tamoxifen in advanced breast cancer.[4] Furthermore, physiological doses of progesterone reverse the anti-tumour effects of tamoxifen in the dimethylbenzanthracene-induced rat mammary tumour model.[5] This was the model that was first used to demonstrate the potential efficacy of long-term tamoxifen,[6] before clinical studies were successfully completed in patients with stage I/II disease.

Fornander and colleagues point out, rightly, that the clinical benefit of tamoxifen in controlling breast cancer probably outweighs the increased frequency of endometrial cancer. Furthermore, patients with early endometrial cancer have a good prognosis. In the light of the observation that tamoxifen may encourage the growth of pre-existing endometrial carcinoma, though this is not supported by the Scottish study, the routine introduction of progesterone therapy would seem inappropriate. The possibility that progesterones may blunt the ability of tamoxifen to control breast cancer could confound the whole purpose of adjuvant therapy with this well-tolerated drug.

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WARNING AGAINST USE OF INTRATHECAL MITOXANTRONE

SIR,—Mitoxantrone hydrochloride clears neoplastic cells from cerebrospinal fluid (CSF) after intrathecal administration (1–2 mg once or twice a week) but neurological signs develop in some patients.[1-4] We thus discouraged such use until we had evaluated animal toxicity studies.[5]

Monkeys who were given mitoxantrone hydrochloride 50 μg intrathecally (about 5 μg/ml CSF) weekly for 10 weeks showed significant neurotoxicity: hypoactivity, muscle tremors, and incoordination (paraparesis). Pathologically the neurotoxicity was characterised by superficial vacuolation and demyelination of white matter. Such changes were seen in animals receiving 30 μg or more a week. Doses as low as 12·5 μg weekly caused some neurotoxicity, characterised by degeneration with demyelination of the nerve roots without involvement of white matter or any behavioural manifestation.

12·5 μg in monkeys is equivalent to about 0·125 mg in a patient (based on a CSF volume in man of 100 ml). The findings in monkeys confirmed those described in patients and precluded phase I clinical trials of intrathecal mitoxantrone.

In view of these findings, Lederle Laboratories warn against the intrathecal administration of mitoxantrone.

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SNIFFER DOGS IN THE MELANOMA CLINIC?

SIR,—A 44-year-old woman was referred to our pigmented lesion clinic with a lesion on her left thigh. This was excised and histological examination confirmed malignant melanoma. It was a superficial spreading lesion with a small nodular component, and tumour thickness (Breslow) was 1·86 mm.

The patient first became aware of the lesion because her dog (a cross between a border collie and a doberman) would constantly sniff at it. The dog (a bitch) showed no interest in the other moles on the patient's body but frequently spent several minutes a day sniffing intently at the lesion, even through the patient's trousers. As a consequence the patient became increasingly suspicious. This ritual continued for several months and culminated in the dog trying to bite off the lesion when the patient wore shorts. This prompted the patient to seek further medical advice.

This dog may have saved her owner's life by prompting her to seek treatment when the lesion was still at a thin and curable stage.

Perhaps malignant tumours such as melanoma, with their aberrant protein synthesis, emit unique odours which, though undetectable to man, are easily detected by dogs with their well-developed rhinencephalon. Although dogs frequently smell and lick infected wounds they tend to remain oblivious to their own pigmented lesions, which are almost always benign unless in the oral cavity or subungual region (David Scarf, personal communication). It is unlikely that the dog was merely fascinated by the appearance of the melanoma since she could smell the lesion through the patient's clothing.

We have not as yet proceeded to a trial of sniffer dogs in our melanoma clinic but the adjunctive use of animals with highly developed sensory modalities in cancer diagnosis is worth considering—and is infinitely better than using dogs to study tobacco carcinogenesis.

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IMMUNOSUPPRESSIVE PROPERTIES OF CYCLOSPORIN METABOLITES

SIR,—Cyclosporin is extensively metabolised in the liver. The immunosuppressive properties of the drug's metabolites are a subject of controversy. Although metabolite 17 has not been proved to be immunosuppressive in rats[1] metabolites 1 and 17 both exhibit considerable immunosuppressive activity in vitro.[2] We have found that, in contrast to kidney graft recipients with frequent rejections, those with a low frequency of rejection had high blood trough levels of cyclosporin metabolites 1 and 17.

Of 78 patients who consecutively received a cadaveric kidney transplant in 1 year, 15 did not have graft rejection for at least 8 months after transplantation whereas 6 patients had been treated for two or more rejection episodes. All patients were on cyclosporin and methylprednisolone. The cyclosporin dose was adjusted to yield blood trough levels in the range of 100–150 μg/l ('Sandimmun-Kit' specific radioimmunoassay; Sandoz). On all serum samples a non-specific fluorescence polarisation immunoassay (FPIA) (Abbott, Wiesbaden) cross-reacting with metabolite 1 (14%) and metabolite 17 (120%) was also used.[3] In addition two blood trough levels of cyclosporin and its metabolites were measured by high-performance liquid chromatography (HPLC)[4] at least 8

BLOOD TROUGH LEVELS (μg/l) OF CYCLOSPORIN AND METABOLITES IN KIDNEY GRAFT RECIPIENTS*

—	Non-rejecting	Frequently rejecting	p
HPLC			
Cyclosporin	134 (24)	128 (27)	NS
Metabolite 1	55 (28)	29 (10)	0·002
Metabolite 17	185 (99)	94 (28)	0·004
Immunoassay			
Specific (Sandoz)	125 (45)	118 (35)	NS
Non-specific (Abbott)	442 (167)	324 (107)	0·045

*Results, as mean (SD), analysed by Mann-Whitney U test.