suppressive effects on IGF-I gene expression and serum levels, tamoxifen also has other properties which would be expected to reduce the proliferative and anti-apoptotic actions of IGF-I on breast cancer cells. These include down-regulation of IGF-I receptors on tumour cells [8] and up-regulation of secretion of inhibitory IGF binding proteins [9,10].

While in general tamoxifen acts to suppress IGF-I gene expression, in the uterus tamoxifen increases IGF-I gene expression, an action which correlates with the uterotrophic action of this compound [11]. In contrast, oestrogen receptor ligands that are 'complete blockers', such as ICI 182780, lead to uterine involution and to down-regulation of uterine IGF-I expression. Interestingly, the uterine expression of IGFBP3, an IGF binding protein that attenuates IGF action, is regulated in a reciprocal fashion: it is increased by ICI 182780 and decreased by tamoxifen [12]. Thus, it appears that oestrogen receptor ligands that cause uterine hypertrophy up-regulate expression of IGF-I and down-regulate expression of an inhibitor of IGF bioactivity, while those that cause uterine involution have the opposite effect. It will be of interest to determine the effect of other ER ligands, such as raloxofene, on IGF-I and IGFBP-3 expression in uterus, bone and mammary gland tissues.

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I.5 Does the Human Uterus Agree with Existing Models? Experiences with Insulin-like Growth Factor (IGF)

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The insulin-like growth factor (IGF) system is believed to be an important mediator of oestrogen action and may also be involved in mediating and modulating the actions of anti-oestrogens. In circulation, the majority of IGFs are bound to specific IGF binding proteins (IGFBP-1 to 6), which modulate the biological effects of IGFs. Low plasma IGF-I concentrations have been reported in breast cancer patients during tamoxifen treatment. IGFs are also believed to be involved in the regulation of oestrogen-induced cellular proliferation in the normal endometrium. © **1998 Elsevier Science Ltd. All rights reserved.**

IN ORDER to examine whether or not long-term tamoxifen treatment was associated with any changes in the plasma or endometrial IGF-system and whether or not these changes were associated with tamoxifen-related uterine and endometrial side-effects, the expression of mRNA for IGF-I, IGF-II and IGFBPs 1–6 in the endometrium (dot and Northern blot techniques) and plasma IGF-I, IGFBP-1 and IGFBP-3 concentrations were determined in postmenopausal breast cancer patients with and without tamoxifen treatment.

The most important finding in our study was that the plasma IGFBP-1 concentrations were significantly increased in tamoxifen patients compared to controls. In contrast to previous reports [2], there were no significant differences in the mean plasma concentrations of IGF-I and IGFBP-3 between the groups. The cross-sectional nature of the study may be an explanation on why we did not find significantly decreased IGF-I levels in patients receiving long-term tamoxifen treatment.

We found a significant correlation between the plasma IGF-I concentration and the volume of the uterus in the tamoxifen ($r = 0.34$, $P = 0.037$), but not in the control group ($r = 0.07$, NS). Plasma IGF-I and IGFBP-1 concentrations in the tamoxifen group were significantly higher in women with a proliferative endometrium than in women with an atrophic endometrium.

IGF-I mRNA was detectable in all endometrial samples of the postmenopausal breast cancer patients with no significant quantitative difference between the tamoxifen-treated and the control patients. IGF-II mRNA expression was not detected in the endometrium. Of the 6 IGFBPs, the mRNA of IGFBP-2, -3, 4 and -6 were detected in all endometrial specimens. In contrast, IGFBP-1 mRNA was not detected in any of the samples. The expression of IGFBP-2 and -4 mRNA predominated in the endometrium of the tamoxifen-treated patients. A statistically significant difference was found between the tamoxifen-treated and the control patients in IGFBP-2 detection. The highest levels of IGFBP-2 and -3 mRNA expression were detected in a tamoxifen-treated patient with grade 1 endometrial adenocarcinoma. The biological significance of this difference between tamoxifen-treated and control patients remains unknown.

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I.6 Tamoxifen Metabolism and Activation: the Reason for Interspecies Differences

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Tamoxifen induces liver tumours in rats by a genotoxic mechanism. Activation to DNA binding products involves, firstly, cytochrome P450-mediated hydroxylation at the α-ethyl position. This occurs in both rats and humans. α-Hydroxytamoxifen is then further metabolised to a sulphate ester in rat hepatocytes by hydroxysteroid sulphotransferase (hST). This activation occurs in bacterial and mammalian cells expressing rat hST, but not in cells expressing human hST. It is proposed that the activation pathway in rats does not occur to a significant extent in humans and thus may not account for the increase in endometrial cancer among women taking tamoxifen.

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