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MELATONIN AND HUMAN CANCER.
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A number of experimental studies supported the view that pineal gland affects neoplastic growth. Data in humans are scanty and controversial. On this ground we have planned some systematic studies in human cancer patients (pts) aimed to evaluate: 1) the clinical significance of serum melatonin (MT) evaluation at 08.00 a.m. and 12.00 p.m. in pts at different stages of disease; 2) the possible variation of MT secretion before and after surgical removal of the primary tumor; 3) the circadian rhythm of serum MT concentration in neoplastic and in control subjects. Regarding point 1, serum MT has been evaluated (RIA kit, Eurodiagnostics, Apeldoorn, Holland) concomitantly with PRL and GH in 148 pts: 35 stage I-II and 50 stage IV breast cancer (BC); 37 stage III-IV lung cancer (14 SCLC, 25 NSCLC); 26 others advanced tumors and in 55 healthy controls. On the whole, pts with advanced tumors showed serum MT levels significantly higher than controls, without any correlation with PRL and GH values. When looking at stage IV vs I-II BC pts, significantly higher MT levels have been found in the former group. An inverse correlation between MT values and Performance Status was apparent. No significant differences in serum MT values have been found in 16 BC pts evaluated 2 days before and 15 days after mastectomy. The presence of a significant circadian rhythm of serum MT, evaluated over a 24 hs span with blood sampling every 4 hs, was confirmed by Cosinor validation with an acrophase at 03.00 a.m. Both controls (15) and patients (15) showed a similar behaviour.
The ultimate significance of altered serum MT concentrations in cancer pts remains to be elucidated.

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ZOLADEX PLUS TAMOXIFEN VERSUS ZOLADEX ALONE IN PREMENOPAUSAL METASTATIC BREAST CANCER.
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In premenopausal women with advanced breast cancer LH-RH agonist (Zoladex/goserelin; 3.6mg depot/28 days) therapy produces serum levels of oestradiol equivalent to those following surgical oophorectomy and promotes objective tumour remissions (CR, PR, S) in approximately 45% of unselected patients. Addition of the antioestrogen tamoxifen (20mg bd) to this regime produces a further small decline in oestradiol levels and induces tumour remissions in 48% of patients. In each instance response to therapy is associated with a survival benefit to the patient, with possibly a lengthening of the time to progression being observed in women receiving the combination of treatments. Application of a series of immunohistochemical markers of hormone and growth factor pathways to the tumour specimens indicates that patients with ER negative tumours which express the EGF-R and which show high rates of cell proliferation do not respond to LH-RH agonist therapy. These data will be discussed in relation to (1) the appropriateness of combining medical castration and antioestrogen therapy and (2) the effective use of these treatments in primary and advanced breast cancer.

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HORMONAL TREATMENT OF ENDOMETRIAL CARCINOMA: AN OVERVIEW AND NEW DEVELOPMENT IN BIOLOGY
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Progestins are routinely used in the treatment of endometrial carcinomas with about 30 percent response rate. After a 10 to 12 month mean response time, the tumors begin to regrow. This clinical situation has been reproduced in the experimental model for human endometrial carcinomas, developed by us. The model consists of growth and maintenance of human endometrial carcinomas of different histologic grade and sex steroid receptor content, in defined hormonal milieu, by serial transplantation in athymic nude mice. Biologically and clinically relevant information on the role of steroid receptors in eliciting hormonal responses, the effect of combination treatment with tamoxifen and progestin and the mechanism of resistance to this treatment after an initial response have been obtained. These studies form the basis for designing and testing rational treatment strategies for human endometrial carcinomas.

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LHRH RECEPTORS AND LHRH AGONIST TREATMENT IN OVARIAN CANCER: AN OVERVIEW
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Considerable evidence exists that ovarian cancer might be gonadotropin dependent. Receptors for LH and FSH have been discovered in these tumors. Proliferation of ovarian cancer cells in vitro could be stimulated by gondotropins. Withdrawal of LH and FSH in animal models of ovarian cancer inhibited growth of these tumors. Phase-II clinical studies have shown that suppression of endogenous gonadotropins by LHRH-agonists can be beneficial in women with advanced ovarian cancer. Respective controlled clinical trials are performed at present. Also direct effects of LHRH analogues on ovarian tumors have been reported. An LHRH like protein was found in human ovarian tissue. We discovered a specific LHRH binding site (Mol. W. 63.2 KDa) in ovarian cancer tissue which is very similar to other human extrapituitary LHRH binding sites, of the low affinity, high capacity typ, e.g. in breast cancer and the placenta. In the latter tissues, LHRH or a related substance has been proposed as an autocrine regulator of cellular function. If this was also the case in ovarian cancer, direct effects of LHRH analogues on the tumor cells could be used as additional therapeutical point of attack.