

3. Studies of Cancer in Experimental Animals

Oestrogen plus progestogen hormonal therapy is usually given in the form of conjugated oestrogens (Premarin®; for oestrogen composition, see the monograph on 'Post-menopausal oestrogen therapy', Table 2) plus medroxyprogesterone acetate or cyproterone

acetate. Studies of the carcinogenicity of conjugated oestrogens in experimental animals are described in the monograph on 'Post-menopausal oestrogen therapy', those on medroxyprogesterone acetate and implanted levonorgestrel are described in the monograph on 'Hormonal contraceptives, progestogens only', and those on cyproterone acetate and the 19-nortestosterone derivatives norethisterone, norethisterone acetate and lynoestrenol are summarized in the monograph on 'Oral contraceptives, combined'. No studies on micro-nized progesterone were available. For studies on progesterone, see IARC (1979).

Female Sprague-Dawley rats, 48 days of age, were given a single intravenous injection of 5 mg 7,12-dimethylbenz[*a*]anthracene (DMBA), separated into four groups of seven rats per group and given DMBA only, DMBA plus oophorectomy, DMBA plus oophorectomy plus Premarin® at a concentration of 1.875 mg/kg of diet or DMBA plus oophorectomy plus Premarin® plus medroxyprogesterone acetate at a concentration of 7.5 mg/kg of diet. The animals were observed for 285 days, at which time body and organ weights, tumour incidence, the plasma concentrations of prolactin, oestradiol and progesterone and bone density were determined in all rats. In two rats per group, the numbers of S-phase cells in mammary tumours were assessed by immunohistochemistry, after injection with bromodeoxyuridine (BdUr) 6 h before killing. Mammary tumours were found in 6/7 rats given DMBA, 0/7 given DMBA plus oophorectomy, 5/7 given DMBA plus oophorectomy plus Premarin® and 5/7 given the preceding treatment plus medroxyprogesterone acetate. The percentages of cells in S phase were (mean \pm standard error) 7 ± 0.5 in tumours from rats given DMBA, 5.5 ± 0.8 in those from oophorectomized rats given DMBA plus Premarin® and 3.1 ± 0.5 in those from oophorectomized rats given DMBA, Premarin® and medroxyprogesterone acetate, the last value being significantly different from the percentage with DMBA alone ($p < 0.01$). Thus, oophorectomy completely inhibited mammary tumour development, and medroxyprogesterone acetate significantly decreased the percentage of S-phase cells in the tumours [number of tumours/rat not specified] (Sakamoto *et al.*, 1997).