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Report on Seminars on Prostatic Cancer in Rome, May 23–25, and in Helsingborg, June 2–4, 1975

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Within one week, two meetings on prostatic cancer took place during Springtime 1975. The first one, organised by Prof. Bracci, was held in Rome 23-25 May and was visited by many urologists. It dealt mainly with the problems and results of hormonal therapy.

In an excellent review of the pathological anatomy of prostatic cancer Mostofi stressed the value of electron-microscopy and scanning electron microscopy. Of special interest are the microvilli that protrude from prostatic epithelial cells into the lumen of the acini. Disturbance of the arrangement and the disappearance of microvilli are sensitive parameters of hormonal control.

Bonucci asked for attention to be paid to the grade of differentiation in histological reports, as the clinical mortality rises when differentiation is poor.

Hodges described the historical experiments of Huggins on the hormone dependency of the prostate in dogs, which led to the endocrine therapy of prostatic cancer. He mentioned Prout's opinion that in a given prostatic cancer treated with hormones, clusters of cells that are independent of androgens can nearly always be found.

Senge reported on the implantation of prostatic cancer tissue into neonatal mice treated with Anti Lymphocyte Serum (ALS) and immunosuppressive drugs. The dependency on exogenous androgens could be well demonstrated in these experiments with histochemistry. Addition of oestrogens or anti-androgens caused metaplastic changes. Schubert reported on the histological and cytological changes after different forms of endocrine therapy for different lengths of time. He found a good correlation between grade of differentiation and oestrogen reaction, but cytological changes were more distinct than histological ones. Silverio warned about false androgen independency in some tumours.

Several authors, (Conti, Lunglmayr, Frick), reported on the difficulties with the use of plasma androgen determinations to check anti-androgen therapy. Not only is diurnal rhythm responsible for different levels of steroids in plasma during 24 h, but also in any given individual several additional factors, like emotional stress, can influence the normal values considerably. Sommerville considered that the mean value of three consecutive determinations taken at the same time of day were necessary. In his series this proved to be 528 ng testosterone/100 ml serum. He developed a radioimmunoassay to determine 6 C19-steroids together, amongst which were testosterone and 5α-dihydrotestosterone (T and DHT).

Bresciani gave an oversimplified, but for urologists understandable, account of steroid-receptors in prostatic epithelial cells. He elaborated on the possibilities of correlation between the presence of steroid receptors and androgen dependency of prostatic cancer, to make it clear that the presence of receptors does not necessarily mean that the tumour will respond to endocrine therapy. It turned out, however, that he did not yet have experience with receptors in human prostatic tissue. Collins called attention to the fact that prolactin enhances the action of testosterone on the prostate.

The second day began with an excellent review by Scott of the several methods of endocrine therapy which are used in prostatic cancer, of which the anti-androgens have attracted much attention recently. Robinson discussed the effect of oestrogens on plasma testosterone levels. He showed that during the first 6 months of oestrogen-therapy testosterone levels fall below 10 ng/100 ml, but rise after 6 months to a new level of 10-80 ng/100 ml. A most interesting finding was that the same results were seen after a daily dose of 1 mg.

stilboestrol as after a dose of 100 mg. He also reported a new anti-androgenic drug, aminoglutethemide which appears to be very effective, but produces too many side-effects.

Völter described the use of aspiration cytology for determining morphological parameters of response to hormonal therapy. He showed some very fine pictures of changes within prostatic carcinoma cells after oestrogen therapy. After castration the changes were mainly those of atrophy.

Becker reported on an excellent prospective study in which after initial treatment to relieve obstruction and either irradiation or castration, 5 different therapeutic regimes (Honvan, prednisolone, diuretics, cyproterone and placebo) were compared. The mortality rate was 7 % after placebo and 26 % after Honvan therapy, but in the latter about half of the patients had died from causes other than cancer.

A separate session was devoted to the use of anti-androgens. Neumann reported that anti-androgens (which he defined very clearly) in animal experiments (mainly with rats and dogs) cause a very definite atrophy and decrease of function, but he stressed the fact that no clinical parameter exists to test these drugs in man. On the other hand Bracci could hardly hide his enthusiasm about the results of treatment with cyproterone acetate, which indeed has the advantage of being non-feminising and having very few side-effects. Ziegler pointed out that using cytological parameters, the effects of oestrogens and anti-androgens show undeniable differences: the oestrogens cause intracellular changes in both cytoplasm and nuclei while the anti-androgens only cause atrophy.

Fergusson showed an excellent film on the technique of hypophysectomy but Becker warned that neither hypophysectomy, nor anti-prolactin therapy will be of major importance until we know more exactly the role of prolactin in prostatic cancer. The meeting was concluded by a round table discussion, presided by Bracci. Unfortunately, the issues were not discussed to full advantage as some of the questions were too difficult to be answered precisely, so that the participants, often too cautiously, circumvented the subject.

In contrast to the Rome Meeting was that organised by the Leo Research Foundation in Helsingborg on the 2nd-4th June. Some 50 people were invited as speakers and participants, most of them outstanding and well known research workers in the field of endocrine control of the prostate and there were only a few urologists who have similar research interests. The small number not only made it possible to have discussions at a high level in a good natured atmosphere, but also to exchange ideas and experience with everyone without reserve. Undoubtedly the output of such a conference must be significantly greater than many congresses of larger scale.

The first day was devoted to different systems of testing hormonal effects on prostatic tissue.

Beaulieu reported on the prostate in organ culture. Like Mostofi he called attention to electron microscopy of organ cultures. Not only the microvilli on the surface of the cells, but also changes in endoplasmic reticulum and Golgi-apparatus as well as changes in the nucleus are important parameters of hormonal influence. Within the acini, basal cells can be distinguished differing from the other glandular epithelial cells in that their protein (RNA) synthesis reacts more strongly to testosterone when measured with 3H-labelling.

Williams-Ashman described how actinomycin-D inhibited transcription of DNA. His results on the polyamines spermine and spermidine in prostatic secretion were very interesting. In his opinion they play a role in the RNA synthesis and therefore on the effect of testosterone. Finally he described some experiments on the so called DNA-unwinding protein, which is profoundly affected by spermidine.

Bruchovsky thought that the hormonal response of prostatic cells could be divided into 3 phases: 1) initiation phase; 2) negative feedback plateau and 3) autophagia. To demonstrate this, it is necessary to count the cells and measure cell proliferation by 3H-thymidine uptake. The initiation phase could be found in prostates with less than the normal number of cells, when androgens stimulate DNA synthesis and cell proliferation. Negative feedback occurs when the number of cells is restored to normal, the phase of autophagia commencing after withdrawal of androgens as by orchiectomy. Finally after adding labelled testosterone to his prostatic tissue explants and measuring cytoplasmic as well as nuclear dihydrotestosterone (DHT), he found that even in the absence of cytoplasmic receptors (as for instance 7 days after castration) DHT is still present in the nucleus, which might indicate that the intranuclear concentration of DHT plays an important role in the autophagia process. Receptors were determined using gel exclusion chromatography.

Neumann stressed the fact that for testing antiprostatic drugs for clinical use in humans, there is no perfect animal model available and a plea was made for more research on human prostatic tissue.

Forsberg reported on experiments with 4 different kinds of oestrogen-cytostatic complexes and their effect upon the rat ventral prostate. Of these the estramustine phosphate (EMP), better known as Estracyt, naturally attracted the attention of the urologists present.

EMP after conversion into EM has an inhibitory effect on 3H-thymidine uptake in both organ cultures and in vivo experiments. In high doses EMP inhibits the growth of rat prostate, but only when these high doses are given long term does it inhibit 5α-reductase. As far as receptors are concerned EMP had a higher affinity than oestradiol (E2).

Sandberg used 5α-reductase, arginase and the deposition of androgens in the dog prostate as models to test an extensive list of cytostatic drugs, most of which did not have any effect at all. Only EMP showed an effect on 5α-reductase, while procarbamazine affected arginase and streptozocin and flutamide reduced the deposition of androgens.

In the round table discussion at the end of the first day Griffiths stated that as the result of a search for non-feminising oestrogens it had been found that mesodihydrodibutyl-stilboestrol mimicked the effect of stilboestrol to a certain extent. Tagnon expressed his opinion that any form of chemotherapy in human patients should start at the very beginning of his disease and not, as has been the normal practice, in the terminal stages.

The second day was mainly devoted to the topic of steroid receptors but included a paper by Eik Nes in which the difficulties of in vivo animal preparations, such as the perfused prostate, were emphasised. One could only have admiration for his outstanding work and his persistence in this field.

Lipsett called attention to his method of determining the metabolic clearance rate of steroids as being the only reliable method of measuring secretion by an organ such as the prostate.

Mainwaring gave an excellent review of the present knowledge of receptor proteins and their meaning in steroid metabolism and this is summarised in Fig. 1. He emphasised that the entry of steroids into the cell is temperature dependent. He also emphasised 3 areas for the study of receptors:

1. Hormone synergism (e. g. prolactin and androgens/androgens and oestrogens)
2. Switch of amplification
3. Acute tissue specificity.

If cytoplasmic receptors are different, they act on different sites of the DNA spiral; if they are similar, they act on similar sites. As long as receptors are not purified, we must accept tissue specificity which in fact could be receptor specificity. To determine receptor specificity Mainwaring has developed an interesting new method, in which acceptors of nuclei-preparations on sepharose columns are extracted. With acceptor complexes of prostate and uterus there was a cross-over of oestrogen response. In his opinion acceptors were non-histone-proteins, but this was contested by Davies. Mainwaring also considered that the purification of receptors ought to have priority in future research.

Tveter reported his experiments on steroid binding in the human prostate. Using sephadex G200 gel filtration he was able to distinguish between receptor proteins and Sex Hormone Binding Globulin (SHBG). The androgen receptor protein did not differ in specificity from the androgen receptor found in carcinoma nor from that in a "normal" prostate (from a total cystectomy specimen in a young patient).

Verhoeven has determined receptors in all kinds of tissues from rats and other rodents by means of ammonium sulphate precipitation. He thought that in all androgen-sensitive tissues the cytosol receptor was similar.

Ritzen described androgen transport and receptors in testis and epididymis. Seminal fluid contains high concentrations of T and DHT. Extracellular Androgen Binding Protein (ABP) is made by Sertoli cells, and then secreted into tubules so that the amount of ABP reflects their function. Sertoli cells as well as germinal cells appeared to contain androgen receptors but interstitial cells did not. Confirmation was obtained from rats with the "Sertoli cells only" syndrome.

Liao told how his attention has switched from receptors to the so called Initiation-Factor activity, which depends on RNA-synthesis and not on protein synthesis. He only recently started his experiments which may prove to be of

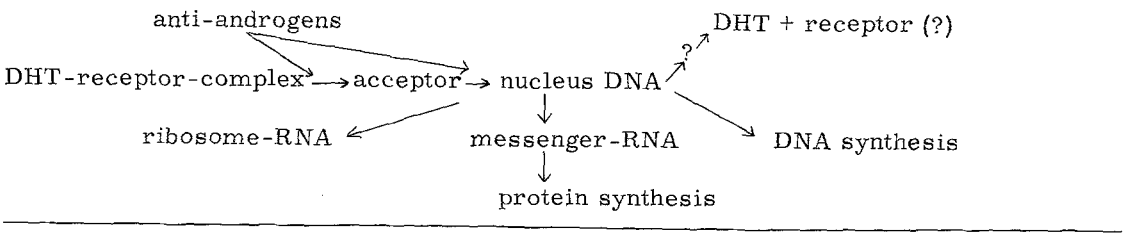

Fig. 1.

importance in the future for the better understanding of the regulation by steroids of cellular function and growth in target tissues.

Robel finally called attention to the fact that many of the androgen receptors are occupied by endogenous androgen which makes the determination difficult. He therefore does a protamine sulphate precipitation and after washing off the excess of androgens performs a radio-immunoassay.

In the round table discussion of the second day many opinions on receptor mechanisms were expressed as well as contested. A major point is that androgen receptors in prostatic cancer can be competitively occupied by oestradiol, but there is also a different and specific E2 - receptor, which binds diethyl stilboestrol (DES), which is not bound by androgen- receptor. The results of the Leiden prostatic cancer research group in this respect were of interest.

The last day was devoted to treatment of prostatic adenoma and carcinoma.

Jönsson reported on the use of Estracyt in 128 patients with advanced prostatic cancer. 50 % of these had a remission that lasted for 6 months or longer although they had already received oestrogen treatment. When EMP was the primary treatment 83 % reacted favourably.

Diczfalusy had made an extensive study of steroid levels in plasma under these treatment modalities and found that oestradiol and oestrone levels went up under treatment with Estracyt. There also seemed to be a significant rise in prolactin levels.

Chisholm presented an excellent review of the present non-surgical treatment of prostatic cancer. Major points in his lecture were the plea to accept the TNM-system for classification and clinical evaluation and the necessity for an objective measurement of relapse.

Mittelman mentioned the results of hypophysectomy in patients with advanced carcinoma. As only 10 % had a regression, this was not encouraging. Of 45 patients who received Estracyt, 19 % had an objective response and 30 % a subjective response.

Voigt reported on studies of androgen metabolism in patients with benign prostatic hypertrophy (BPH). It turned out that plasma T and DHT levels did not undergo significant changes with ageing, but E_2 levels increased. The change in E_2/T ratio was the important finding, but its significance in the pathogenesis of BPH is not yet clear. Dwelling on receptor determinations in prostatic adenoma tissue, he described a receptor, different from androgen- receptor, which he called storage-receptor. Again further studies have to be done to understand the meaning of this.

Finally Coffey stressed morphometric analysis of BPH histological sections as a possible method of measurement of steroid effect. He expressed his hope that further investigation into the aetiology of BPH might ultimately lead to prevention rather than cure.

Reflecting on the significance and the value of the two meetings for urologists as well as research workers in the fields of prostatic carcinoma, several items arise that deserve attention. Most of these make a very positive contribution and only some a negative.

1. There is still not much evidence that anti-androgens have any advantage over oestrogenic compounds or castration in the treatment of prostatic carcinoma.
2. There is still no perfect animal model to test anti-androgenic and cytostatic drugs against human prostatic cancer.
3. Clinical evaluation of the treatment of prostatic cancer still has many shortcomings.
4. Despite the countless, excellent, experiments in animal tissue in vitro and in vivo, there is a growing tendency to switch to research on human prostatic tissue, however arduous a task this may be.
5. Electron microscopy may be important.
6. There are certain indications that the use of cytological material, obtained by aspiration biopsy (Franzen) will play an important role, not only for diagnostic purposes but also for checking on hormonal dependency and treatment.
7. Steroid receptor determinations in cytoplasm as well as nuclei of prostatic cancer tissue have to be done on a large scale to find out whether they are of significance in the evaluation of hormonal therapy.
8. Clinical evaluation has to be based on a reliable system of staging and classification, preferably using the TNM system of the UICC, and on objective measurement of progression and relapse.

It was gratifying to note that several European cooperative groups have been formed to bring together and compare results in the fields of research into human prostatic cancer. We hope to see and hear more of them in the near future.

List of speakers at the seminars:

H. Becker
Universitäts-Krankenhaus Eppendorf, Hamburg, F. R. G.

A. Bonucci
Clinica Urologica dell'Università di Roma, Italy

U. Bracci
Clinica Urologica dell'Università di Roma, Italy

F. Bresciani
Instituto die Patologia Generale dell'Università di Napoli, Italy

W. P. Collins
King's College Hospital Medical School, London U. K.

C. Conti
Instituto di Patologia Medica dell'Università di Roma, Italy

F. Di Silverio
Clinica Urologica dell'Università di Roma, Italy

J. D. Fergusson
Department of Urology, University of London, U. K.

J. Frick
Urologische Universitätsklinik, Innsbruck, Austria

C. V. Hodges
University of Oregon Medical School, Portland, Oregon, U. S. A.

G. Lunglmayr
Urologische Universitätsklinik, Wien, Austria

L. Martini
Instituto di Endocrinologia dell'Università di Milano, Italy

F. K. Mostofi
The Armed Forces Institute of Pathology, Washington D. C., U. S. A.

F. Neumann
Schering AG, Berlin, F. R. G.

M. R. G. Robinson
Pontefract General Infirmary & The Hydes Hospital, Southgate, U. K.

G. E. Schubert
Pathologische Abteilung der Universität, Tübingen, F. R. G.

W. W. Scott
Department of Urology, The Johns Hopkins University, Baltimore, Maryland, U. S. A.

T. Senge
Urologische Abteilung des Josefs-Hospitals, Herne-Sodingen, F. R. G.

I. F. Sommerville
Endocrine Unit, Chelsea Hospital for Women, London, U. K.

A. Vermeulen
Rijksuniversiteit Gent, Interne Kliniek, Gent, Belgium

D. Volter
Urologische Abteilung der Universität, Tübingen, F. R. G.

H. Ziegler
Zytologisches Labor der Abteilung für Urologie der Universität Tübingen, F. R. G.

E. -E. Baulieu
Lab. Hormones, Hôpital de Bicêtre, Bicêtre, France

N. Bruchovsky
Department of Medicine, University of Alberta, Alberta, Canada

G. D. Chisholm
Hammersmith Hospital, London, U. K.

P. Davies
Tenovus Institute for Cancer Research, Welsh National School of Medicine, Cardiff, U. K.

E. Diczfalusy
Reproductive Endocrinology Research Unit, Karolinska Hospital, Stockholm, Sweden

K. B. Eik-Nes
Institute for Biophysics, University of Trondheim, Trondheim, Norway

J. -G. Forsberg
Institute of Anatomy, University of Bergen, Bergen, Norway

K. Griffiths
Tenovus Institute for Cancer Research, Welsh National School of Medicine, Cardiff, U. K.

G. Jönsson
University of Lund, Department of Urology, Lund, Sweden

S. Liao
Department of Biochemistry, The Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois, U. S. A.

M. B. Lipsett
The Cancer Center, Inc. Cleveland, Ohio, U. S. A.

I. Mainwaring
Endocrinology Group, Imperial Cancer Research Fund Labs., London, U. K.

A. Mittelman
Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

F. Neumann
Schering A.G., Berlin, F.R.G.

M. Ritzen
Karolinska Hospital, Stockholm, Sweden

P. Robel
Lab. Hormones, Hôpital de Bicêtre, France

A.A. Sandberg
Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

H.J. Tagnon
Department of Internal Medicine, Brussels, Belgium

K.J. Tveter
Rikshospitalet, Oslo, Norway

G. Verhoeven
3319 Chapel Creek Drive, Dallas, Texas, U.S.A.

K.-D. Voigt
II. Medizinische Klinik, Abt. für Klinische Chemie Universitätskrankenhaus Eppendorf, Hamburg, F.R.G.

H.G. Williams-Ashman
The Ben May Laboratory for Cancer Research, University of Chicago, Chicago, U.S.A.

The complete text of the seminar in Helsingborg will be published in the next issue of "Vitamins and Hormones".

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