22 cases of human breast cancer. Of 17 patients in whom the tumour was receptor positive, 11 received endocrine treatment (ovariectomy alone, or ovariectomy associated with tamoxifen in 7 premenopausal women, and tamoxifen only in 4 postmenopausal women). Two patients with a receptor positive and 1 with a receptor negative tumour, all of whom received endocrine treatment, died from carcinomatous disease 1-3 years after radical mastectomy, and one with a receptor positive tumour died from senility. 13 patients (11 with a receptor positive and 2 with a receptor negative tumour) are still alive 2-5 years and 5 almost 1 year, after mastectomy. Thus only 2 out of 17 patients with receptor positive cancer and one out of the 3 patients with receptor negative cancer died 1-3 years after mastectomy.

The retrospective study of 24 women with breast cancer who were treated by radical mastectomy, and also ovariectomy in five women presenting with lymphnode metastases or of child bearing age, revealed that 4 patients, of whom 1 was ovariectomized, died from carcinomatous disease 2-3 years, and one (ovariectomized) from cardiovascular accident 2 years after radical mastectomy. Seven of the remaining 19 patients (1 ovariectomized) are still alive after more than 6 years, 10 (2 ovariectomized) after more than 2 years and 2 almost one year after surgery.

From a comparison of the two groups it becomes clear that the high survival rate in the latter group of patients is presumably due to the presence of a hormone dependent tumour. Whilst receptor studies may be employed in determining the choice of treatment their main usefulness is to be found in evaluating the prognosis.

8. Endocrine treatment of breast cancer,
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9. Suppression of corpus luteum function by D-Leu^{6}(des-Gly-NH$_2$ ^{10},Proethylamide^{9})GnRH in premenopausal women with breast cancer,
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Mastectomy, radiotherapy, adjuvant chemotherapy and ovariectomy are employed in conjunction for the treatment of premenopausal breast cancer. In an effort to suppress ovarian function we administered an analogue of GnRH, which in the experimental animal induces down regulation, to three such patients. 10 µg were injected daily for 8 days beginning on the 7th, 8th or 9th day of the cycle. Serum FSH, LH, estradiol, progesterone and prolactin (PRL) were measured daily prior to injection. In addition on days 1, 2, 5 and 8 blood was collected continuously for 12 h to assess pituitary FSH and LH secretory release patterns. The acute increments in LH and FSH were 8- to 16-fold and 5- to 9-fold, respectively, during the first day; the increments however during days 5 and 8 were decreased by 50 %. No change in basal FSH, LH and PRL levels was recorded throughout the sampling period of 8 days; the values of LH and FSH remained within the range for the follicular phase. Plasma estradiol in 2 out of 3 increased to midcycle levels by the 5th postinjection day but was not followed by a midcycle LH surge nor by a rise in serum progesterone which remained at follicular levels. In all three patients vaginal bleeding occurred 4-6 days earlier than expected thus shorting the luteal phase in one cycle and causing anovulation in two cycles. Normal length cycles were recorded in the subsequent months.

The above data indicate that repetitive administration of this GnRH analogue can effectively suppress corpus luteum formation and/or function in premenopausal women with breast cancer and may thus be used in the future as an adjuvant for the treatment of this disease or as an ovulation inhibitor. The reestablishment of regular cycles upon discontinuation of this peptide indicates the reversibility of the above effect on ovulation and underscores the potential of this agent as a contraceptive.

PROSTATE CANCER

10. Carcinoma of the prostate: endocrine aspects of aetiology,
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The evidence for an endocrine (androgen/oestrogen) role in the aetiology of carcinoma of the prostate will be examined from 3 groups of data.

1. Epidemiological data: Necropsy studies have shown that patients with cirrhosis of the liver have less prostatic cancer than controls. Anthropometric studies have shown no characteristic differences from controls but patients with cancer of the prostate tend to have more body hair and to be less obese. The differences in the incidence between negroes in Africa and USA have been ascribed to genetic differences. Sexual activity, marital status, circumcision and the number of children have been studied in respect of the incidence of carcinoma of the prostate and the findings will be reviewed. The data concerning the relationship between benign prostatic hypertrophy and prostatic cancer will be examined.

2. Plasma measurements: Sex hormone changes with age have shown that there is a decrease in testosterone, dihydrotestosterone (DHT), androsterone and dehydroepiandrosterone; there is a marked increase in oestradiol and SHBG, LH and FSH also increase with age.

In attempting to define sex hormone differences between normal controls, benign prostatic hypertrophy and carcinoma of the prostate, differing results have been reported but most series have shown no differences for

testosterone, DHT, androstanediols, prolactin, LH and FSH.

The reported changes in plasma hormone levels before and after prostatectomy will be discussed.

3. Prostatic tissue measurements: The levels of testosterone and DHT in normal, benign and malignant tissue will be reviewed. The levels of zinc in prostatic diseases and the relationship of zinc to hormone uptake by the tissues is examined.

11. Plasma testosterone (T), dihydrotestosterone (DHT), androstenedione (A), free testosterone fraction (FTF) and sex hormone binding globulin capacity (SHBG) in prostatic adenocarcinoma, F. SCIARRA, C. PIRO, V. TOSCANO, E. PETRANGELI, S. CAIOLA, F. DI SILVERIO[1], U. BRACCI and C. CONTI, Istituto di Clinica Medica Generale V, Università di Roma, [1]Clinica Urologica, Università di Chieti, Italy

T, DHT, A, FTF and SHBG in patients with prostatic adenocarcinoma and aged 52 to 65 years were within the normal range for subjects of that age. After orchidectomy a dramatic fall in T (16 ng ± 1.6 SD/dl), DHT (5.4 ng ± 0.8/dl) and FTF (0.8 ± 0.1%) was observed, whilst SHBG increased ($8.8 \pm 1.4 \times 10^{-8}$ M) and A showed no significant modification (160 ng ± 80/dl). After 200 mg/day cyproterone acetate (CPA) without orchidectomy the decrease in plasma androgens was less significant (T = 148 ng ± 73/dl; DHT = 17 ng ± 6/dl; FTF = 1.54 ± 0.26%), whilst A was not modified (160 ± 70/dl) and SHBG showed a slight increase ($7.3 \pm 0.9 \times 10^{-8}$M). All these parameters were evaluated every day for 5-12 days immediately after orchidectomy or CPA treatment, and restudied after 2-3 months. The effect of orchidectomy in association with CPA was also studied. As CPA has an inhibitory action on target tissue, its administration in prostatic carcinoma may potentiate the effects of castration.

12. Hormone receptors in prostatic tissue, N. BRUCHOVSKY and P.S. RENNIE, Department of Cancer Endocrinology, Cancer Control Agency of British Columbia, Vancouver, Canada, V5Z 3J3

The success of the estrogen receptor test in predicting the hormonal status of breast cancer has fostered mounting interest in the potential use of androgen receptors in the medical and surgical management of prostatic cancer. In breast cancer, patient selection with the estrogen receptor test increases response rates from 15-35% to 60% or slightly higher. Since the response rate in unselected patients with prostatic cancer is already 60-80%, the impact of a receptor test on this predetermined high rate is unlikely to be very important. Nevertheless, it remains possible that the receptor test might be useful in identifying the small percentage of nonresponders in the group of patients with untreated metastatic disease, and, furthermore, it might be applied to the selection of the minority of patients who will benefit from endocrine therapy of reactivated disease.

Unfortunately, the measurement of the concentration of androgen receptor in the cytoplasm of the human prostate is hampered by several problems. From a conceptual standpoint, one of the more serious of these is the strong possibility that most of the receptor is localized in the nucleus owing to the elevated concentration of dihydrotestosterone, especially in hyperplastic and carcinomatous tissue. We were persuaded by this line of reasoning to measure the quantity of receptor in highly purified nuclei. The following results, expressed in terms of molecules per nucleus, were obtained; normal prostate 900 ± 180 (mean ± S.E.M., n = 7); hyperplastic prostate, 1600 ± 260 (17); well-differentiated carcinoma, 1800 ± 160 (7). The 2-fold increase in the amount of receptor in carcinomatous nuclei appeared to be explained by the chance finding that such nuclei contained twice as much DNA as nuclei from normal tissue. We infer, therefore, that the concentration of receptor in carcinomatous tissue is elevated in proportion to the DNA content of the nucleus.

In an extension of this work, the nuclear concentration of dihydrotestosterone was measured by radioimmunoassay and compared to the amount of receptor. The number of molecules per nucleus of dihydrotestosterone was 11,000 ± 3000 (mean ± S.E.M.), 50,000 ± 6000 and 36,000 ± 7000, respectively in normal, hyperplastic and carcinomatous prostates. Thus, irrespective of the normal or abnormal condition of the prostate, the nucleus of the prostatic cell is characterized by an apparent capacity to accumulate dihydrotestosterone in excess of the quantity of receptor. This feature is most pronounced in hyperplastic prostate.

In view of the direct relationship between the amounts of nuclear receptor and DNA, we investigated the binding reaction between the two molecules in more detail. Extracts of nuclei from rat ventral prostate were digested with micrococcal nuclease to yield receptor-chromatin complexes of varying sizes; the complexes were separated in linear 7.6-76% (v/v) glycerol density gradients. With extensive digestion of DNA, receptor labeled with radioactive dihydrotestosterone was released from the chromatin. After 5% digestion of DNA to acid soluble products only a trace amount of labeled receptor was detected in the unbound form. In the latter instance most of the receptor was recovered from the gradients in association with five A_{260} peaks representing oligomeric and monomeric nucleosomes with a repeat length of 182 ± 3 (mean ± S.E.M.) base pairs. The concentration of receptor was highest in the A_{260} peaks which contained large oligomers of nucleosomes and lowest in fractions containing monomers, Similar experiments were performed with chromatin from nuclei of normal and hyperplastic human prostates; free receptor was recovered only after the chromatin was digested with micrococcal nuclease. We conclude from these observations that the androgen receptor is bound to linker DNA in