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PRIMARY HORMONAL TREATMENT OF BREAST CANCER IN ELDERLY WOMEN

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Elderly women with primary breast cancer are most often treated by a mastectomy or wide excision of the lump. Tamoxifen has been shown to inhibit tumour growth in elderly women with advanced or metastatic disease. We have undertaken a pilot study to evaluate this type of treatment in primary operable breast disease. Tamoxifen (10mg four times daily) was administrated from 1976 until 1981 to 56 women over 70 years of age and presenting a breast cancer confirmed by needle biopsy. In 26 patients (46.4%) a definitive improvement was observed after 3-6 months therapy by a significant reduction of the perpendicular diameters of the tumoral opacity (more than 50% of the summed lenghts).
In 17 cases (30.4%) we objectivated a stabilization of the tumoral opacity and 13 failures (23.2%) were recorded.
Among the 26 patients who responded favourably to the endocrine therapy, 5 women died with metastasis after three years.
In the 17 patients who were initially stabilized, 3 deaths occurred through metastasis and 6 patients were lost from view.
Among the 13 women who failed to respond to endocrine therapy, 3 deaths occurred with generalized disseminated lesions and 5 were lost from view.
These studies suggest that the survival in patients with endocrine resistant breast cancer whether the resistance is immediatly obvious or not is considerably shortened.
The time of onset of the resistance appears to be unimportant.

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The Effect of Tamoxifen on Normal and Malignant Colon Cells

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Classically, the antitumor activity of tamoxifen (TAM) is thought to be due to competition with estrogen for binding to the estrogen receptor (ER). However, tissues also contain specific high affinity antiestrogen binding sites for TAM (AEBS) distinct from the ER (Nature 288:273, 1980). TAM is also an antagonist for calmodulin (BBRC 118:27, 1984) and histamine (BBRC 131:750, 1985). To investigate possible mechanisms of antitumor action, we analyzed TAM binding and growth effects on normal and malignant colonic epithelium. Specific binding to microsomal (MF) and cytosolic (CF) fractions of colonic tissues from surgical specimens was determined by Scatchard analysis. TAM binding was lower in CF (71 ± 57 fmol/mg) than MF (342 ± 103 fmol/mg). The Kd (5×10^{-9} M) was identical in normal and malignant colon tissue. Estradiol (0.1 μM) did not inhibit TAM binding. The growth effects were determined by addition of TAM (0.8 to 10 μM) to cultured normal human colon epithelium and colon adenocarcinoma cells (LoVo). TAM produced a dose response decrease in growth of normal and malignant cells (20 to 90%). Estradiol (1 to 10 μM) also produced growth inhibition (40% maximum). Histamine (1 to 10 μM) did not affect cell growth and did not negate the TAM effect. Calmodulin (2 μg/ml) totally blocked the growth inhibitory effects of a calmodulin antagonist, trifluoperazine (10 μM), but did not block the TAM inhibitory effect. These data suggest that AEBS may play an important role in the growth inhibitory effects of TAM on colon cells. Competition with estrogen and antagonism with histamine or calmodulin do not appear to be significant in this regard.

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THE SYNTHESIS OF SOME SULPHUR-CONTAINING TAMOXIFEN ANALOGUES

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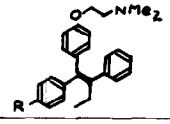
Tamoxifen (1) is the antioestrogen drug most widely used in the treatment of hormone-responsive breast tumours. It has two principal problems: (a) a low affinity for the oestrogen receptor (ER) and (b) the development of drug resistance during prolonged treatment. There is thus a need for the creation of second generation antioestrogens.

The metabolic hydroxylation of tamoxifen *in vivo* gives 4-hydroxytamoxifen (2). This product has a very high affinity for ER *in vitro* although it is not an effective drug *in vivo*, where there is rapid glucuronidation and excretion.

Our research programme involves a study of compounds which are designed to resist metabolic hydroxylation at position-4 whilst capitalising on the enhanced affinity for ER which is associated with it. We shall describe syntheses of a range of tamoxifens bearing a sulphur substituent at position-4, including 4-methylthiotamoxifen (3). Details of separation of *(E)*- and *(Z)*-isomers will be given. Biological data on the binding of some sulphur-containing tamoxifen analogues in cytosol and whole-cell assays will be given.



(1) R = H,
(2) R = OH,
(3) R = SCH_3.

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PROSTATIC TUMOR INHIBITING ANTIESTROGENS

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The use of antiestrogens from the phenylindole-, stilbene- and triphenylethene-series for the treatment of the prostatic carcinoma (PC) was studied. Compounds were tested for their affinities to androgen-, estrogen- and progesterone-receptors, their antiandrogenic effect in intact and castrated mice and rats, and their antitumor effect on the rat R 3327-PC and the human PC 82 in nude mice. Most of the compounds had good affinities to the estrogen receptor from calf uterine and R 3327-PC-cytosol, but not to androgen or progesterone receptors. Their antiandrogenic effect in intact rats and mice was strong and even comparable to that of DES. In the case of the phenylindoles, this antiandrogenic effect is not directly associated to the estrogenic activity, as these antiestrogens have more than 100 times lower uterotrophic potencies than DES. In the rat, none of our compounds had direct antiandrogenic properties. In the mouse, however, the phenylindoles exerted a significant antagonistic effect. All of the antiestrogens tested had a strong antitumor activity on established R 3327-tumors, which was comparable to or even slightly better than that of DES or castration. One of the phenylindoles was also tested in the PC82-tumor model. Its tumor inhibiting activity was identical to that of castration. Therefore, these antiestrogens may be of great interest for the therapy of the prostatic carcinoma because of their much lower side effects compared to those of DES.