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INTERACTION WITH THE ANDROGEN RECEPTOR AND ANTI-ANDROGEN ACTIVITY OF ANANDRON IN THE PROSTATE OF DIFFERENT SPECIES.

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The relative binding affinity (RBA) of the pure non steroidal antiandrogen Anandron (RU 23908) for the androgen receptor was measured in the prostate of different species. After 2h incubation at 0°C of cytosols prepared from the prostate of rat, hamster, dog and human (BPH) with (3H) testosterone or (3H) RU 1881, the RBAs of Anandron were respectively equal to 1.4 $\pm$ 0.3 (n = 10), 10 $\pm$ 1(n = 2), 24 $\pm$ 5 (n = 5) and 9 $\pm$ 3 (n = 4). The higher affinity for the androgen receptor of hamster and dog prostate than for that of rat prostate, was related to a 5-8 times greater anti-androgen potency of Anandron in the first two species than in rat as measured by the inhibition of the trophic effect of testosterone propionate on the prostate of castrated animals. The difference was even more marked in intact animals (against endogenous androgens). Although RBA values were somewhat different from on human sample to the next, we can speculate that the active antiandrogen dose of Anandron might be lower in man than in the rat.

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ANANDRON POTENTIATES THE CASTRATING EFFECT OF THE LHRH ANALOG BUSERELIN IN THE RAT.

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When buserelin (0.04-25µg/kg/day) was given s.c.daily for 15 days to male rats, prostate weight decreased but never as much as after orchidectomy since testosterone secretion was never totally suppressed. The castrating effect of buserelin was exerted directly in the testes (in contrast to man) since LH concentration was unchanged, while testes weight as well as testosterone secretion were decreased. The combination of the pure nonsteroid antiandrogen Anandron (20 mg/kg/day) with even low doses of buserelin led to a complete decrease in prostate weight. This could be explained by: 1) additivity of effects: inhibition by Anandron of the action of residual testosterone unsuppressed by buserelin on the prostate and prevention by buserelin of the rebound testosterone increase induced by Anandron; 2) potentiation by Anandron of the direct castrating effect of buserelin on the testis since testis weight and testosterone secretion were lowered more by the combination than by buserelin alone. Anandron might increase the sensitivity of LHRH receptors to LHRH analog in the testes, as has been shown in the pituitary. In contrast, the combination of the antiandrogenic steroid progestin cyproterone acetate with buserelin on testis weight and testosterone and only partially potentiated prostate atrophy. If such actions also exist in the human, addition of Anandron to LHRH analog treatment would not only counter flare-up and adrenal androgen effects on the prostate, but also lower the peptide doses required for chemical castration.

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CANCER OF THE PROSTATE - IS THERE A NEED FOR AGGRESSIVE TREATMENT?

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Adenocarcinoma of the protate constitutes 18% of all cancers in men, and is a major cause of neoplastic death second only to carcinoma of lungs and large bowel. In spite of the high incidence of the disease, there is still disagreement as to the right treatment. We reviewed 101 patients in stages T_{0_b}, T_1+T_2, T_3 (NoMo) who were treated by non radical prostatectomy and no other treatment. The follow-up of these patients was 58 months. The actuarial five and ten years survival according to stage was: 91.30% and 64.62% respectively in stage T_{0_b}; 60.61% and 34.11% in stage T_1+T_2 and 41.67% in Stage T_3. Survival rates resembled those quoted in the literature. Our results justify a less aggressive approach to carcinoma of the prostate.

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ORCHIECTOMY ASSOCIATED WITH ANANDRON (RU23.908) OR PLACEBO IN TREATMENT OF STAGE D PROSTATE CANCER: PRELIMINARY RESULTS OF A RANDOMIZED, DOUBLE-BLIND FRENCH COOPERATIVE STUDY

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To determine the value of total androgen blockade, a comparative randomized double-blind study was conducted on stage C & D prostate cancer pts who had received no previous hormone therapy. From May 84-March 87, 140 pts were randomized between 2 arms: 300 mg Anandron or a placebo. This interim report covers 67 pts with stage D disease (29 orchiectomy + Anandron; 38 orchiectomy + placebo); both groups were similar for age, bone pain, performance status, hemoglobin. Although Anandron group pts experienced more side effects, treatment never had to be discontinued. Subjective results have not been improved by the combined treatment. The best objective response rates using NPCP criteria were seen in 49% of pts treated by castration only and in 64% of castration + Anandron arm. The actuarial progression-free rate at 6 and 12 mo. is higher with Anandron (p=0.06). The median of the distribution was increased by 3 mo. The actuarial survival rate is increased at 6 and 18 mo. The median distribution was reached by 15 mo. in the placebo group but has not been reached in the Anandron group. These interim results seem to confirm that total androgen blockade improves response, progression-free and survival rates in stage D prostate cancer.