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

both rat and human prostate.

To determine whether the nuclear receptor is essential for the expression of hormonal sensitivity, we compared the amount of nuclear androgen-binding and the activities of acid phosphatase and plasminogen activator in the transplantable prostatic adenocarcinoma of Nb rats. Androgen-stimulated tumours were found to have more nuclear receptor and less acid phosphatase activity than autonomous tumours. Also the plasminogen activator activity was 7-fold lower in the androgen stimulated tumours than in the latter. These observations are consistent with the view that a diminished concentration of nuclear androgen receptor in prostatic carcinoma is associated with an increasing grade of malignancy.

13. Comparison between the contents of cytosolic steroid hormone receptors in the Dunning R-3327 prostatic adenocarcinoma of the rat and in human prostatic carcinoma. E. DAHLBERG, M. SNOCHOWSKI and J.-Å. GUSTAFSSON, Departments of Chemistry and Medical Nutrition, Karolinska Institutet, Fack, S-104 01 Stockholm, Sweden

The R-3327 transplantable rat prostatic adenocarcinoma was investigated with regard to receptors for hormonal steroids. It was found that glucocorticoid (dexamethasone) receptors, and progestin (R 5020) receptors were non-detectable in all tumors analyzed, i.e. 7 and 4 tumors, respectively. Estrogen (R 2858) receptors, and androgen (R 1881) receptors were detected in 5 of 6, and 8 of 9 tumors, respectively. The analyses were carried out using a dextran-coated charcoal technique, and the binding parameters were calculated according to Scatchard. The apparent dissociation constants ($K_d$) for estrogen and androgen receptors in the Dunning tumor were similar, and ranged from 0.57 to 1.85, and 0.73 to 1.85, respectively. The maximum number of binding sites ($B_{max}$) for the estrogen receptors ranged between 638 and 5,810 fmol/g tissue (8.31 - 90.2 fmol/mg protein; 304 - 1,260 fmol/mg DNA), and those for the androgen receptor ranged between 1,490 and 25,100 fmol/g tissue (19.4 - 363 fmol/mg protein; 710 - 5,450 fmol/mg DNA). In all cases containing both androgen and estrogen receptors, the former were more abundant.

Since several authors have suggested that this rat tumor may serve as a model for cancer of the human prostate, we compared our steroid receptor analyses of the Dunning tumor to those obtained with the same technique in primary and metastatic cancer of the human prostate. In a series of 25 biopsies from primary human prostatic carcinoma, methyltrienolone receptors were detected in 20 cases. In our series of 5 metastases from human cancer of the prostate, we found methyltrienolone (R 1881) receptors in 4 cases ($B_{max}$ 110 - 28,500 fmol/g tissue), glucocorticoid receptors in 3 cases ($B_{max}$ 4,730 - 13,600 fmol/g tissue), and progestin receptors in 2 cases ($B_{max}$ 424 - 1,410 fmol/g tissue), but none of the metastases contained detectable estrogen receptors.

Hence, it may be concluded that although the Dunning tumor and the human cancer of the prostate are both androgen-dependant, and contain androgen receptors in most cases, the rat model seems to differ from metastatic prostate cancer with regard to steroid receptor content. On the other hand, it is possible that it is a suitable model for primary cancer of the human prostate. It would thus be of interest to compare this, and other animal tumors with primary cancer of the human prostate in order to find the most optimal model system for studies of the hormonal control of human prostatic cancer.

14. Distribution of dihydrotestosterone and of nuclear androgen receptors between stroma and epithelium of human benign hyperplastic prostatic tissue (BPH), D.A.N. SIRETT, S.K. COWAN, A.E. JANECZKO and J.K. GRANT, University Department of Steroid Biochemistry, Royal Infirmary, Glasgow G4 0SF, Scotland, U.K.

Previous work in our laboratory has indicated that 1) testosterone 5α-reductase activity is located predominantly in BPH stroma rather than in the epithelium, and 2) BPH androgen receptors are found predominantly in the nuclear fraction of whole tissue samples. To further examine stromal-epithelial relationships in BPH tissue, we have measured the concentrations of endogenous dihydrotestosterone (DHT) and of nuclear androgen receptors in separated epithelium and stroma. Endogenous androgens were ether-extracted from tissue homogenates, and DHT separated by Lipidex column chromatography and quantitated by RIA. Crude nuclei were extracted with buffer containing 0.5 M KCl, and the receptor concentration was determined by exchange with [$^3$H]DHT. Similar concentrations of DHT were found in stroma and epithelium, when results were expressed in terms of the DNA content of the separated tissue (stroma: 5.0 ± 1.2 ng/mg DNA; epithelium: 6.2 ± 2.6 ng/mg DNA, n = 6). All results mean ± S.E.M.). Epithelial enrichment of DHT was evident in terms of tissue protein (stroma: 93 ± 15 pg/mg protein; epithelium: 468 ± 98 pg/mg protein, n = 6). Receptor concentrations, expressed on a DNA basis, were similar in nuclear extracts from both components (stroma: 556 ± 76 fmol/mg DNA; epithelium: 697 ± 182 fmol/mg DNA, n = 8). These results suggest 1) low testosterone 5α-reductase activity in BPH epithelium does not prevent the accumulation of large amounts of DHT by this component, and 2) both epithelium and stroma from BPH tissue contain nuclear androgen receptors and so are probably androgen-sensitive.

15. Prostatic cancer - diagnostic and prognostic methods, F.H. SCHRÖDER, Erasmus Universiteit Rotterdam, Department of Urology, Rotterdam, The Netherlands

About 9% of all malignant tumors diagnosed clinically are prostatic carcinomas. This amounts to about 50 new cases per 100,000 males per year and makes prostatic cancer