index, which is also modified by differences in body build and muscularity.²⁷ In general our results accord with observations from the United States of a clustering of negative health habits among smokers, which may have become more pronounced in recent years.⁸

We can only speculate why the characteristics of smokers in Finland seem to be changing. In the past smoking was considered to be a "normal" habit; but with the Finnish antismoking legislation from 1977, increased antismoking education, and changing public attitudes smoking is being regarded more as a deviant behaviour. Thus today smokers may be personalities more prone to risk taking and unhealthy behaviours than earlier. It may be hypothesised that the hard core of current smokers, who hitherto have resisted anti-smoking campaigns, consist of an increasing selection of people with unfavourable health behaviour. In another Finnish study²⁸ persistence in smoking was associated with greater use of alcohol and coffee, possibly due to a common pathophysiology of dependence.²⁹ On the other hand, the average number of cigarettes smoked daily by current smokers did not increase from 1982 to 1987 as one would expect for the hypothesis of an increasing cluster of negative health habits.

In conclusion our population based data from large samples of middle aged Finnish men and women suggest that the metabolic effects of smoking are apparently increasingly overridden by the present behavioural characteristics of smokers such as high alcohol and saturated fat consumption and little exercise. The earlier generally accepted notion that smokers weigh less than non-smokers¹¹ may thus soon turn out to be anachronistic. It also seems plain that antismoking health education aimed at young and middle aged men should place more emphasis on correcting an unhealthy lifestyle as a whole.

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Intralesional tumour necrosis factor combined with interferon gamma in metastatic melanoma

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Recombinant tumour necrosis factor α and interferon gamma are cytokines that show synergistic antitumour activity in vitro against clonogenic human tumour cells.^{1,2} Remission rates of up to 40% after direct injection of recombinant tumour necrosis factor α into the tumour have been reported.² We looked at the therapeutic potential of these two cytokines used together in seven patients with advanced metastatic malignant melanoma.

Patients, methods, and results

The study was approved by the hospital ethical committee. Three women and four men with a median

age of 44 years (range 28 to 57) took part. All patients had progressive disease in more than two organ sites, which was distributed as follows: skin (seven patients), lymph nodes (three), lung (three), bone (two), and brain (one). They had all previously been treated with chemotherapy, with a median of five drugs (range four to 11), and three had also received interferon alfa. Cerebral and cutaneous metastases in one woman had previously responded to chemotherapy with the DJV3 combination (vindesine, dacarbazine, carboplatin, vinblastine, and vincristine), and another patient had had a prolonged remission with interferon alfa, as already reported.^{3,4}

The planned treatment regimen was recombinant interferon gamma 100 $\mu\text{g}/\text{m}^2$ body surface area intramuscularly thrice weekly, followed by injection of recombinant tumour necrosis factor α once weekly into the lesion at an initial dose of 5 $\mu\text{g}/\text{m}^2$ and increasing to a maximum of 150 $\mu\text{g}/\text{m}^2$ if tolerance permitted. Selected subcutaneous lesions were injected, repeatedly when possible, except in one patient who lacked a suitable lesion and was injected subcutaneously.

The median length of treatment was four weeks, ranging from one to six weeks for recombinant tumour necrosis factor α and from one to nine weeks for recombinant interferon gamma. The median cumulative doses achieved were 105 μg (range 10-300) for recombinant tumour necrosis factor α and 1500 μg (range 400-1900) for recombinant interferon gamma.

The toxicity associated with recombinant tumour necrosis factor α was considerable and independent of dose. Six patients had severe rigors. One patient had a cardiovascular collapse with unrecordable blood pressure and pulse after an injection of 10 μg into the lesion. He was resuscitated with intravenous fluids and steroids. A second patient, with cerebral metastases, developed severe rigors, which were followed by generalised convulsions. Treatment with recombinant tumour necrosis factor α was stopped in these two patients and continued with recombinant interferon gamma alone.

Important haematological, hepatic, or renal toxicity was not seen.

None of the subcutaneous lesions injected with recombinant tumour necrosis factor α regressed. One patient was injected twice into the lesion with both cytokines in combination, again with no response. Metastases advanced in more than one site in all patients.

Comment

The toxicity of recombinant tumour necrosis factor α was severe even at small doses. Feinberg *et al*

reported irreversible cortical blindness in a patient with cerebral metastases from adenocarcinoma of the lung after its intravenous administration.⁵ They attributed this complication to cardiovascular toxicity rather than to toxicity to the central nervous system itself. Our results suggest, however, that the toxicity of recombinant tumour necrosis factor α might prohibit its use in the presence of cerebral metastases, which are particularly prevalent in patients with metastatic malignant melanoma.

We conclude that for the dosage and regimen used recombinant tumour necrosis factor α combined with recombinant interferon gamma has no activity against this tumour and that the complications associated with the tumour necrosis factor are considerable.

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Rational restriction of out of hours requests for haematology tests

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In 1985 we introduced guidelines to restrict the demand for requests for haematological tests outside normal working hours in this district general hospital.¹ The demand for on call tests had reached over 700 a month, and the medical laboratory scientific officers were unable to guarantee an adequate on call service. The introduction of the guidelines led to a fall in demand for such tests, which was partly sustained over a year.¹ We report the results after a further two years.

Methods and results

Guidelines on appropriate tests for different clinical conditions and their availability were issued to all house officers. The availability of a test was stated clearly as yes or no for each clinical condition according to whether we believed that its results would appreciably affect the management of a patient during the period outside normal working hours.

The figure shows the demand for such tests during the four years before and three years after the guidelines were introduced compared with the number of patients treated. The rates of increase were obtained from the slopes of the least square fit regression lines. For the three years after the intervention the rate (5.92 tests/month) was almost the same as that for the preceding four years (6.12 tests/month). The 95% confidence interval for the difference between the slopes was -2.07 to 2.41 . As zero difference is near the middle of this interval there is no evidence that the slopes are different.² Assuming that the existing circumstances

continue, the previously intolerable rate of 700 tests a month will be reached within the year.

The correlation coefficient for the ratio of the numbers of tests to patients treated a month gave an R^2 value of 0.27 before and 0.01 after the intervention. Labour costs fell initially by 28%, but previous values were regained within months.

Numbers of requests for haematology tests outside normal working hours and of inpatients treated each month during four years before and three years after introduction of guidelines to restrict demand for out of hours haematology tests