6. OESTROGEN ANTAGONISTS

61. COMPARISON OF THE EFFECTS OF TAMOXIFEN, TRIOXIFENE AND LY 117018 ON THE GROWTH OF DMBA-INDUCED RAT MAMMARY CARCINOMA. Wakeling, A. E. and Valcaccia, B. Bioscience Department, Imperial Chemical Industries PLC, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England.

Groups of rats with established DMBA-induced mammary tumours (11-18 tumours/group) were treated orally, once daily with increasing doses of tamoxifen, trioxifene (0.25, 1.0, 2.5mg/kg) or LY 117018 (1.0, 2.5, 10.0mg/kg) for 28 days. The area of each tumour was measured at the start of the study and at weekly intervals thereafter. Animals were ovariectomised 2 weeks after the final drug dose and tumours which regressed to less than 50% of their original size were classified as hormone dependent. Total tumour areas after 28 days (percent of initial area) were control 218, tamoxifen 128, 66, 100 (0.25, 1.0, 2.5mg/kg groups respectively), trioxifene 120, 142, 187 (0.25, 1.0, 2.5mg/kg) and LY 117018 136, 124, 150 (1.0, 2.5, 10mg/kg). Considering only those hormone-dependent tumours originally present the percentages were control 131, tamoxifen 95, 50, 68, trioxifene 87, 89, 168, LY 117018 84, 104, 140. Clinical responses were compared as CR+PR+NC (complete, partial remission > 50% or no change, < 25% increase) versus PD (progressive disease > 25% increase) after 28d treatment. For tamoxifen (CR+PR+NC/PD) responses were 10/2, 11/1 and 15/0 for 0.25, 1.0 and 2.5mg/kg groups respectively; for trioxifene 7/5, 10/3, 8/10 (0.25, 1.0, 2.5mg/kg) and for LY 117018 9/4, 8/3, 5/7 (1.0, 2.5, 10.0mg/kg). These data clearly indicate that of the three compounds tamoxifen is the most potent and efficacious antioestrogen.

62. HORMONAL POTENTIALITIES OF FEMALE GONADS IN TAMOXIFEN-TREATED QUAIL EMBRYOS. Guichard,* A. and Scheib,** D. - *U. 166 INSERM, Maternité Port-Royal, 75014 PARIS **Institut d'Embryologie, CNRS, 94130 Nogent S/Marne (France)

The embryonic development of the female gonads can be disturbed by early treatment of the quail eggs with an anti-estrogen, tamoxifen (Tam). In the left ovary, proliferation of the germinal epithelium into a cortex is markedly inhibited, while on both sides, the medulla becomes more developed and keeps a cordonal organization. The effects of Tam on the hormonal potentialities of 15 day female gonads have been investigated by radioimmunoassay of their steroid contents which have been compared with those of control gonads.

The results indicate that Tam does not depress the hormonal levels in the treated gonads : their estradiol (E_2) content is increased while that of testosterone (T) is less modified ; consequently, the E_2/T ratio is higher in the treated gonads than in controls. These results corroborate electron microscopical observations showing in the medulla the presence of active steroidogenic cells, confined inside solid cords. Thus, it appears that the drug preventing estrogen effects on target receptors, inhibits the cortical development and not the female secreting tissue. Tamoxifen exerts opposite effects to those produced by diethylstilbestrol, at both cytological and steroidogenic levels.

63. IRREVERSIBLE AND PHOTOAFFINITY INHIBITORS OF AROMATASE. C. E. Snider, J. G. Kimball, and R. W. Brueggemeier, College of Pharmacy and the OSU Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio 43210, USA.

Several 7α-substituted androstenediones are potent competitive inhibitors of the biosynthesis of estrogens, with the most effective being 7α-(4'-amino)phenylthioandrost-4-ene-3,17-dione. Derivatives of this 7α-thioether compound have been prepared as potential irreversible inhibitors and examined for their abilities to inactivate microsomal aromatase from human term placenta. Three alkylating compounds produced time-dependent losses of enzymatic activity at varying rates. The inactivation kinetics were initially psuedo-first order, but began to plateau at later time periods. Modifications of buffer and pH conditions minimized this phenomenon, indicating that nonenzymatic hydrolysis of the alkylating inhibitors was occurring. Addition of substrate androstenedione to the incubations provided protection of the enzyme complex. The enzyme kinetics of a photoaffinity inhibitor, the azide analog, were examined under both dark conditions and uv-irradiation. In the dark, the azide was a very potent competitive inhibitor, with an apparent K_i of 1.3 nM. Under uv-irradiation, a time-dependent loss of activity was also observed. These studies indicate that the 7α-substituted compounds are interacting at a secondary binding site to greatly enhance the affinity of the enzyme for the synthetic inhibitors. This work is supported by HD 15014 from NIH.