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KETOCONAZOLE IN THE TREATMENT OF PROSTATIC CANCER.
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Ketoconazole, an imidazole derivative, is an orally active antifungal agent. It inhibits in high dose (KHD) the biosynthesis of testicular and adrenal androgens. The therapeutic and endocrine effects of KHD were evaluated in 30 patients with disseminated prostatic cancer. The first seven patients were untreated and medical castration with the expected clinical response was easily achieved. However interference with cortisol biosynthesis prompted us to evaluate adrenal steroidogenesis. This evaluation was performed in another seven patients in relapse after bilateral orchidectomy. These patients received 400 mg KHD q 8 hrs for 28 days. Three challenges of 0.5 mg ACTH IV were given on days 0, 14 and 28. Dexamethasone 0.5 mg bid was added from day 14 till day 28. The basal plasma levels of the androgens (testosterone, androstenedione and dehydroepiandrosterone) were lowered by half and their stimulation was almost completely inhibited. Basal cortisol and aldosterone were not affected but KHD therapy blunted their response to ACTH challenge. Basal and stimulated plasma 11-deoxycortisol, 11-deoxycorticosterone and plasma corticosterone were increased by the treatment. The 17 α hydroxyprogesterone and progesterone were 2 to 5 fold increased.
All other patients received KHD treatment 200-400 mg q 8 hrs for symptomatic disease. No objective remissions were recorded. Subjective remissions, especially pain relief, were obtained in 40% of patients. Gastric discomfort was a common side effect. Generalized bone pain in relapsed patients remains an indication under close monitoring. Newer and more specific imidazole molecules are awaited for clinical trials.

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ADRENAL ANDROGEN ABLATION IN THE TREATMENT OF PROSTATE CANCER
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To assess the value of both testicular and adrenal androgen suppression in the treatment of patients with advanced prostatic cancer, two studies have been undertaken. Fifty patients with untreated symptomatic metastatic or locally advanced prostate cancer were randomised to receive either orchidectomy (O), O plus Ketoconazole (K), O plus Dexamethazone (D), or O plus Cyproterone acetate (C). The median follow-up is 12.4 months. Thirty patients previously treated with endocrine therapy who had relapsed and were symptomatic received in addition to their previous therapy, either K or D. Regular endocrine assessments throughout follow-up of the previously untreated patients showed no significant difference in serum testosterone or dihydrotestosterone, but marked additional suppression of the adrenal androgen androstenedione in the groups treated by O plus D and O plus K. Progesterone was significantly increased in O plus K and decreased in O plus D patients. Cortisol was significantly decreased in O plus D patients and LH increased in O, O plus K and O plus D. Significant side effects in the O plus K group lead to poor patient compliance and abandonment of this limb of the study. No significant difference in response has been seen in any of the 4 treatment groups. In the previously treated group, further falls in the already castrate range of testosterone and dihydrotestosterone and androstenedione were seen. Objective responses were found in 25% of patients, and in some, prolongation of survival. No parameter has been identified to indicate those who will respond. Additional adrenal androgen depletion did not appear to have any added benefit in new patients and has only limited value in those with hormone unresponsive 'disease'.

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SYNERGISTIC HORMONAL COMBINATIONS IN THE TREATMENT OF ADVANCED PROSTATIC CANCER
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Withdrawal of testicular androgens leads to active, receptor-mediated lysis of prostatic cells, termed "autophagia". The intracellular effects of surgical castration in the rat model include a fall in tissue and nuclear dihydrotestosterone levels and the discharge of nuclear androgen receptor into the cytoplasm. We studied the ability of cyproterone acetate (CA), diethylstilbestrol (DES), CA plus DES, megestrol acetate (MA) plus DES, and LHRH agonists plus RU23908 to mimick these effects. CA and MA acted synergistically with a "mini-dose" of DES to produce changes virtually identical to those caused by orchiectomy. On this basis, a combined therapy of CA (200 mg daily) and DES (0.1 mg daily) was used in 47 previously untreated, symptomatic Stage D2 prostate cancer patients. Serum testosterone levels were reduced to 67%, 19% and 18% of the initial value after 1,7 and 28 days of treatment, respectively. Castrate levels of testosterone were achieved in 65% of patients by 7 days and 92% by 28 days; the mean time was 17 days. On the basis of NPCP criteria, the initial objective response rate was 98%. Significant features of response were quick relief from pain, lack of major side effects and clinical resolution of soft tissue disease even in the face of progressive skeletal metastases. After 18 and 24 months of therapy, 67% and 35% of patients were alive while 43% and 37% of survivors were free of disease progression (Kaplan-Meier). We conclude that the combination of CA and mini-dose DES acts promptly and synergistically to effect both a medical castration and a peripheral androgen blockade with a high probability of gaining benefit in terms of symptomatic improvement.

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RESULTS OF A DOUBLE-BLIND MULTICENTRIC CLINICAL TRIAL OF THE COMBINATION 'CASTRATION PLUS ANANDRON (R)'.
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It has been postulated on the basis of animal experiments that the administration of a pure non-steroidal antiandrogen would benefit advanced prostate cancer patients undergoing surgical castration (CX) because the antiandrogen would block the action of unsuppressed adrenal androgens on the prostate. The results of open clinical trials have supported this hypothesis We present the first results of a double-blind controlled clinical trial with the non-steroidal antiandrogen Anandron (R) (Roussel Uclaf) showing a statistically significant improvement in previously untreated patients with stage D2 prostate cancer. Patients were orchiectomized and received orally either placebo (n=32), 150mg (n=36) or 300mg (n=30) Anandron (R) daily. Follow-up ranged from 6 to 24 mths (median=15). At 6 mths, more patients in the active drug groups had improved bone pain ($p<0.10$), performance status ($p<0.05$) and normalized PAP. The percentage of patients with objective tumor regression (NPCP criteria) at 6 or 12 mths was significantly higher ($p<0.05$) in the Anandron treated groups (52 and 58%:placebo=25%), but it is premature to draw conclusions on time to progression and survival (longer follow-up will be available at the symposium). Side-effects rarely led to discontinuation of treatment. Biological parameters were within normal limits Assay of plasma hormones showed that testosterone was drastically decreased, that cortisol was unaffected, but that adrenal androgens were reduced. In conclusion, according to results in 98 patients evaluable at 6 mths or more, Anandron (R) brings about an objective improvement in the response to CX by opposing the action of a slightly reduced levels of adrenal androgens on the prostate.