

Insulin (nmol/L)/glucose (mmol/L)	0-2 h	2-4 h
Control	0.065 (0.008)	0.066 (0.010)
Anorexia nervosa (A)	0.011 (0.017)	0.031 (0.006)
Anorexia nervosa (B)	0.055 (0.004)	0.070 (0.006)

Anorexic patients were divided into two groups, groups A and B, the latter comprises four patients who developed severe hypoglycaemia after intravenous glucose infusion. Values are mean (SE).

Table: Ratios of integrated insulin/glucose responses

infusion, four patients developed rebound hypoglycaemia with plasma glucose values less than 2.2 mmol/L: 2.0, 1.8, 1.9, and 2.1. These patients tended to have higher insulin and lower glucose responses than others. The ratios of integrated insulin/glucose response during (0–2 h) and after (2–4 h) intravenous glucose infusion give an estimate of insulin sensitivity (table). There was no difference between the patients who developed severe rebound hypoglycaemia and those who did not, with respect to age, duration of illness, or body-mass index.

We found that approximately 20% of patients with anorexia nervosa developed hypoglycaemia with plasma glucose concentrations less than 2.2 mmol/L after intravenous glucose. This potentially serious complication of intravenous alimentation should be considered when treating severely emaciated patients.

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Atopic dermatitis and staphylococcal superantigens

SIR—It has been suggested that mitogens such as superantigens produced by commensal staphylococci initiate or perpetuate dermatitis.¹ The staphylococcal superantigen toxic shock syndrome toxin (TSST-1) causes toxic shock syndrome by activating T-lymphocytes, leading to massive cytokine release.²

We studied 68 survivors of toxic shock syndrome between 1991 and 1995. All were diagnosed according to the US Center for Disease Control and Prevention criteria and all had staphylococci producing TSST-1. Data were checked with the patients' general practitioners and hospital notes. Patients were admitted to hospital between 0.2 and 12 years (median 3.2) before interview. They were aged 2 to 56 years (median 20), and included seven men and 61 women.

14 complained of dermatitis starting after their episode of toxic shock. None had dermatitis before this time, or a history of atopy. The dermatitis started after the peeling of skin during the first 2 weeks of the illness, and was described as eczematous, with areas of erythema. The rash was most pronounced on extensor surfaces of the limbs, and in two cases involved the face. General practitioners had treated all patients with emollients; five received topical corticosteroids. It has proved difficult to find appropriate matched controls; however, long-term follow-up of intensive-care survivors

who had septic shock did not identify dermatitis as a problem,³ suggesting that this complication relates specifically to patients recovering from toxic shock syndrome.

Eight patients had swabs taken of skin with dermatitis and nasal flora, and serum IgE assayed (median age 25 years, median period after toxic shock syndrome, 6 years). *Staphylococcus aureus* was not cultured, but four patients had increases in IgE, suggesting atopy (median IgE 290 kIU/L, range 200–680). Dermatitis might therefore be a consequence of the substantial immune activation during exposure to staphylococcal superantigens, leading to anergy or loss of skin T cells. Alternatively, residual TSST-1 bound to keratinocytes may disturb the cytokine repertoires and migration patterns of dermal T cells.⁴ In view of the long-term persistence of this disorder in these patients, the first mechanism is more probable. We note that patients with Kawasaki syndrome (which may be caused by superantigen) show an increased frequency of atopic dermatitis.⁵

These observations suggest that bacterial superantigens may initiate an atopic process in the skin.

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Haematogenous dissemination of prostate epithelial cells during surgery

SIR—Eschwége and colleagues (Dec 9, p 1528)¹ report their results in 14 men with nested reverse transcription PCR (RT-PCR) with prostate-specific membrane (PSM) primers before and shortly after radical prostatectomy. Specifically, they report that three of 14 men were PSM RT-PCR positive before surgery, increasing to 12 of 14 men shortly after surgery, and 7 of 14 men 3 days after surgery. They conclude that haematogenous dissemination of prostate epithelial cells occurs in men during radical prostatectomy.

We have reported a similar observation in a series of 28 men, and we have now accumulated 3 month, and in some 6 month, follow-up with PSA primers in a non-nested RT-PCR technique with probe hybridisation enhancement.² Evidence of intraoperative haematogenous dissemination was recorded in eight (28%) and over 90% had evidence of PSA-positive cells in the surgical field. The peripheral venous blood in these men was assessed at 3 and 6 months, and these results showed significant ($p=0.021$) positive RT-PCR conversion in 25% of our study population. Notably, we identified that 25% (7/28) of men were RT-PCR positive preoperatively, which increased to 50% (14/28) 3 months postoperatively. These numbers are very similar to those reported by Eschwége et al and support their conclusion that haematogenous dissemination may, in fact, occur during radical prostatectomy. We have, however, recorded conversion to a negative status in two men who became positive intraoperatively and remained positive until 6 months. Therefore, the clinical significance of intraoperative

haematogenous dissemination determined by the RT-PCR assay remains uncertain.

In addition, long-term clinical and PSA-progression-free survival after radical prostatectomy in men who have pathologically organ-confined disease does not accord with the finding that the vast majority of men will progress, as Eschwège's data suggest.³ Conversely, men with organ-confined disease after radical prostatectomy can progress for reasons that remain unclear, including the possibility of local tumour spillage and haematogenous dissemination.⁴ Together, these observations indicate that haematogenous dissemination of prostate epithelial cells occurs during radical prostatectomy; however, only a proportion of these cells have the biological capability to implant and subsequently progress.

The potential for antiandrogen neoadjuvant therapy to improve progression-free survival after radical prostatectomy remains to be established. However, the enthusiasm for neoadjuvant hormonal therapy must be tempered by the small sample size, the short-term follow-up, and the limited understanding of the androgen-regulated nature of the PSM gene.⁵ Nevertheless, these observations do offer potential strategies to improve outcomes after radical prostatectomy in men with pathologically organ-confined disease harbouring a biologically aggressive carcinoma. Indeed, prostate cancer, much like breast carcinoma, does seem to be entering the category of a systemic disease.

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SIR—The detection of circulating tumour cells in cancer patients is not, by any means new. Indeed, several previous studies, some dating back over half a century, have elegantly demonstrated the presence of circulating malignant cells in the peripheral blood of patients with advanced disease, and at operation.¹ In their study, Eschwège and colleagues² reiterate a well-known event in the biological behaviour of cancer.

It is inevitable that tumour cells will disseminate into the blood stream during manipulation of a primary cancer. This is simple mechanical shedding due to tumour handling. This logical event does not occur only during manipulation. Previous studies have shown that tumours, whether manipulated or not, continually shed malignant cells in the circulation.³ These studies have also shown that most malignant circulating tumour cells do not survive, with as little as 0·1% being responsible for the formation of secondary deposits. Metastasis therefore does not rely on the random survival of cells released from the primary tumour, but from the selective growth of specialised subpopulations of highly metastatic cells, endowed with properties that allow them to successfully complete each step of the metastatic cascade.

It would be naïve to think that the simple presence of malignant cells in the circulation means that they represent micrometastases. We applaud Eschwège and co-workers' caution in calling the cells they detect by their sensitive molecular approach "prostatic epithelial cells", by contrast with others who named these cells "micrometastases".⁴ Although it would be reasonable to assume that these cells may be malignant, the evidence that they are cancerous is lacking from all the studies investigating this occurrence. The marker used to detect the cells (prostate specific membrane antigen) may be tissue specific, but it is not tumour specific—a limitation often overlooked.

The suggestion that adjuvant androgen ablation might prevent dissemination is interesting and attractive, but why should hormonal manipulation do so? What is known from antiandrogen treatment is that it will lead to programmed cell death of hormone-sensitive cells, which would diminish tumour load.⁵ Such cell death may indirectly lead to fewer viable tumour cells being shed in the blood stream, but not to the mechanical shedding caused by manipulation, especially of hormone-insensitive cells. Should future studies prove these circulating PSA-positive or PSMA-positive cells to be malignant, more extensive work would be required to assess their metastatic capability. Until such evidence is available, these hypersensitive assays should be regarded as an important part of research into the biological behaviour of prostate cancer, but should not influence clinical decisions.

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SIR—Eschwège and colleagues¹ resurrect the possibility of surgical dissemination previously suggested in breast cancer and colon cancer. Oliver in his Dec 9 commentary mentions the absence of a randomised trial comparing surgery with placebo in solid tumours, with the exception of prostate cancer. However, such a model for comparison is available.

In randomised screening trials, surgery is delayed in the control group by about 18-24 months (lead time) compared with the screened group; hence the first few years of follow-up would offer a comparison between early surgery and late surgery. In the conventional theory, surgery is thought not to influence the natural history of cancer, and survival is determined by the presence of micrometastases before diagnosis. Proponents of this theory would predict an identical number of deaths in both the groups for the first few years. Contrary to this belief, if dissemination were to occur at the time of surgery it would lead to excess deaths in the screened group for the first few years. Screening trials have been carried out for breast, lung, and colon cancer. All these cancers were treated surgically after diagnosis. A meta-analysis of annual cumulative mortality of all the published screening trials in breast cancer² (stratified by age 50 years) which has looked at mortality in the early years showed that there was excess mortality in the screened group in the first

few years. Exclusion of data from the Canadian trial did not change the conclusion. In women older than 50 years the excess mortality in the screened group was seen in only the first year, whereas in younger women it persisted for the first 6 years after randomisation. An excess mortality in the screened group was evident in both the randomised trials of screening for lung cancer^{3,4} even beyond 6 years of follow-up. In the colon cancer screening trial,⁵ the group that had biennial screening for occult blood in stool had early excess deaths compared with controls for the first 10 years.

Thus all the published screening data suggest that early intervention in the form of surgery has had a detrimental effect on the natural history of cancer. It is tempting to compare the model of surgical dissemination to the interaction between observer and observed in quantum physics. The model offers justification for systemic manipulation in a neoadjuvant setting to obviate the early detrimental effect of surgery.

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Neuropsychiatric reactions with mefloquine chemoprophylaxis

SIR—The incidence of severe neuropsychiatric reactions when mefloquine is used for prophylaxis against malaria has been estimated variously as 1:20 000,¹ 1:15 000,² and 1:13 000³ travellers. These figures have been questioned by some authorities and have become subject to scrutiny by the popular media. As a result, practitioners may have become confused and uncertain how to advise patients intending to travel to or reside in malarious countries.

In July, 1993, mefloquine was adopted by the British army as the standard chemoprophylaxis for East Africa. Since then 6085 British troops have taken a full course of mefloquine. They were deployed on exercise in Kenya or operations in Rwanda and Angola for 4-16 weeks and took mefloquine 250 mg weekly for at least 1 week before departure and for 4 weeks after return to the UK. The weighted mean tour duration in Africa was 8·3 weeks per soldier and the weighted mean duration of chemoprophylaxis was 13·3 weeks per soldier. On Nov 15, 1995, the first severe neuropsychiatric reaction to occur in a British soldier as a result of mefloquine was diagnosed during an exercise in Kenya. It occurred 2 days after he had taken his sixth weekly mefloquine tablet, 4 weeks into the exercise. There had been no symptoms before this. He was a previously healthy 26-year-old private with no personal or family history of neurological or psychiatric illness. His weight was 63 kg. The single witnessed episode occurred in an office. He experienced a visual hallucination of the grim reaper standing behind the chaplain and this was associated with an auditory hallucination of incoherent voices. This terminated spontaneously after 15 min. Mefloquine was

Event	Date	Day	Plasma mefloquine ($\mu\text{mol/L}$)	Plasma mefloquine metabolite ($\mu\text{mol/L}$)
Last tablet taken	Nov 13, 1995	0
Reaction	Nov 15, 1995	2	(1·6-3·6)*	(12-15)*
1st blood sample	Nov 23, 1995	10	1·28	14·00
2nd blood sample	Nov 30, 1995	17	1·59	10·50
3rd blood sample	Dec 7, 1995	24	1·08	7·12

Plasma concentrations of mefloquine and its main metabolite were measured by high performance liquid chromatography.⁴ *Likely concentration ranges on day 2, based on interpretation of later figures by Dr Y Bergqvist, Falun Central Hospital, Sweden.

Table: Plasma concentrations of mefloquine and its main metabolite

discontinued and chemoprophylaxis with doxycycline substituted. He was flown back to the UK before the scheduled end of the exercise and admitted to an army psychiatric unit. There was no recurrence of his symptoms over the next fortnight. Unfortunately, no blood sample was taken at the time of the reaction and so the levels of plasma mefloquine and its main metabolite are unknown. However, serial blood samples were taken commencing immediately upon his return, 8 days after the reaction, in order to attempt to extrapolate back to the levels likely to have existed at the time of the reaction (table). The levels considered likely at the time of the reaction are similar to those observed in healthy Swedish volunteers taking mefloquine and are not excessive (Y Bergqvist, Falun Central Hospital, Sweden).

The experience of the British army with mefloquine indicates that the incidence of a severe neuropsychiatric reaction arising during a period of prophylaxis lasting 3 months is not higher than 1:6000. Steffen and colleagues found that of 139 164 travellers who stayed in East Africa for less than 1 year, the incidence of such reactions was 1:10 600. However, 97·6% stayed 4 weeks or less⁵ indicating a likely total duration of prophylaxis of 9 weeks. In terms of patient-weeks of use, the military incidence of a serious neuropsychiatric reaction of mefloquine is 1:80 935 which is very comparable to that observed by Steffen et al which was not higher than 1:95 400.

We agree with previous investigators¹⁻³ that the incidence of severe neuropsychiatric reactions to mefloquine chemoprophylaxis is extremely low and, on the basis of the case reported here, probably not related to any excessive concentration of mefloquine or its main metabolite in plasma. Practitioners who give advice to travellers to African and other countries where mefloquine is the chemoprophylactic agent of first choice should weigh the very small risk of a severe neuropsychiatric reaction to the drug against the much higher risk to the traveller of contracting potentially drug-resistant *Plasmodium falciparum* malaria with its attendant morbidity and mortality.

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