independent variant, the prognosis might be worse than if no tamoxifen had been given.

Another potentially sinister side to tamoxifen prevention is the risk of other cancers. Carcinoma of the endometrium was reported more frequently in the Swedish adjuvant study but not in the Scottish trial [9, 15]. Such malignant change would be consistent with an oestrogen agonist effect. Another theoretical risk of this effect is the development of hepatocellular carcinoma, which has been observed in rats given high dosages of tamoxifen. However, this is unlikely to be a problem in women given the agent [16]. Nevertheless these possibilities underline the need for close monitoring of volunteers taking part in these trials.

A simple study design is needed. Tamoxifen 20 mg daily has few side-effects. Treatment should continue for at least 5 and probably for 10 years. The control group would receive either placebo or be untreated. The foundations for a trial for prevention of breast cancer are now in place. A study of sufficient statistical power will require national and international cooperation and a European initiative would be timely. Recruitment needs to be rapid and extensive so that the momentum can be maintained. If enough centres make a commitment we may know in 5–10 years whether tamoxifen reduces the incidence of breast cancer. To ascertain the effect on mortality may take longer. However there is the intriguing possibility that tamoxifen might decrease mortality from coronary heart disease as well as reducing deaths from breast cancer.

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The Madison Meetings

THE POTENTIAL chemopreventive activity of tamoxifen (inhibition of initiation and growth of DMBA-induced mammary carcinomas) has been known since the mid-seventies [1]. Tamoxifen can reduce the incidence of contralateral primary cancers in patients already operated on for one breast cancer [2]. The issue of the feasibility of a large scale intervention study to verify the effectiveness of anti-oestrogens in preventing breast cancer is being increasingly addressed. Critical aspects are long-term tolerability of the drugs and the identification of the high-risk group of women which could benefit from the intervention.

The results of one pilot study were published in 1989 [3]: tamoxifen was compared to placebo and given to 200 women. Acute toxicity was suggested to be low and accrual and compliance satisfactory. Furthermore, biochemical monitoring of lipids and clotting factors suggested that anti-oestrogens may reduce the risk of cardiovascular disease (CVD). Trevor Powles and his colleagues report that their experience now includes over 400 women, and the findings of the pilot study have been confirmed and extended (p. 680).

To review all available data supporting the hypothesis of breast cancer prevention with tamoxifen, a workshop was held in Madison, Wisconsin, in October 1989 [4]. A second meeting, again in Madison, was held in June 1990, by which time new data had become available from the two-year toxicity study conducted at the University of Wisconsin.

Arguments in favour of breast cancer chemoprevention (perhaps chemosuppression is a better term) are the experimental studies in animals [5]; the reduction of incidence of contralateral tumours in patients treated with tamoxifen as an adjuvant therapy; the potential favourable effect on coronary heart disease and on bone density (prevention of osteoporosis and decreased number of bone fractures).

Major concerns are the risk of liver carcinogenesis (as shown by experimental studies conducted at ICI), uterine carcinogenesis (as suggested by the Stockholm study with 40 mgs of tamoxifen a day) and a series of other possible biological effects, namely increased risk of thrombophlebitis, and symptomatic effects, such as hot flushes and gynaecological symptoms. It has been argued that this 'co-morbidity' should be taken into account when considering cost-effectiveness; moreover it has been argued that tamoxifen could simply delay the onset of the tumour and not actually prevent them.

On the other hand, it has been argued that cancer of the liver is so rare that even if prolonged administration of tamoxifen could double the risk of this cancer, this might be balanced by a suggested potential reduction in ovarian cancer. Finally, it has been stated that prescription of tamoxifen in benign conditions (e.g. mastalgia, fibrocystic disease) has been increasing, and it is now evident that there is an urgent need for a better knowledge of the consequences of prolonged administration of this drug. For the moment, approval has been given to accrue 10–15,000 women into the U.K. national trial and a large clinical trial on hysterectomized women (to avoid the risk of endometrial cancer)

is under discussion in Italy (Milan and Bologna Cancer Centres). Additionally, a very detailed 'vanguard' study is presently under planning at the University of Wisconsin (1500 volunteers, aged 55–69) to address the main issues of long-term tolerability and side-effects of tamoxifen.

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The Conundrum of Kaposi's Sarcoma

INTRODUCTION

KAPOSI'S SARCOMA (KS), first described by the Hungarian pathologist Moritz Kaposi in 1872 [1], is an increasingly challenging puzzle. Is KS a genuine malignancy or a hyperplastic response to angiogenic growth factors? Why is its incidence increasing outside the risk groups for AIDS, as reported from Sweden by Bendsöe and colleagues [2] (p. 699)? Why is it prevalent in homosexuals with AIDS but not in haemophiliacs? Why does the classical pre-AIDS form of KS occur ten times more frequently in men than women? Is there a transmissible KS agent?

CELL BIOLOGY

KS lesions have two main cellular components, endothelial layers and aggregations of spindle cells [3, 4]. It is not clear whether the endothelial cells are of vascular or lymphatic origin, or whether the spindle cells derive from endothelium or smooth muscle. The use of cell markers has been inconclusive [5, 6], though it appears that most KS cells of both types are positive for CD34 antigen, which is characteristic of bone marrow stem cells and vascular endothelium (J.J. Brooks, J. Armes and C. Fisher, pers. comm.). Only recently have KS cells been propagated in long-term culture [5, 6], and these appear to be endothelial [5, 7].

The concept of KS as a malignant tissue of clonal origin has been questioned, with suggestions that early lesions at least are hyperplastic [8, 9]. KS lesions are frequently multicentric, but seldom resemble metastases. Early lesions regress spontaneously or following withdrawal of iatrogenic immunosuppression in organ transplant recipients. Lesions often disappear within days after the onset of chemotherapy. The pattern of KS growth is consistent with a hyperplastic response to local angiogenic growth factors. Nevertheless, a malignant, clonal lineage of cells may exist as a minority cell population in the tumour, but not be apparent morphologically, as Reed–Sternberg cells are in Hodgkin's lymphoma; these cells could have a paracrine angiogenic effect. Alternatively, the lesions may be polyclonal, similar to lymphoblasts in infectious mononucleosis; conceivably, late stage KS lesions may then allow the emergence of a true malignancy as a further step in transformation.

There have been reports of oncogenes in KS detected by DNA transfection [10, 11]. Transfected murine 3T3 cells developed KS-like angiosarcomas following inoculations into mice [10]. Nude mice injected with cultured human KS cells also develop KS-like tumours composed of murine cells [12]. The one oncogene identified in KS is homologous to the *hst* oncogene belonging to the fibroblast growth factor family [11]. However, it was not active in the original KS lesion and may have arisen as an artefact of the DNA preparation.

Growth factors influence the proliferation of KS cells. Some virally transformed cells in culture release angiogenic factors which have a mitogenic effect on KS cells [6]. Of particular interest is the finding that a secreted form of the tat protein of HIV acts as a mitogen on certain KS clones [13]. This observation indicates that HIV may act to promote KS growth by a more direct means than by immunosuppression. Transgenic mice expressing the *tat* gene of HIV developed lesions not dissimilar to KS [14]. The *tat* gene was expressed in dermal or epidermal cells, not in the proliferating endothelial cells, suggesting a paracrine effect. Curiously, only male mice transgenic for *tat* had KS-like nodules [14].