTLV-III) infection in seronegative haemophiliacs after transfusion with factor VIII. *Lancet* 1983;ii: 223-6.
- 5 Delamothe T. New AIDS figures. *BMJ* 1991;302:197. (26 January.)
- 6 Lever AML, Webster ADB, Brown D, et al. Non-A, non-B hepatitis occurring in agammaglobulinaemic patients after intravenous immunoglobulin. *Lancet* 1984;ii:1062-4.
- 7 Williams PE, Yap PL, Gillon J, et al. Non-A, non-B hepatitis transmission by intravenous immunoglobulin. *Lancet* 1988;iii:501.

SIR,—Professor J D Cash states that he is disappointed with the Department of Health's position regarding the need for doctors and patients to have access to particular products regardless of where these products may have been manufactured.¹

He bases his concern on a perception that imported products derived from blood will be less safe if the source material is obtained from compensated donors. This view is highly simplistic and attempts to extrapolate data and information from earlier studies of single donor units of blood obtained from remunerated and non-remunerated donors. Extending these data to plasma derivatives, which are prepared from large pools of plasma, however, is not justifiable.

In 1978 the United States Food and Drug Administration promulgated regulations requiring the labelling of single donor units of blood and blood components to indicate whether they had been obtained from remunerated or non-remunerated donors. In considering whether to extend this requirement to include plasma derivatives as well the agency concluded: "No available data demonstrate that final plasma derivative products derived from volunteer donor plasma carry a lower risk of transmitting

hepatitis to recipients than do similar products manufactured from paid donor plasma."²

Data resulting from the evaluation of reagents used in detecting antibody to hepatitis C virus in haemophilic patients show that the incidence of this marker is similar in many countries, even those with little or no use of imported coagulation factor concentrates. Transmission of AIDS has also occurred in countries relying solely on concentrates derived from domestic, non-remunerated donors. Plasma derivatives produced from pooled donations have been associated with viral transmission regardless of donor status. Within recent years the industry has made remarkable progress in minimising this potential by implementing rigorous programmes to screen donors and aggressive processing steps such as monoclonal antibody purification, solvent-detergent treatment, pasteurisation, and combinations of these innovations.

Plasma derivatives shown to be safe and effective for their intended purpose should be available for patients, regardless of their source.

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- 1 Cash JD. Supply of blood products. *BMJ* 1991;302:849. (6 April.)
- 2 *Federal Register* 1978 Jan 13. (43 FR 2142.)

Penicillin prophylaxis in children with sickle cell disease

SIR,—From their recent survey Dr David Cummins and colleagues concluded that "doctors' knowledge about sickle cell disease was generally poor" and that most general practitioners interviewed "did not prescribe penicillin prophylaxis for children with sickle cell disease."¹ Ever since its value was first established by Ferguson and Scott in the United States² and by Warley et al in east Africa³ penicillin prophylaxis has been used throughout the world, notably in the West Indies⁴ and Ghana.⁵

I can see at least three important reasons why some doctors do not prescribe prophylactic penicillin for their patients with sickle cell disease, even though they are aware of the proved value of such treatment. Firstly, the delay in acquiring immunity to the pneumococcus and the emergence of strains resistant to penicillin, not to mention problems of compliance, with the resultant severe infection are perceived as "potential disadvantages of prophylactic penicillin."⁶ Secondly, patients not receiving long term penicillin prophylaxis but who are seen more frequently than the "four to six monthly outpatient visits" have done well.⁷ Thirdly, some doctors may use penicillin prophylaxis selectively rather than for all patients because they realise that deaths have often had more to do with what I call the "global circumstances" of the crises that preceded the death than whether the patient was receiving penicillin. Long term treatment with penicillin is but one of several factors that proper surveillance is meant to monitor.

Dr Cummins and colleagues' suggestion that home visiting and counselling should be stepped up to help parents supervise their children is supported by the finding in Jamaica that "compliance reached nearly 100 percent in a domiciliary visiting programme."⁸

Finally, it is well to remember that, apart from the effect of the external environment (microbes, ambient temperature, partial oxygen pressure, exercise, etc) on sickle cell disease, the patient's genetic make up may modify the disease, making it worse, as, for example, if the patient has concomitant glucose-6-phosphate dehydrogenase

did not give a history of diarrhoea or vomiting.

An x ray film of her left shoulder showed a pathological fracture of the neck of the humerus, and after histological examination of the bone an IgG myeloma was diagnosed. Her renal function and serum lithium concentration improved with fluid replacement, and she received chemotherapy for her myeloma. At discharge from hospital she had normal renal function.

There is conclusive evidence that non-steroidal anti-inflammatory drugs can increase serum lithium concentrations, diminish renal clearance of lithium, and possibly induce lithium toxicity. General practitioners caring for patients being treated with lithium should be aware of this interaction. Patients receiving lithium and non-steroidal anti-inflammatory drugs should initially have their serum lithium concentrations checked every four to five days. The dosage of lithium may have to be reduced after assessment of any drug interaction.⁴

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- 1 Goddard J. Lithium intoxication. *BMJ* 1991;302:1267-9. (25 May.)
- 2 Ragheb M. The clinical significance of lithium-nonsteroidal anti-inflammatory drug interaction. *J Clin Psychopharmacol* 1990;10:350-4.

Supply of blood products

SIR,—The letters of Mr J P Betts¹ and Dr M B Rodell² contain several misleading statements, which, because they may have formed the basis of the only advice received by ministers, deserve a response.³

Mr Betts expresses no surprise that I am a champion of national self sufficiency in blood and blood products yet seems to forget that in 1987 I raised serious doubts that our government had fully understood what its representatives from the Department of Trade and Industry and the Department of Health had agreed in Brussels.¹ Moreover, I pointed out that the United Kingdom's commitment to self sufficiency in these negotiations had been made without consultation with any senior operational managers from the blood transfusion service. I now do indeed champion self sufficiency, based on unpaid blood donors, because it forms the central feature of the European Community directive 89/381, to which our government gave its support. Mr Betts should understand that the issues have nothing to do with the blood transfusion services seeking a monopoly for the supply of blood products. Indeed, the directive makes plain that the central issue is the availability throughout the European Community of plasma products from unpaid blood donors and that in seeking this object the commissioners have made specific provisions to enable the movement of products from one part of Europe to another. Such arrangements must surely have the support of Mr Betts for they run contrary to the concept of monopolies.

Mr Betts will insist that the principles contained in this directive are simplistic. That may be so, but all these simplicities were recounted to European Commissioners by representatives of commercial companies in the consultative period before the directive was approved by ministers, and it would seem clear that the objections of the companies were rejected. Moreover, we must conclude that in the critical consultation period commissioners were well aware that products from unpaid donors had transmitted HIV and hepatitis C virus but that the "hit rate" from products derived from paid donors was substantially higher.

Though I welcome the thoughtful and constructive comments made by Dr Rodell,² I would suggest that the American Blood Resources

Association, which represents the interests of the major suppliers of plasma products derived from paid donors, needs to reflect whether the view of the Food and Drug Administration in 1978, that plasma products derived from unpaid donors have a risk of transmitting viruses that is identical with that of products derived from paid donors, has been substantiated. Much has happened since 1978, as many patients with haemophilia will testify. Most of the fortunate ones lived in those countries in which the quantity of commercially derived factor VIII concentrates prescribed was small.

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- 1 Betts JP. Supply of blood products. *BMJ* 1991;302:1205. (18 May.)
- 2 Rodell MB. Supply of blood products. *BMJ* 1991;302:1205. (18 May.)
- 3 Cash JD. Blood transfusion services and the European Community. *BMJ* 1990;300:481.

SIR,—I am concerned by Mr J P Betts's selective quotation of two episodes of the transmission of non-A, non-B hepatitis associated with intravenous immunoglobulin preparations.¹ He implies that these two episodes may somehow be related to crown immunity protecting the manufacturers concerned, the Bio Products Laboratory² and the Scottish National Blood Transfusion Service Protein Fractionation Centre.³ He does not mention that there have been other well documented episodes involving commercial manufacturers in the United States⁴ and Sweden¹⁴ and further possible episodes in Italy⁷ and Sweden.¹

Mr Betts also fails to mention that the intravenous immunoglobulin preparation manufactured at the Scottish Protein Fractionation Centre was extensively investigated before the episode of transmission of non-A, non-B hepatitis that we reported⁸ and was shown to be safe as far as such transmission was concerned.⁹ Scottish intravenous immunoglobulin was awarded a product licence in 1985 on the basis of clinical and laboratory data submitted, and I understand that the question of avoiding standard regulatory procedures in the United Kingdom by using crown immunity was never considered by the Protein Fractionation Centre.

I believe that Mr Betts has diverted attention from the important issues concerning the safety of intravenous immunoglobulin preparations with respect to transmission of non-A, non-B hepatitis. Factors such as the quality of the starting plasma (including screening of donors for infection with viruses), the fractionation technology used, and various treatments after fractionation (some of which are thought to be virucidal) need to be considered.¹⁰ Furthermore, prospective or retrospective screening of recipients for possible transmission of non-A, non-B hepatitis needs to be undertaken, as has been described for several intravenous immunoglobulin preparations.¹¹⁻¹⁴

When assessing the safety of intravenous immunoglobulin preparations with respect to non-A, non-B hepatitis it should be noted that in the episode we reported only one batch out of 110 was implicated.¹ Since that time a further 55 batches have been used and detailed follow up of immunodeficient recipients has not identified any further cases of non-A, non-B hepatitis (P L Yap, A A M Todd, and P E Williams, unpublished data). Interestingly, our experience has paralleled that of a commercial manufacturer, which undertook a detailed study of the safety of intravenous immunoglobulin after the initial report of transmission of non-A, non-B hepatitis,¹ and was able to report the safety of the preparation with respect to this disease.¹¹ In addition, only four out of 40 recipients were infected (three transiently) in our episode of non-A, non-B hepatitis,¹ and this shows the difficulty of organising prospective

clinical studies to assess safety when the rate of transmission of the disease is so low. This also highlights the importance of close prospective monitoring of recipients of intravenous immunoglobulin (even if asymptomatic) and of good documentation to be able to detect such a rare occurrence and to be able to ascribe the transmission of non-A, non-B hepatitis with confidence to a single batch of the preparation.

I consider that Mr Betts has selectively quoted data to support a contentious opinion. I believe that the key to safety lies in using high quality donor plasma and well proved fractionation technology combined with large scale prospective clinical trials before an application for a product licence and, if necessary, selective surveillance after licensing. The priority is clearly to identify the virus (or viruses) involved in the rare episodes of non-A, non-B hepatitis associated with intravenous immunoglobulin so that *in vitro* "spiking" studies can be used to assess the virucidal activity of the various fractionation methods and treatments after fractionation. We therefore hope, in collaboration with other groups,^{14,15} to use the polymerase chain reaction¹⁶ to investigate whether hepatitis C virus played a part in the transmission of non-A, non-B hepatitis associated with intravenous immunoglobulin.

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- 1 Betts JP. Supply of blood products. *BMJ* 1991;302:1205. (18 May.)
- 2 Lever AML, Webster ADB, Brown D, et al. Non-A non-B hepatitis occurring in agammaglobulinaemic patients after intravenous immunoglobulin. *Lancet* 1984;ii:1062-4.
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SIR,—We agree with Professor J D Cash that the quality of plasma and safety from viral contamination are the highest priorities in supplying medications derived from plasma.¹ Drawing the conclusion that the issue of paid versus unpaid donors is synonymous with the degree of quality and safety is troublesome.

Firstly, the distinction between paid and unpaid donors is far from clear. The method of recruiting donors and the form of compensation (monetary, gifts, or other benefits) may not be the most

