

Sergiy Vozianov
Bakhron Ishmuradov

Androgen Deprivation Therapy for Prostate Cancer

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ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER

2023

NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE
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Androgen Deprivation Therapy for Prostate Cancer

In the monograph concerning hormonal treatment of prostate cancer special attention is paid to androgen deprivation therapy. Molecular, hormonal and cellular mechanisms of prostate cancer pathogenesis and progression are discussed. Results of animal research and clinical use of luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens and low dose of estrogens for androgen deprivation are described.

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CONTENTS

INTRODUCTION.....	5
CHAPTER 1.....	7
Endocrine aspects.....	7
of pathogenesis of prostate cancer.....	7
1.1. Hormonal regulation of the prostate.....	7
1.2. Hormonal, cellular and molecular determinants of prostate cancer growth.....	26
1.3. Molecular mechanisms of prostate cancer progression and resistance to endocrine therapy.....	33
CHAPTER 2.....	38
Pharmacology of hormonal drugs for treatment of prostate cancer.....	38
2.1. Strategy and methods of androgen deprivation.....	38
2.2. Estrogens.....	40
2.3. LHRH agonists.....	50
2.4. Non-steroid antiandrogens.....	61
2.5. Steroid antiandrogens.....	68
CHAPTER 3.....	72
Low dose estrogen - antiandrogen therapy (LEAT) of prostate cancer: lessons from animal research.....	72
3.1. Theoretical background.....	72
3.2. Flutamide and diethylstilboestrol.....	74
3.3. Flutamide and hexestrol.....	76
3.4. Flutamide and fosfestrol.....	93
3.5. Flutamide and chlorotrianisene.....	102
3.6. A comparative evaluation of antiprostatic flutamide activity in combination with estrogenic drugs.....	105
CHAPTER 4.....	108
Endocrine monotherapy of prostate cancer.....	108
4.1. Classification of prostate cancer and general	

principles of its palliative treatment.....	108
4.2. Castration	113
4.3. Estrogens	118
4.4. LHRH agonists.....	131
4.5. Non-steroid antiandrogens	142
4.6. Steroid antiandrogens.....	154
4.7. Other drugs.....	164
CHAPTER 5.....	167
Combined endocrine therapy of prostate cancer....	167
5.1. Castration and estrogens	167
5.2. Castration and antiandrogens	170
5.3. LHRH agonists and antiandrogens	1755
CHAPTER 6.....	179
Low dose estrogen-antiandrogen therapy of prostate cancer.....	179
6.1. Clinical effectiveness	179
6.2. A comparative assessment of clinical results after LEAT and conventional treatment.....	190
6.3. A comparison of treatment results shown by hormonal study	194
6.4. Long-term results of hormonal therapy	196
CHAPTER 7.....	198
Neoadjuvant hormonal therapy of prostate cancer	198
List of abbreviations	204
References	205

INTRODUCTION

Nowadays prostate cancer is the most common cancer in American men, other than skin cancer, and the second leading cause of cancer death in American men, behind only lung cancer. About 1 man in 41 will die of prostate cancer. The American Cancer Society's estimates for prostate cancer in the United States for 2023 are: about 288,300 new cases of prostate cancer and about 34,700 deaths from prostate cancer (<https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html>).

The number of prostate cancers diagnosed each year declined sharply from 2007 to 2014, coinciding with fewer men being screened because of changes in screening recommendations. Since 2014, however, the incidence rate has increased by 3% per year overall and by about 5% per year for advanced-stage prostate cancer.

Based on data obtained for 2016-2020, the number of new cases of prostate cancer was 113.4 per 100,000 men per year and the number of deaths was 18.8 per 100,000 men per year. Approximately 12.9 percent of men will be diagnosed with prostate cancer at some point during their lifetime, based on 2017-2019 data. In 2020, there were an estimated 3,343,976 men living with prostate cancer in the United States (<https://seer.cancer.gov/statfacts/html/prost.html>).

Human and animal prostate develops and functions under multiple control of hormones - androgens, estrogens, prostaglandins, prolactin and some others. Undoubtedly, male sex hormones, testosterone and its active metabolite, dihydrotestosterone, play the leading role.

In the history of medicine PC has become the first inoperable malignant metastatic tumor for which an effective palliative conservative treatment was found (Huggins, Hodges, 1941; Huggins et al., 1941 a, b). This is particularly important since, as a rule, PC is diagnosed rather late, when 40 % of patients show metastatic development. PC is characterized by early metastases and low effectiveness of antitumorous chemical agents. Castration and/or hormonal therapy of PC patients increase survival rate considerably. When a tumor is diagnosed in its C stage, a 5-year survival is observed in 5 % of untreated patients, while in case of endocrine therapy this makes 30 %,

and for stage D, 10 % and 20 %, respectively. 5 % of PC patients diagnosed in stage D showed 10- year survival if they received endocrine therapy while none of untreated patients survived this period (Lepor et al., 1982).

Hormonal therapy of PC is based on the present knowledge of regulation of structure and functioning of the prostate, first and foremost of the epithelium of tubular alveolar structures where adenocarcinoma develops. Many fundamental cellular and molecular mechanisms underlying malignant transformation of prostatic tissue and resistance to endocrine therapy have been elucidated (Marcelli, Cunnigham, 1999).

During last 10-15 years the strategy and tactics of PC endocrine treatment changed considerably. A real success is associated with a discovery and clinical use of LH-releasing hormone (LHRH) agonists, androgen receptor blockers etc. Thus it has become possible to do without surgical castration and long-term administration of estrogenic drugs. The latter is of special importance because of severe hormonal, metabolic, cerebrovascular, cardiovascular and other complications of estrogen therapy that often resulted in fatal outcome. However, standard estrogen monotherapy is still widely used in some countries because these drugs are cheaper and also due to the fact that some doctors demonstrate certain conservatism and are badly informed about new possibilities of PC therapy.

This book is a result of many years' co-operation between clinicians and research workers who combined their efforts in order to improve management of PC patients. A considerable place in this book is devoted to experimental substantiation and clinical experience of using different modalities of low-dose estrogen-antiandrogen therapy of inoperable PC, proposed and developed by the authors.

Screening, which includes prostatic specific antigen (PSA) determination and transrectal ultrasound diagnosis, promotes early PC identification. In some cases, combined endocrine therapy with LHRH analogues and antiandrogenic drugs prior to radical prostatectomy (neoadjuvant therapy) results in lessening the tumor volume, facilitates surgery and improves prognosis (Solomon et al., 1993). This aspect was also depicted in the book.

Endocrine therapy of PC is a dynamic, rapidly developing field of medical science and practice. Many related issues are still discussed in literature, at specialized international congresses and symposia. While working on this book the authors tried not only to present their own views but also to summarize the experience acquired by their colleagues around the world.

ENDOCRINE ASPECTS OF PATHOGENESIS OF PROSTATE CANCER

1.1. Hormonal regulation of the prostate

The human and animal prostate develops and functions under multiple control of hormones - androgens, estrogens, prostaglandins, prolactin and some others. Undoubtedly, male sex hormones, testosterone and its active metabolite, dihydrotestosterone, play the leading role.

Androgens. The prostate is a typical target organ for androgenic hormones. It is a classical example of almost absolute hormone dependency (Reznikov, 1998). Results of castration of laboratory male animals are well known: lessening of the volume of this organ, cell number and total DNA content by 75-80 %, atrophy of the acinar epithelium, degeneration of terminal departments of ducts, lack of prostatic «juice» production, atrophic changes in the stromal cells. Replacement therapy with antiandrogenic drugs restores completely the structure and functioning of the gland. These are androgenic hormones that facilitate a necessary equilibrium between proliferation and death of PC epithelial cells. At the level of cell genome they regulate mitosis and apoptosis. Thus, according to terminology introduced by V. Rosen (1984), the prostate should be considered a hormonedependent polycompetent structure since androgens induce both selective and general trophic effects in it. This is in line with the criterion for androgen-dependent cells and tissues proposed by W. Mainwaring (1977) that includes the ability of androgenic hormones to induce replication of nuclear DNA followed by mitotic division of a cell.

The testes and the adrenal cortex are main sources of androgens in males. 95 % of circulating testosterone is synthesized by testicular interstitial cells (Leydig cells). Daily production of this hormone is 5-8 mg. In addition, Leydig cells synthesize and secrete some androstenedione into circulation.

In the adrenal glands androgens are synthesized in the cortical *zona reticulosa*. They produce androstenedione and dehydroepiandrosterone (dehydroisoandrosterone). Daily a human male produces about 2.4 mg androstenedione (Bardin, 1986). Though both hormones have a weak androgenic activity they can convert into more active androgenic compounds, which is of special importance in pathology. Under physiological conditions, peripheral conversions of these hormones yield 5 % of circulating testosterone.

All natural androgens belong to C₁₉-steroid group, i.e. cyclopentanoperhydrophenanthrene hydrocarbon-derivatives that have 19 carbon atoms. Even slight modifications in chemical structure of androgen molecule effect its biological activity considerably.

A common substrate for androgen steroid biosynthesis is cholesterol, which is synthesized locally or delivered with blood. A special enzyme system that is present in mitochondria of steroid-producing cells splits off a part of cholesterol side chain thus converting it into pregnenolone. In Leydig cells this reaction is activated by pituitary luteinizing hormone, in adrenocorticocytes - by adrenocorticotrophic hormone. Further process of formation of androgen steroids is associated with a series of pregnenolone and progesterone conversions that are catalyzed by microsomal enzymes. It has already been mentioned that in the testes end products of androgen biosynthesis, which are secreted in blood, are testosterone and androstenedione (Fig. 1.1).

Androgen biosynthesis as well as formation of intermediate compounds requires NAD or NADPH as cofactors. The former is necessary for 3 β -hydroxysteroid dehydrogenase reaction that facilitates a number of essential biochemical reactions, in particular, pregnenolone conversion into progesterone or dehydroisoandrosterone conversion into androstenedione. In the presence of NADPH, 17 β -hydroxysteroid dehydrogenase converts androstenedione into testosterone. This step is reversible but dynamic equilibrium is shifted towards testosterone formation.

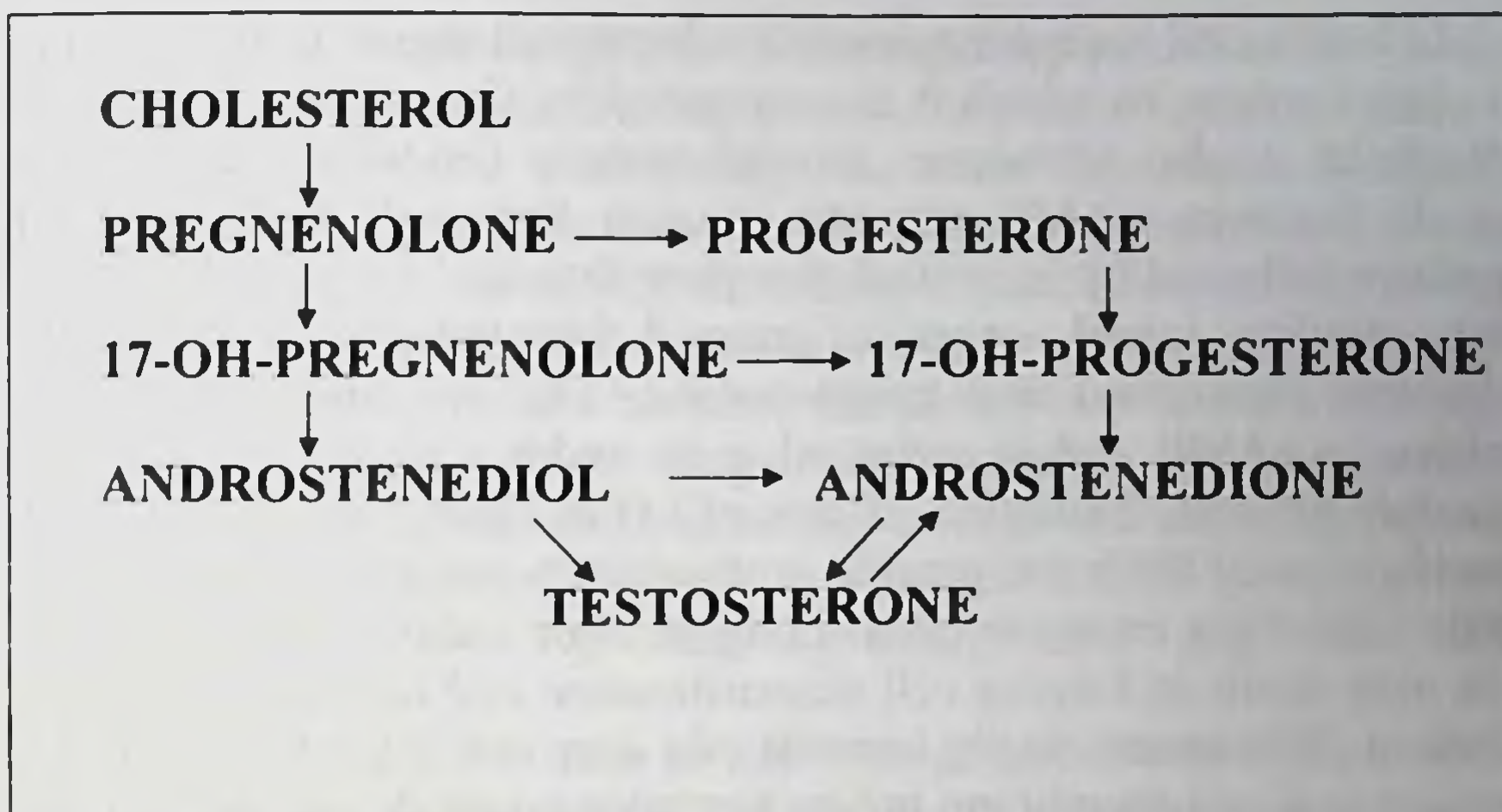


Fig. 1.1. Biosynthesis of androgens in Leydig cells

The main regulator of androgenopoiesis in male sex glands is pituitary LH, which belongs to glycoprotein hormone family, together with FSH, thyrotropin and chorionic gonadotropin. Their molecular structure is presented by of alpha- and beta-subunits, and amino acid sequence alpha-subunit is less variable while beta-subunit composition is particular for each hormone and responsible for its different biological properties. Molecular mass of purified human pituitary LH is about 28000 Da of which 14000 Da fall within alpha-subunit. Carbohydrate (oligosaccharide) component makes about 16 % of LH molecular mass (Catt, Pierce, 1986).

LH is synthesized by special pituitary cells, gonadotropocytes. LH is stored there inside secretory granules and is secreted into blood

Under stimulation by hypothalamic decapeptide, LH-releasing hormone (LHRH)

Activation of LH-dependent steroidogenesis in Leydig cells starts with the perception of LH hormonal signal by specific membrane receptors. These protein molecules are distinguished for their ability to bind and live, with high affinity, LH molecules. A molecule of human LH solubilized receptor is asymmetric with molecular mass of approximately 180000 DA. It binds only one LH molecule thus forming a complex with sedimentation constant of 7.5 S. Hydrophobic nature of LH receptor corresponds to its localization in a double lipid layer of interstitial cell membrane.

LH-activated receptor transmits a hormonal signal to the enzyme, adenylate cyclase, to which it is conjugated by G-proteins. As a result, intracellular cyclic adenosine monophosphate (cAMP) concentration rises. In its turn, cAMP activates protein kinase A in Leydig cell cytoplasm followed by increased phosphorylation of functional proteins, which regulate initial stages of steroid biosynthesis, in particular, cholesterol conversion into pregnenolone. This reaction is extremely sensitive to cAMP and is activated even under a slight rise of cyclic nucleotide content. Biological effects of LH in Leydig cells also include intensification of RNA and protein synthesis as a manifestation of general trophic LH effect on these cells. Long-term or excessive LH effect on testes may result in Leydig cell desensitization and decreased androgen formation. This occurs partly because of a decrease in the number of LH receptors in a cell membrane but to a greater extent due to inhibition of postreceptor transmission of a hormonal signal. Apparently, in Leydig cells there exists an autonomous mechanism of androgenopoietic self-regulation that protects them from excessive stimulation. It is believed that it functions under physiological conditions as well. That is why steroidogenesis in these cells is desynchronized: while some cells are «working», others are temporarily resting.

The phenomenon described is very important for further consideration of possibilities of pharmacological inhibition of testicular androgen secretion by LHRH agonists as a method to treat PC.

LH effect on testosterone formation in the testes depends, to some extent, on the supporting effect of another pituitary hormone, prolactin. The ability of prolactin to potentiate LH steroidogenic effect under physiological conditions is thought to be related to an increase in LH receptor number as well as to regulation of contents of testosterone biosynthesis precursors in Leydig cells (Bartke, 1976).

Pituitary regulation of testicular endocrine function cannot be considered apart from the hypothalamic action. It is the hypothalamus that plays the central role in the integrated hypothalamic-pituitary-testicular axis. This important site in the diencephalon is the point where LHRH is formed and accumulated, and it has direct anatomic connection with the pituitary gland. The most remarkable feature of this connection is the portal system of the venous vessels, which facilitate a direct circulatory route along which hypothalamic LHRH is delivered to the pituitary gonadotropocytes. In the same fashion other hypothalamic releasing hormones (liberins and statins) are delivered to the adenohypophysis.

The portal system originates in the capillary plexus in the median eminence, the vessels stretch along the pituitary stem forming numerous sinusoids in the anterior lobe. Though the adenohypophysis is supplied with some arterial blood the main blood supply is accomplished through the portal venous vessels. LHRH stimulates LH and FSH secretion though FSH response is slightly weaker and delayed.

LH molecular structure has been elucidated in full, and a number of LH-based pharmacological drugs implemented in oncurologic, endocrinologic and gynecologic practices were developed. The sequence of amino acid residues in the molecule of natural LHRH is as follows:

(Pyro) - Glu - His - Trp - Ser - Tyr - Gly - Leu - Arg - Pro - Gly - NH₂.

LHRH-stimulated release of LH from granules, which are stored in gonadotropocytes, starts with LHRH binding to specific receptors on gonadotropocyte membranes. This initiates exocytosis with a further increase in gonadotropin biosynthesis. However, stimulating mechanisms differ considerably from that characteristic for LH action in Leydig cells. The main difference is that calcium ions, not cAMP, act as second messengers of LHRH effect on exocytosis. Owing to LHRH-induced rise in the intracellular concentration of free calcium ions, protein kinase C is activated. This enzyme catalyzes phosphorylation of proteins, which participate in the release of pituitary protein hormones. Leukotriens, which are formed from arachidonic acid as a result of LHRH-effected metabolism of cellular membrane phospholipids, are also involved in exocytosis.

As to long-term LHRH effects, an increase in gonadotropin synthesis in particular, they are cAMP-mediated. Transcription of respective genes is activated as a result of cAMP-dependent protein kinase phosphorylation of DNA-binding protein (CREB), which belongs to transcription factors.

A number of LHRH binding receptors in pituitary gonadotropocyte membranes determines, to a great extent, gonadotropic response to hypothalamic stimulation. It is worth mentioning that synthesis of receptor molecules is induced by LHRH itself, that is up-regulated but a prolonged stimulation of LHRH receptors decreases their number.

It has been proved that the main sites of LHRH synthesis in the brain of primates are the medial preoptical area, the anterior hypothalamus and the arcuate nucleus. Neurosecretory cells of these nuclei have axons with terminals located closely to capillaries in the external layer of the median

eminence of the hypothalamus. LHRH-containing neurosecretory granules are stored in these terminals.

Under the effect of neurotransmitters, LHRH is released from granules into the capillary plexus of the median eminence. Numerous contacts of LHRH-producing cells and their axons with synaptic terminals of nervous fibers, which are abundant in the hypothalamus, provide a neuroanatomical substrate for this connection. It is known that the hypothalamus integrates nervous signals from the brain cortex and stem, limbic and other CNS structures. Thus, in the hypothalamus the nervous regulation «switches over» to the hormonal regulation followed by a cascade strengthening of the regulatory signal within the hypothalamic-pituitary-testicular axis.

Norepinephrine is a recognized stimulator of LHRH release into the pituitary portal vessels in males. The median eminence is permeated with numerous fibers of noradrenergic neurons with their cell bodies in the brain stem.

Endings of the nervous cell fibers that are part of tuberoinfundibular dopaminergic tract are located in the external layer of the median eminence. Bodies of respective neurons are concentrated in the hypothalamic arcuate nuclei. Dopamine may both stimulate and inhibit LHRH release but in males this dopamine function is beyond comparison with that of norepinephrine.

As to serotonin, it is most probable that in males it refers to neurotransmittal regulators, which inhibit LHRH and, respectively, LH and testosterone secretion. Cell bodies of serotonergic neurons are located in the medial nuclei of the brain raphe, their processes are projected to the anterior hypothalamus, suprachiasmatic nuclei and median eminence.

Acetylcholine, gamma-aminobutyric acid, nitrogen oxide, stimulatory amino acids (aspartate, glutamate), interleukins, angiotensins and other hypothalamic regulators and modulators may be involved in regulation of LHRH release.

A great importance of neuropeptides, opioids first of all, in neuroendocrine regulation of LHRH secretion should not be neglected. Betaendorphin has an inhibitory effect on LHRH release into the portal system, which results in a considerable decrease in LH secretion.

Neuropeptide Y, galanine and other hypothalamic neuropeptides related to gastrointestinal peptides, belong to hypothalamic factors, which modulate LHRH secretion and adenohipophysis sensitivity to LHRH.

LH is released in a pulsatile fashion, in healthy men it makes 8-14 pulses a day. This pulsation depends on the pacemaker rhythm of hypothalamic LHRH secretion. «A biological clock», which generates this type of gonadotropic rhythms of the hypothalamic-pituitary system, is located within the hypothalamus. A total surgical deafferentation of the hypothalamus does not abolish the pulsation. But this occurs after electrolytic destruction of the hypothalamic arcuate nuclei. That is why it may be considered a gonadotropic pacemaker.

Testicular testosterone secretion is also under pulsatile fluctuations. In addition, it changes over the day and is maximum in the morning. That is why it is strongly recommended that during clinical diagnostic tests LH and testosterone contents are measured in joint blood samples taken three times with a 20-30-min interval. When the test is repeated blood samples should be taken in the same time.

Testicular testosterone goes into circulation and produces a tonic inhibitory effect on LH secretion at the hypothalamic and pituitary levels (Fig. 1.2).

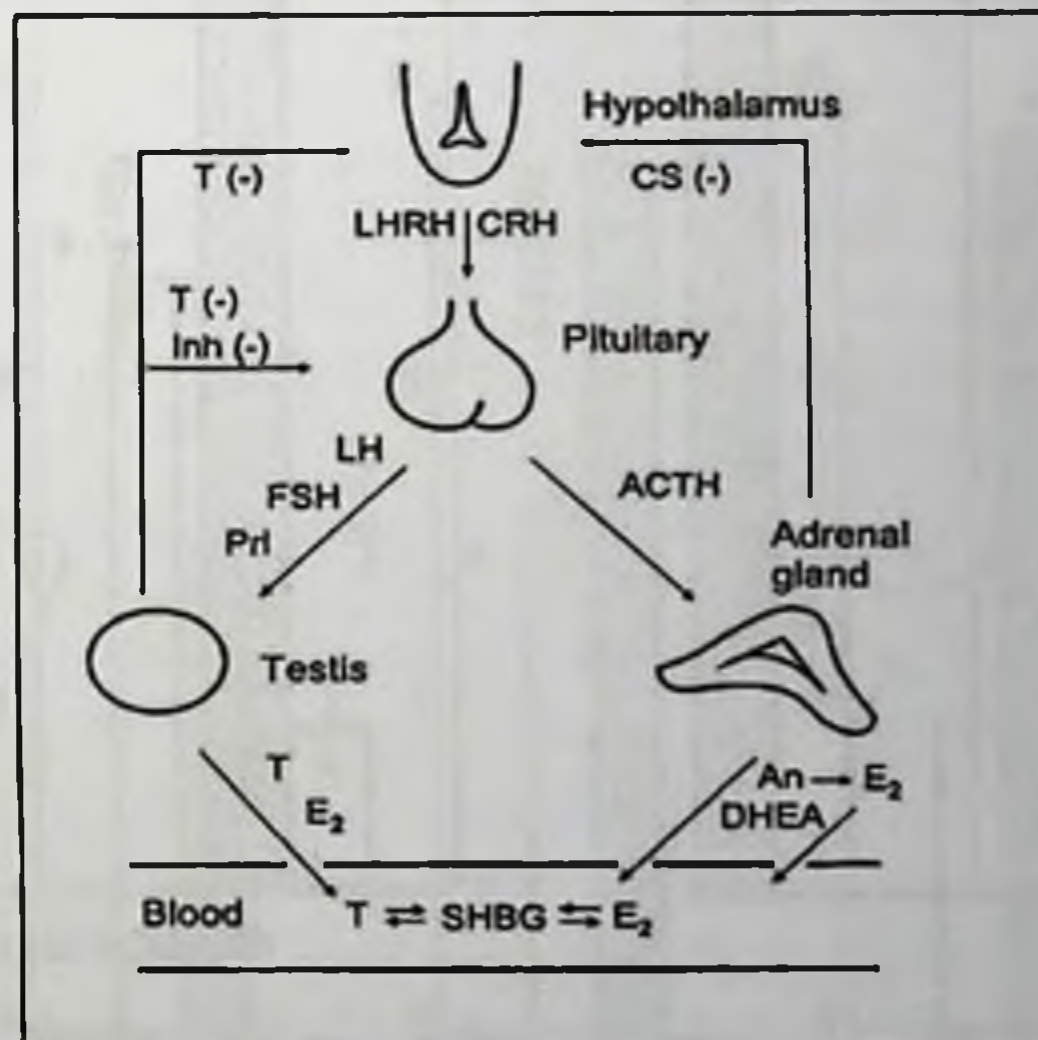


Fig. 1.2. Scheme of neuroendocrine regulation of androgen and estrogen secretion in a male organism

T, testosterone; An, androstenedione; DHEA, dehydroepiandrosterone; E₂, estradiol; Inh, inhibin; CS, corticosteroids; SHBG, sex hormone binding globulin; LH, luteinizing hormone; LHRH, LH-releasing hormone; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; Prl, prolactin.

In physiology this mode of regulation of functional activity of the peripheral endocrine glands is known as negative feedback. Thus the rate of testicular androgens formation and secretion depends on the integrity of the hypothalamic-pituitary-testicular system. Due to this mechanism there is an abrupt increase in blood (Fig. 1.3) and urinary gonadotropin levels following castration, as well as an increase of frequency and amplitude of LH release pulses. On the contrary, systemic testosterone administration or its implantation in the hypothalamus results in weakening of LH pulsation.

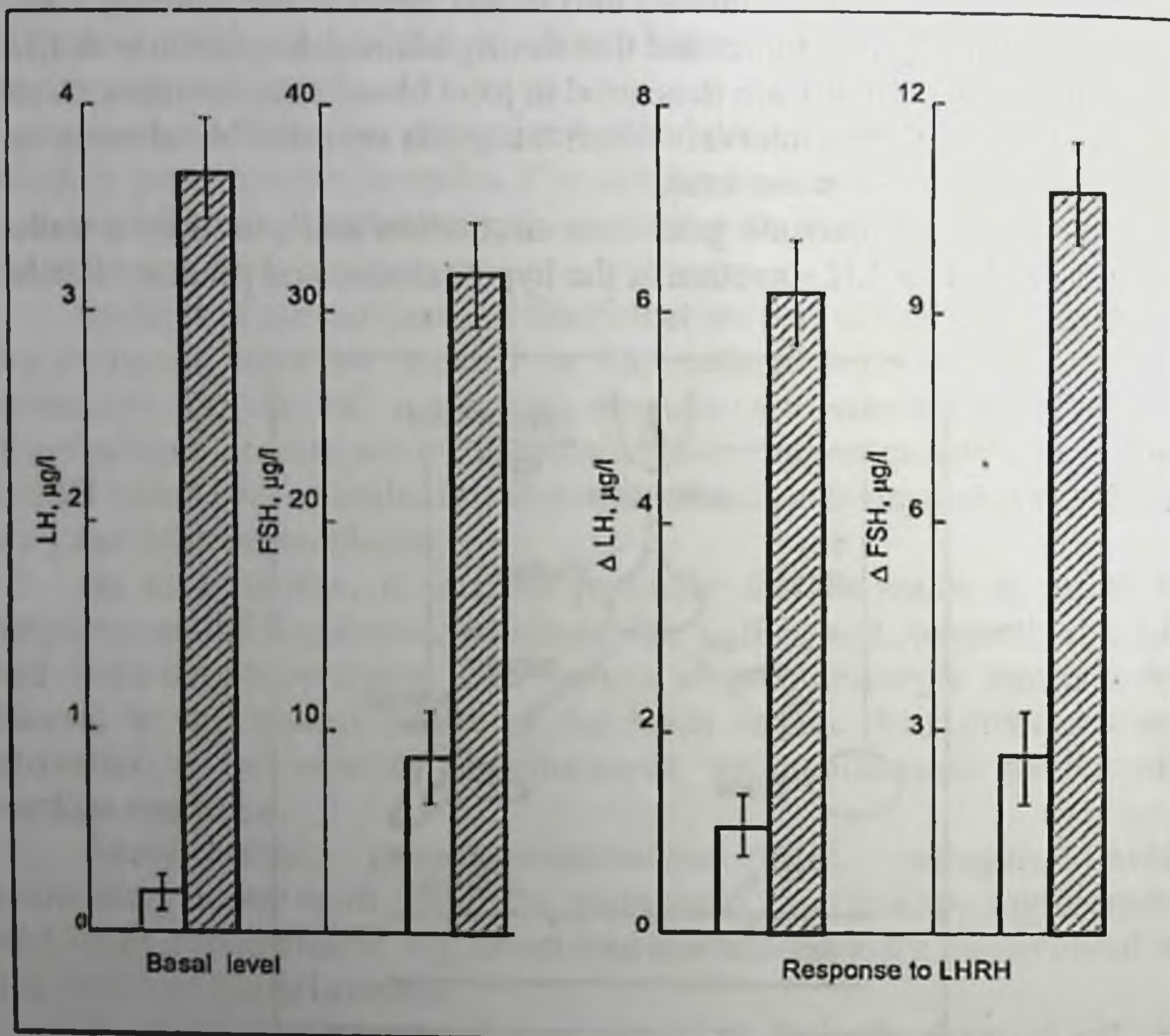


Fig. 1.3. Increase in basal levels of immunoreactive gonadotropins in blood plasma and an enhancement of gonadotropin response to LHRH (LH, FSH 30 min after intravenous infusion of LHRH in a dose of 25 ng) in male rats three days after castration:

□ - control, ▨ - castration.

At the hypothalamic level, the negative feedback loop is closed in its mediobasal area, the arcuate nucleus area seems to be a main point of triggering. This is proved by preservation of feedback following total surgical isolation of the mediobasal hypothalamus from the CNS structures, which are located above, and also by feedback disappearance in males after electrolytic destruction of the arcuate nucleus.

At the pituitary level, testosterone inhibition of LH secretion is accomplished due to the fact that it reduces gonadotropocyte response to LHRH. At the hypothalamic level, down-regulation is more complicated. Undoubtedly, testosterone inhibits LHRH release in blood, however the mechanism of such inhibition has not been understood yet.

First of all, it is still unknown which neurotransmitters participate in the process. Perhaps, serotonin (Naumenko et al., 1983) and gamma-aminobutyric acid are responsible for it. It is possible that testosterone effect on LHRH secretion is mediated by neuropeptide Y.

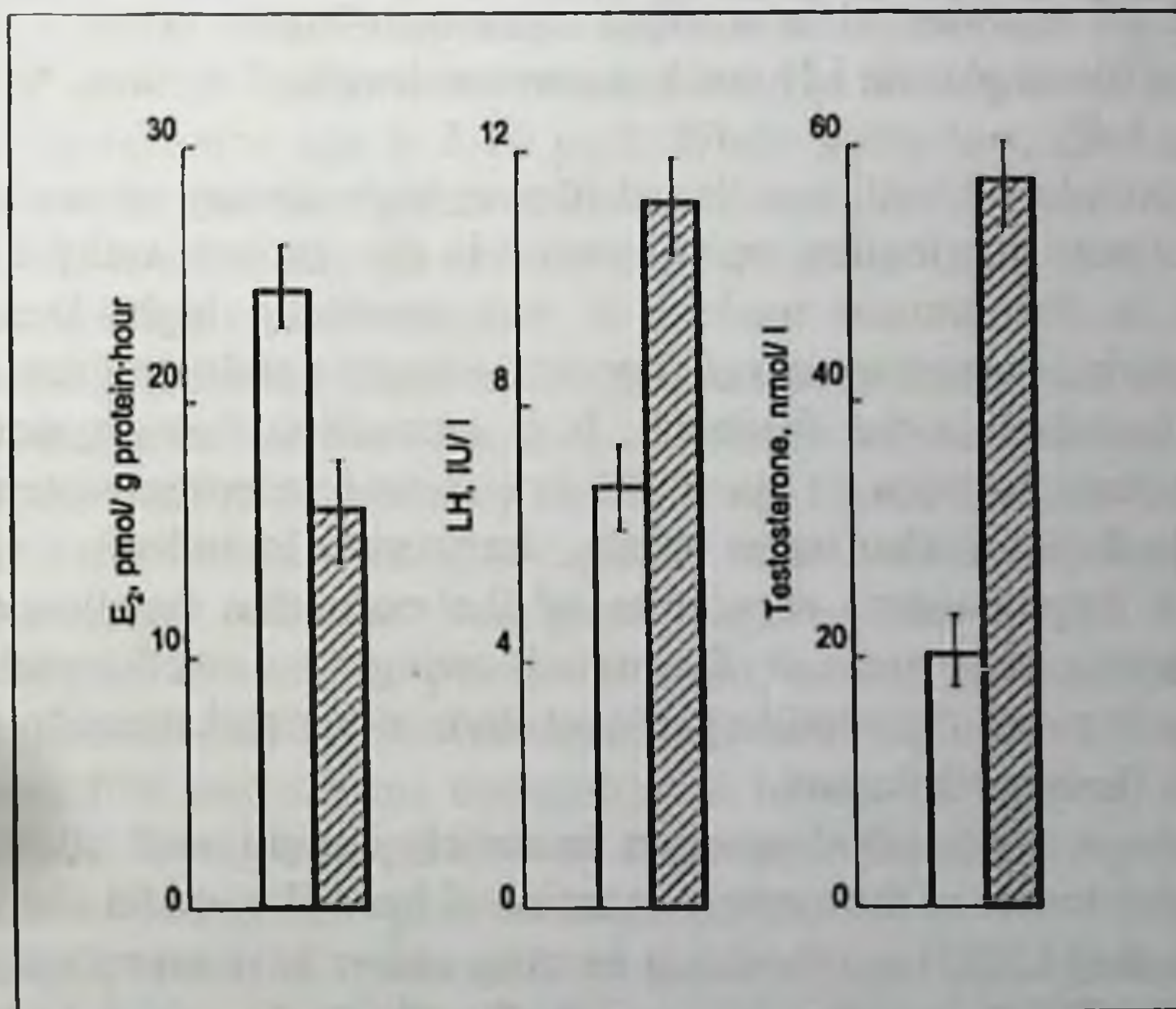


Fig. 1.4. Effect of 1,4,6-androstatrien(e)-3,17-dione (ATD), steroid aromatase inhibitor, on the rate of testosterone conversion into estradiol-17 β (E₂) in the hypothalamus, bioactive Lh I and testosterone contents in male rat blood plasma:

□ - control, ▨ - 24 h following first ATD administration (25 mg/kg i.v. twice a day)

This hypothesis is based on a considerable decrease in LH secretion in castrated male rats after neuropeptide Y injection in the brain third ventricle (Reznikov, McCann, 1993 a, b), which is very much similar to the effect of systemic testosterone administration. The presence of neuropeptide Y-synthesizing neurons in the arcuate nucleus, decrease of hypothalamic neuropeptide Y concentration in response to orchietomy and its recovery under testosterone replacement therapy are completely in line with this hypothesis. Interaction of neuropeptide Y-ergic and serotonergic neurons in the considered process cannot be excluded.

An indispensable condition for testosterone inhibition of LH secretion is its prior conversion into its functionally active metabolites - DHT and estradiol-17 β . In the pituitary, DHT is a main regulatory agent while in the hypothalamus it acts synergistically with estradiol which is formed locally by neurons. Reduction of feedback estrogen component in the hypothalamic-pituitary-testicular system by pharmacological inhibition of C₁₉-steroid aromatase enzyme complex results in the increase of blood plasma LH and testosterone levels (Reznikov, Sinitsyn, 1990, Fig. 1.4).

In accordance with mentioned above, high density of sex steroid receptors tissue distribution was observed in the pituitary and the hypothalamus, in the arcuate nucleus it was especially high. Due to it neuroendocrine tissues selectively uptake androgens and estrogens, which are thus included in the feedback. It is interesting that physical and chemical characteristics of the CNS sex steroid receptor proteins are identical to those in other target organs, the prostate included.

Thus, hypothalamic regulation of the endocrine function of the pituitary-testicular system is facilitated owing to a well-coordinated interaction between the peptidergic, neurotransmitter and steroid receptor systems in the hypothalamus.

We have not touched upon an extremely complicated question of neuroarchitectonics of the systems mentioned here. We would like just to emphasize that LHRH-synthesizing neurons rather have no receptors for sex steroids. Those receptors are mainly found in cells which belong to noradrenergic, GABA-ergic, opioid neurotransmitter systems (Johnson, Everitt, 1990). Apparently, they are also present in neurons, which synthesize serotonin and neuropeptide Y.

The hypothalamic-pituitary-testicular system is under modulatory effect of the pineal gland, lateral nucleus of the brain septum and other

extrahypothalamic CNS structures. In particular, electrolytic destruction of the mentioned brain septum structure results in a decrease in testosterone synthesis and secretion, disturbs photoperiodic regulation of the testes.

Androgen, as well as glucocorticoid, production in the adrenal glands is under pituitary adrenocorticotrophic hormone control (Fig. 1.2). The amount of biologically active androgenic hormones of adrenocortical origin may increase following orchiectomy. This is viewed as a compensatory response to the deficiency of testicular androgens and supports the growth of prostate adenocarcinoma. A deficient glucocorticoid formation (for example, in congenital adrenal cortex hyperplasia) causes an increase in ACTH secretion, which stimulates androgen synthesis in *zona reticulosa* of the adrenal cortex.

Steroid hormones, which were synthesized in the glands, enter the circulation simply diffusing through a membrane of steroid-producing cell and vascular wall. This process depends completely on the intensity of steroidogenesis. Testosterone concentration in blood plasma in healthy men of reproductive age is 3-15 $\mu\text{g/l}$. While aging testicular androgen production in men decreases with a respective decrease in blood testosterone level: at the age over 80 it is within 0,5 - 6 $\mu\text{g/l}$ but often it is close to the lower normal range.

In the circulating blood androgens are found as a part of steroid-protein complexes and also in a free, i.e. protein unbound, form. The free testosterone fraction makes only about 2 % of a total hormone content in blood. It is this fraction that is biologically available for the prostatic cells and other target cells, i.e. biologically active. The rest 98 % of the hormonal pool is bound to plasma proteins, among them sex hormone-binding globulin (SHBG) is considered to be most significant. That is why measuring free testosterone concentration (direct or indirect, based on blood SHBG level) is of paramount importance for assessing biological effect of circulating androgens on target cells.

SHBG, which is synthesized in the liver, is a glycoprotein with a molecular weight of 90 kDa. It has a high affinity for estrogens and androgens ($K_{as} = 10^7 - 10^9 \text{ M}^{-1}$). As to affinity diminution steroids should be ranged as follows: DHT, testosterone, androstane diols, estradiol. SHBG was found in the blood of humans and other primates but not in rats and mice. Estrogens stimulate synthesis of this protein in the liver, androgens, on the contrary, suppress the process. However, such a simple

scheme of regulating blood SHBG content does not reflect the complexity of multihormonal control and does not fall within some clinically established facts. For example, in aging blood SHBG level increases considerably with a moderate decrease in circulating testosterone concentration. As a result, the amount of biologically available androgens decreases. Perhaps, this generally accepted statement should be reevaluated since positive, not negative, correlation between blood testosterone and SHBG levels was found in this age group (Carlstrdm et al., 1990). More detailed information on SHBG, its properties and regulation can be found in reviews by W. Rosner (1990), R. Hampl, L. Starka (1996).

Androgens are rather quickly distributed and metabolized in tissues. In healthy men, testosterone half-life in blood is 30-40 min.

In the prostate, seminal vesicles, other target organs as well as in the liver and the intestine, androgens undergo various metabolic transformations. The metabolites formed have androgenic activity which is greater or less than that of the initial product. For example, tissue androstenedione conversion into testosterone or testosterone conversion into DHT is viewed as functional metabolism of hormones, i.e. activation route. It prevails in androgen-dependent organs, the prostate first of all. But the liver and the intestine are main organs of androgen inactivation. Steroid tetrahydroforms, androsterone and etiocholanolone, which are called neutral 17-oxosteroids, are formed there (Fig. 1.5). In the liver, they turn into water-soluble compounds by forming sulfuric and glucuronic acid ethers which are then excreted with urine and feces.

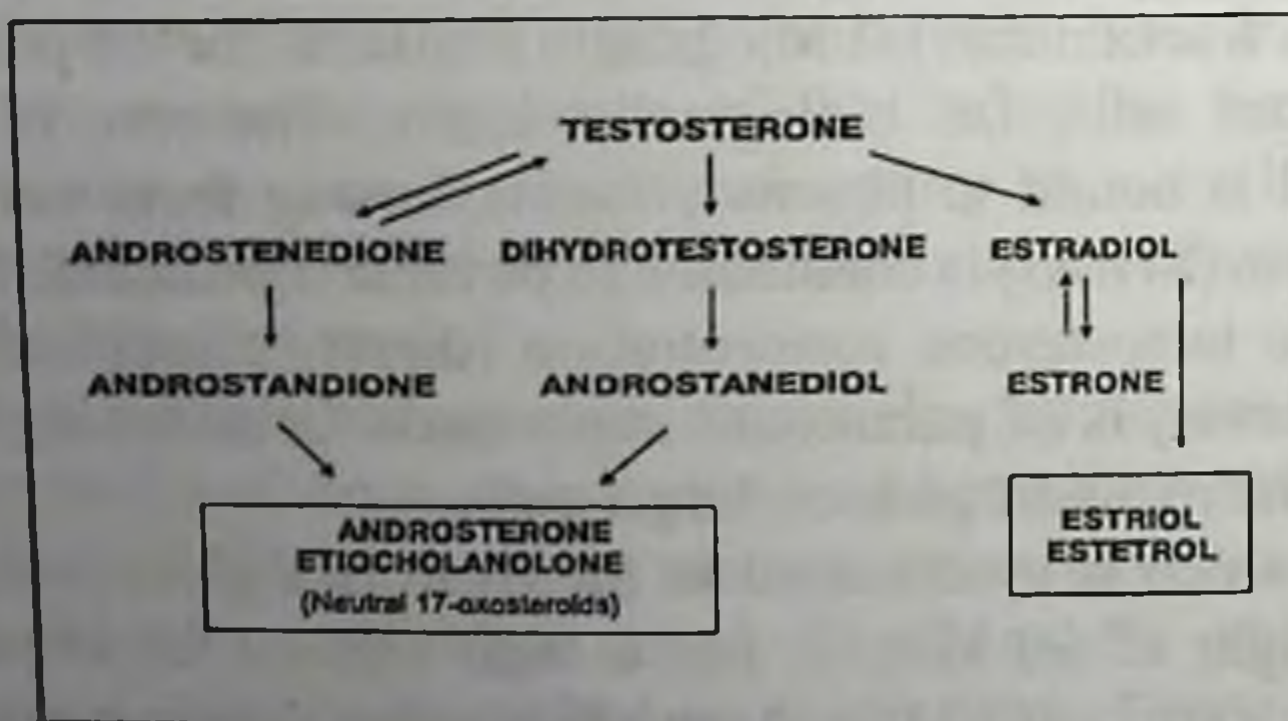


Fig. 1.5. Main pathways of testosterone metabolism

Glucuronides and sulphates make about 90 % of excreted androgens. Only one-third of excreted 17-oxosteroids is formed from

testicular androgens, the rest is made of adrenocortical androgens. That is why when an appropriate method for assessing blood testosterone and other androgen contents was developed, there was no more need to determine daily 17-oxosteroids excretion in order to assess gonadal androgen function.

Accomplishing androgen biological effects in the prostate and other androgen-dependent organs is possible only after dissociation of steroid-transport protein complex and penetration of free steroid into the cytoplasm of a target cell where it undergoes functional metabolism and binds to specific cytoplasmic receptors. Testosterone conversion into DHT facilitates strengthening of a hormonal signal. This reaction is irreversible, it is catalyzed by 5 α -reductase, NADPH-dependent enzyme.

This process was thought to be active in the prostate epithelial cells. However, according to N. Bruchovsky et al. (1980), 5 α -reductase activity in a healthy human prostate is localized mainly in the stromal cells. A concept on stromal-epithelial relation in accomplishing testosterone biological effects in the prostate emerged. According to this concept, in the stromal elements DHT initiates production of paracrine factors that stimulate (EGF, epidermal growth factor) or suppress (TGF β , transforming growth factor) prostatic epithelium function and proliferation. In addition, it was found out that as to quantity, 5 α -androstan-3 α ,17(3-diol (3 α -diol) and androsterone were main testosterone metabolites in the normal human prostatic tissues while DHT prevailed in hyperplastic and carcinomatous tissues (Hammond, 1978).

3 α -Diol and its 3 β -epimer formation from DHT is catalyzed by NADPH-dependent 3 α - and 3 β -hydroxysteroid dehydrogenases of the microsomal fraction. A reversible reaction of 3 α -diol formation is of special significance. This metabolite is viewed as a form of reserving active metabolite (DHT) in the prostate. 3 β -Diol is a regulator of secretory activity of the prostatic epithelium.

The existence of two isoenzymes, steroid-5 α -reductase and 3 β -hydroxysteroid dehydrogenase, was discovered, their distribution in tissues was studied, the structure of complementary DNA and their expression in the human prostatic cells was elucidated (Labrie et al., 1993, 1994; Andersson et al., 1994). The human gene of type 1 5 α -reductase is located on a short arm of chromosome 5, that of type 2 - on a short arm of chromosome 2. Type 2 isoenzyme prevails in prostatic tissues and according to immunohistological studies, specific staining is shown

mostly in the stromal cells while the epithelium demonstrates a weak immunohistochemical reaction. This method allows showing a considerable amount of type 1 5α -reductase in the glandular epithelium of the prostate.

Studies of androgen metabolism in isolated prostatic cells of young rats showed that epithelial cells are 29 times more active than stromal ones in their ability to produce DHT (Orlowski, Clark, 1991). Taking into consideration discrepancies between this and other studies the issue, undoubtedly, needs further elaboration.

One of the most important problems of physiology, which is directly related to hormonal therapy of PC, is the ratio between the testes and the adrenal glands in their contribution to DHT production in prostatic tissues. After castration only 5 % of the initial testosterone concentration is left in men's blood, however prostatic DHT concentration makes 40% of the metabolite amount in intact men (Labrie et al., 1993). This is explained by the ability of the prostate to convert inactive steroids of the adrenal origin - dehydroepiandrosterone, dehydroepiandrosterone sulphate and androstenedione - into active androgen, DHT. This is the reason why after castration contents of androstanediol, androsterone and their glucuronides - main excreted androgen metabolites - showed only a twofold decrease. Proceeding from these data F. Labrie et al. (1993 a, b) concluded that in men aged 65 years adrenal androgens provide 40 % of DHT in the prostate gland but not 5-10 % as it was thought previously proceeding from animal studies. A man and other primates are unique in this respect in the animal world, i.e. their adrenals secrete large amounts of dehydroepiandrosterone, its sulphate and androstenedione. The authors mentioned introduced a special term «intracrinology» for that part of endocrinology, which deals with active metabolite formation in tissues.

In aging, the rate of testosterone metabolism in prostatic tissues slows down. Perhaps, this is due to a decreased testosterone supply to cells because the rate of 5α -reductase reaction is limited by the amount of the available substrate and the synthesis of the enzyme itself is androgen-induced. It cannot be excluded that changes in intracellular DHT, 3α - and 3β -diols concentrations in aging facilitate hyperplastic and neoplastic transformation of the prostatic epithelium.

About 75 % DHT, which circulates in a healthy man blood, are products of extragonadal testosterone metabolism, the rest 25 % is secreted by the testes. Normal blood DHT content is 10 times less than

testosterone level. Because of high DHT affinity for SHBG and because of its low content in blood plasma the DHT contribution to integrated biological effect of androgens on the prostate is not significant. DHT formation in prostatic tissues is of major importance.

A selective uptake of circulating testosterone and its retention in prostatic cells are facilitated in the presence of androgen receptors in the soluble fraction of the cytoplasm. Two types of prostatic protein receptors - α - and β -proteins were found. The former binds testosterone, DHT and estradiol ($K_{as} = 10^7 \text{ M}^{-1}$) and forms complex I with a sedimentation constant of 3.5 S. The properties of this protein remind those of blood plasma SHBG. Apparently, its main function is to provide the necessary amount of biologically active hormones and prevent from their premature degradation.

Of main importance for realization of specific androgen response is P-protein, which has a high selective affinity for DHT ($K_{as}=1.9 \cdot 10^9 \text{ M}^{-1}$) and a low capacity of steroid binding, which is typical for hormone receptors. The DHT - receptor complex has an oligomeric structure with a sedimentation constant of 8-9 S. It dissociates forming monomers (3.5-4.5 S) that are able to get in the cell nucleus where they interact with the DNA acceptor sites.

Cytoplasmic androgen receptors are subacid proteins with a molecular weight of 99 kDa and isoelectric point of approximately 6.8. The described A and B isoforms possess similar functional activities (Gao, McPhaul, 1998). Receptor proteins were purified, complementary DNA was cloned, its structural analysis was performed and amino acid sequence of human androgen receptors was elucidated (Chang et al., 1988 a, b; Lubahn et al., 1988; Trapman et al., 1988; Tilley et al., 1989). The receptor gene is located in the X chromosome in 11-12q locus (Brown, 1989). It encodes synthesis of receptor protein, which consists of three functional domains. A small central domain is responsible for binding receptor molecule to the chromosome DNA, the C-terminal domain facilitates protein binding to a hormone and the N-terminal domain is involved in regulating the transcription.

Cytoplasmic androgen receptor belongs to a superfamily of liganddependent transcription factors. When binding an androgen it turns into its active state and undergoes conformational changes, followed by translocation to the nucleus of a target cell.

Nuclear binding of the receptor protein (which is included in a hormone-receptor complex) activates gene transcription. As a result, biogenesis of ribo- and polysomes increases, as well as synthesis of regulatory, structural and functional proteins including androgen-dependent enzymes (Fig. 1.6). These early events develop in the prostate cell during several hours following testosterone administration (Mainwaring, 1977). The synthesis of proteins secreted by the gland increases as well as production and release of the prostatic «juice», activities of RNA-polymerase, aldolase, phosphatases, phosphodiesterases, glucosamine-6-phosphate synthetase, phosphofructokinase rise. The prostate immediately responds to androgens by increasing the volume of the acinar epithelium cytoplasm, contents of RNA, protein, fructose, prostatic antigen, prostatic acid and alkaline phosphatases. The three latter components are detected in the blood serum.

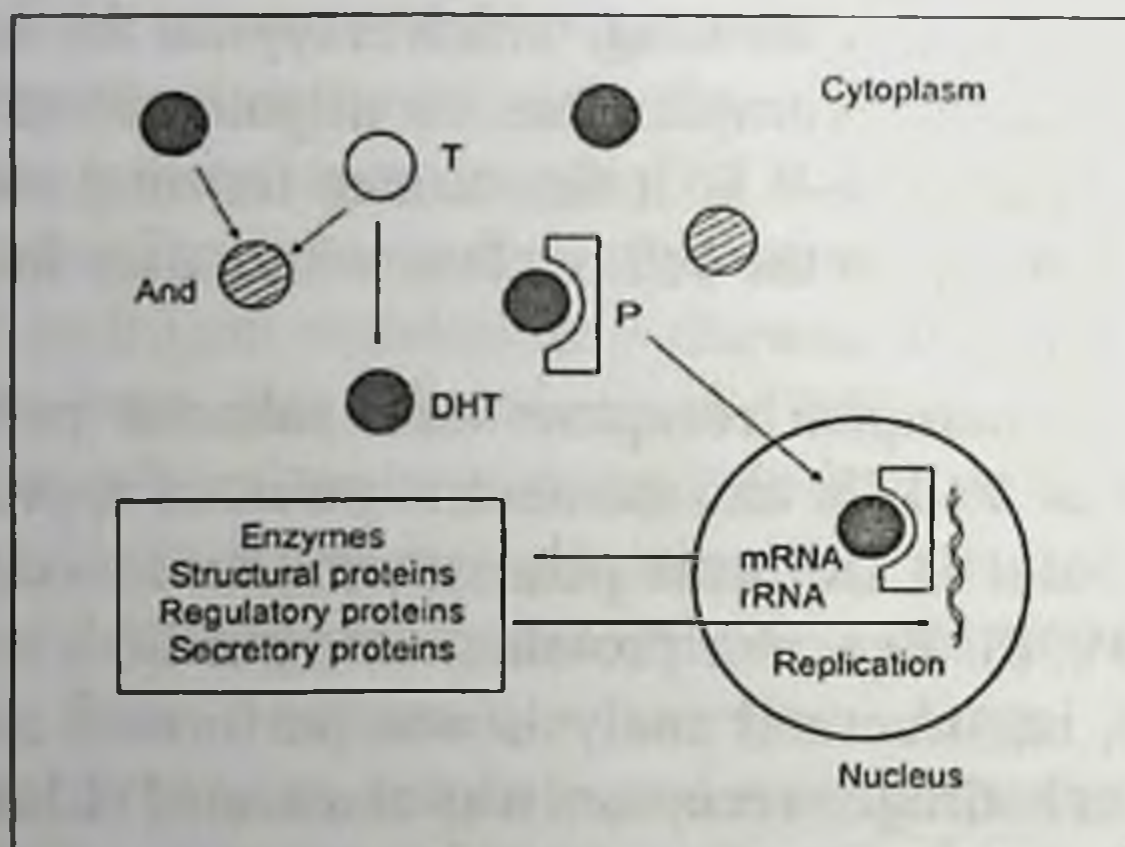


Fig. 1.6. Scheme of testosterone action in the epithelial cell of the prostate gland:

T - testosterone; DHT - 5 α -dihydrotestosterone; And - androstenediol; R - receptor

Under the effect of the androgen DNA-polymerase, thymidine kinase activities increase, DNA replication and cell division take place in the prostate. These late effects are observed 24-36 hours and later after the beginning of androgen action.

The results of our numerous experimental studies, which were carried out with the use of selective blockers of androgen cellular receptors, proved convincingly that these receptors directly participate in

androgen-induced effects in the prostate - increased DNA, RNA and protein synthesis, increased fructose production, intensified proliferation of the epithelium and sustained normal histological structure and weight of the gland (Reznikov, Varga, 1988).

An increase in the amount of the epithelial cells in the prostate is facilitated not only by intensified proliferation, i.e. by mitotic activity, but by deceleration of apoptosis - programmed cell death. In the absence or deficiency of androgens, the glandular epithelium undergoes atrophy, and stromal elements are prevalent in the prostate (Fig. 1.7).

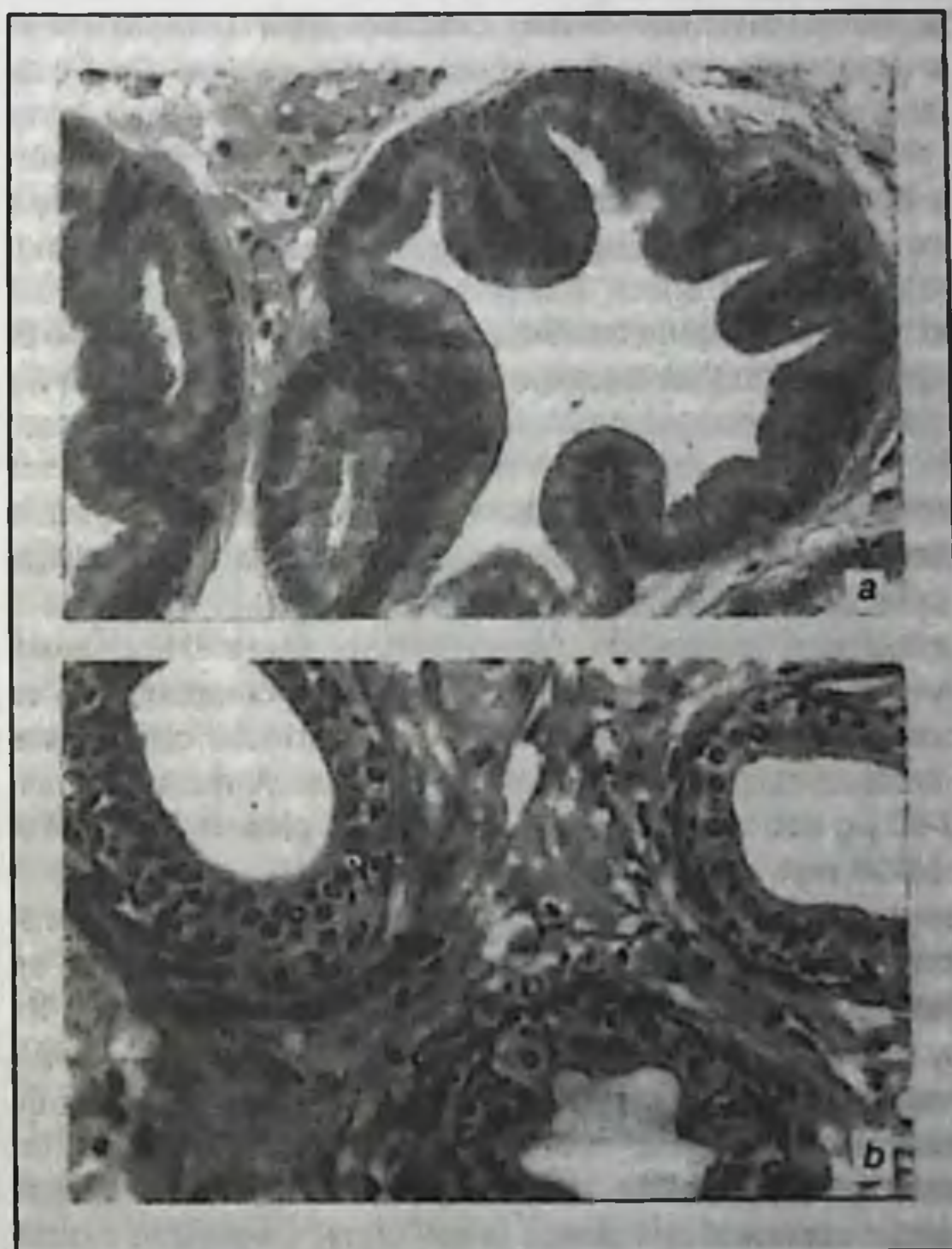


Fig.1.7. Histological structure of the rat ventral prostate. Hematoxylin and eosin staining, x 200:

(a) - normal; (b) - 28 days after castration. Acinar atrophy, lowering of the height of the glandular epithelial cells are clearly seen.

The involution of the prostatic tissues following castration is an active and energy-dependent process, which is initiated by attenuation of the androgen inhibitory effect on apoptosis. According to G.J. Steenbrugge (1991), programmed cell death begins with an abrupt

decrease in the number of androgen nuclear receptors (normally, there are about 10 000 receptor molecules in the nucleus of the prostate epithelial cell) during 12 hours after castration. Chromosomal DNA splits into low molecular fragments under the effect of the nuclear Ca^{2+} , Mg^{2+} - dependent endonuclease, which is activated by increased intracellular contents of calcium ions. On days 2 and 3 after castration the number of apoptotic bodies in the prostatic epithelium increases sharply. At the same time there is an increase in the expression of *c-fos* and *c-myc* protooncogenes, heat shock proteins, TGF-gene and of testosterone-repressed genes - glutathion-S-transferase Xb-i and TRPM-2. It is interesting to mention that the expression product of the TRPM-2 gene is not detected in the normal prostatic tissues. In contrast to *c-fos* and *c-myc*, this protein is not a transcriptional factor in a cascade of intracellular events, which result in a cell death. Most likely, it is a cell defense.

Estrogens. The testes (Sertoli cells) and extraglandular tissues, adipose cells first of all, are sources of endogenous estrogens in male organism. In these tissues, circulating testosterone and androstenedione convert, under the effect of aromatase enzyme complex, into estradiol and estrone, respectively. Estrogens of extraglandular origin make about 90 % of total circulating estrogenic hormones. A male organism produces 48-60 μg estrogens daily. In male blood plasma estradiol concentration is 20-30 ng/l.

Some morphologic and functional changes in the prostate that can be observed in orchietomized laboratory animals following estrogen administration, demonstrate estrogen-sensitivity of this organ. It is also proved by the presence of estrogen receptors in separate cell clones. They prevail in the central part of the gland, the so-called male utricle.

Possible physiological role for endogenous estrogens in the competent cells of the prostate comes to trophic effects. Their direct action on androgen-dependent cell clones is still under discussion though some authors reported estradiol ability to inhibit DHT formation (Leav et al., 1971). However it is not proved by measurements of the prostate weight in castrated dogs to whom estradiol was administered simultaneously with continuous replacement therapy with testosterone propionate or DHT. Under DHT administration, estrogen-induced lessening of the glandular size was more pronounced than under testosterone propionate administration, though in the case of 5α -reductase inhibition the changes would be quite opposite (Holscher et al., 1979). It is possible that estrogens disturb

androgen-receptor interaction in the prostatic cells, in the meantime, there is information on the increase of androgen receptor synthesis in the PC tissues under the effect of estrogens (Mobbs, Johnson, 1998).

Direct regulatory effect of endogenous estrogens is obviously less significant than indirect effects, which are accomplished by changing secretion and bioavailability of androgenic hormones. Experimental and clinical data show three such modes:

1. lessening gonadotropic stimulation of the testes;
2. direct inhibition of Leydig cell function;
3. increase of circulating SHBG level.

The first way seems to be the prevailing one. It starts from estrogen inhibition of hypothalamic LHRH synthesis and release and as a result, LH and testicular androgen secretion decreases considerably.

Estrogen direct inhibitory action on steroidogenesis in Leydig cells is observed *in vitro* in experiments with rat (Sairam, Berman, 1979) and human (Daehlin et al., 1983) testicular tissues. Estrogens directly inhibit the development and growth of Leydig cell population in gonads (Abney, 1999). In addition to a decreased gonadotropin secretion, testicular steroidogenic response to gonadotropic stimulation reduces. And, finally, estrogens induce SHBG synthesis in the liver. Due to its concentration in the blood plasma rises and, respectively, the amount of free testosterone decreases.

In elderly men, testicular estrogen production rises. When androgen levels in systemic circulation are moderately decreased it results in a shift in androgen-estrogen balance towards female sex hormones. When such a shift is pronounced enough, it may cause age-related sclerotic atrophy of the prostate.

Prolactin. Prolactin action on the prostate results in growth-stimulating effect (Boyns et al., 1975), which is manifested in the weight increase, intensified secretory activity, increased fructose and citric acid levels and DNA and RNA synthesis. These changes are not caused by prolactin direct effect on metabolic processes in the gland. The reason is that on the one hand prolactin supports testicular androgen formation (see above), and on the other hand, it potentiates stimulatory effect of male sex hormones on prostatic tissues, which is proved by experiments in hypophysectomized and castrated rats (Portnoy, Grodzovskaya, 1984).

It is well known that the number of cytoplasmic androgen receptors in the prostate is increased under prolactin effect. In addition, prolactin

promotes testosterone conversion into DHT. Both effects are accomplished with cAMP as a second messenger. As to regulation of prolactin secretion, it should be mentioned that the release of this pituitary hormone is tonically inhibited by dopamine, which gets to the portal circulation from fiber terminals of tuberoinfundibular dopamine tract. The same effect is observed when neuropeptide Y is administered to the brain third ventricle in males (Reznikov, McCann, 1993) whereof it could reach the pituitary gland through the ependyma cells, which line the ventricular fundus.

Under definite conditions, stress for example, prolactin secretion is stimulated by hypothalamic thyrotropin-releasing hormone. The same effect is produced by the neuropeptide galanine. Prolactin formation and secretion are increased under estrogen effect, and this should be taken into consideration as a factor, which complicates estrogen therapy of PC (in particular, it promotes gynecomasty).

Together with androgens, estrogens and prolactin other hormones play certain roles in regulating growth, structure and function of the prostate. Cellular growth factors play a special role among factors of para- and autocrine regulation. They are of great importance for initiation and development of PC. The role of prostaglandins, F_{2a} in particular, is essential. For the first time, prostaglandins were obtained from extracts of the prostatic tissues and seminal fluid. The synthesis of these substances in the prostate rises under prolactin effect, and testosterone increases specific reception of prostaglandin F_{2a} by prostatic cell membranes. The data available show that prolactin and prostaglandin F_{2a} occupy the same receptor sites on cell membranes.

1.2. Hormonal, cellular and molecular determinants of prostate cancer growth

Hormonal profile in PC. Taking into consideration that normal and neoplastic prostates are androgen-dependent and the fact that PC is «a privilege» of elderly men, it is understandable to establish connections between this disease and age-related changes in the endocrine status. The latter include decrease of free testosterone level and increase of testosterone bound to blood plasma proteins, rise in circulating estrogen levels and normal or moderately decreased testosterone concentration, which causes the shift in androgens/estrogens ratio towards estrogens (Tiktinsky, 1990).

The results of three-year randomized crossover controlled epidemiological study of 1700 men aged 39-70 (Gray et al., 1991) are of interest. It was shown that blood plasma free testosterone level decreased on average by 1.2 % a year, that of total testosterone - 0.4 % a year, SHBG level increased by 1.2 % annually. Blood DHT and estrogen contents remain at the same level at the age of 39-70, dehydroepiandrosterone level decreases by 3.1 % a year. Age-related changes of pituitary hormones secretion are characterized by an annual increase of LH level by 1.3 %, that of FSH by 1.4 %, prolactin level decreases by 0.4 % a year. Illnesses, bad habits, alcohol abuse, obesity, psychotropic drugs, chronic and acute psychoemotional stress produce negative effect on sex hormones secretion. However, numerous studies do not confirm the hypothesis on etiological role of hormonal imbalance in PC.

Androgens do not induce PC, they only promote malignant transformation of the glandular epithelium and further stimulate tumor growth. At the same time correlation between plasma androgen concentrations and PC spreading as well as response to hormonal therapy was observed. According to A. Portnoy and F. Grodzovskaya (1984), the British group for prostate cancer study published summarized data on hormonal profiles in PC patients submitted by several clinics. Blood plasma testosterone level was significantly higher in metastatic disease and even much higher in case of extracapsular invasion. At the same time no difference in estradiol, LH, FSH and prolactin levels was observed depending on PC stage and metastatic spreading. Increase in blood plasma growth hormone level was significant.

Literature data on blood plasma testosterone content in PC patients as compared to healthy men are contradictory. Several authors report an increased hormone concentration in PC (Chanadian et al., 1979), others do not confirm this data (Sciarra et al., 1990). No difference in blood plasma DHT levels was noted.

Table 1.1. Androgen function in PC patients and healthy men according to blood plasma analysis

Parameter	Healthy men (n = 9)	PC patients (n = 19)	P
Testosterone, nmol/l	7.7 ± 1.3	11.7 ± 1.1	<0.05
DHT, nmol/l	0.38 ± 0.14	0.42 ± 0.07	> 0.5
SHBG, nmol ³ H-DHT/l	12.5 ± 1.5	26.9 ± 2.8	< 0.001
FTI	67.6 ± 14.6	42.5 ± 4.0	> 0.05

Testosterone was radioimmunologically assayed, DHT - using the same assay following testosterone inactivation with potassium permanganate (from Puri et al., 1981). FTI, free testosterone index (see text)

We have studied the androgen status in PC patients without distant metastases ($T_{1-2}N_xM_0$ and $T_3N_xM_0$ stages) and healthy men of the same age. As Table 1.1 shows, blood plasma total testosterone level is significantly higher, DHT content is within normal range and DHT share in the circulating androgen pool is decreased. Attention should be paid to a twofold increase in plasma SHBG level and a pronounced trend to a decreased free testosterone index (FTI) which is calculated as

$$FTI = C_T / C_{SHBG} \times 100,$$

where C_T is testosterone concentration, C_{SHBG} is blood plasma 3H -DHT-binding capacity under ligand saturation (Tsatsoulis et al., 1990). The reason for an increase of testosterone level may be either deceleration of its degradation due to high SHBG concentration or an increase of gonadotropic stimulation of testes because of low FTI.

A conclusion on sufficient androgen saturation of the body as an indispensable condition (but not the cause) for PC is confirmed by the fact that this pathology was never observed in eunuchs or men who were castrated before puberty (Schroder, 1991). Even long-term administration of large doses of testosterone propionate, DHT and androstane diols to laboratory animals separately or in various combinations does not reproduce malignant transformation of the prostate, and we had an opportunity to make sure of it ourselves. Experimental modeling of prostatic adenocarcinoma in rats is possible only using chemical carcinogens together with exogenic hyperandrogenization. These facts convincingly prove that excessive endogenous androgens cannot be considered the original cause for neoplastic transformation of prostatic tissues.

In a prospective study (Eaton et al., 1999) no relationship between blood androgenic hormone levels (with an exception of androstane diol glucuronide) and risk of PC development was shown. At the same time it is quite possible that the risk of PC is in some way associated with androgen metabolism (Lunn et al., 1999), kinetics and bioavailability. Referring to a number of studies in epidemiology F.H. Schroder (1991) reports a relationship between diet and PC incidence. In case of high content of animal fats in diet, testosterone bioavailability is increased

owing to a decreased SHBG level. This type of diet that is called «western diet» is associated with a significantly higher prevalence of PC in populations studied. Thus, it should be admitted that androgens play a permissive role in PC onset.

The question of testosterone metabolism in tissues of PC patients seems to be important. In tumorous prostatic tissue 5 α -reductase activity is much lower than in normal one (Klein et al., 1988). As a result, DHT concentration decreases while the level of unmetabolized testosterone rises (Krieg et al., 1979). On the whole, in cancerous tissue the intensity of testosterone transformation into DHT is characterized by individual variability. Often high DHT concentrations are found in differentiated tumors. Low DHT level in a malignant gland is observed under low cell differentiation and prevailing androgen-resistant cell populations.

Lately, some features in the expression of four isoforms of 17 β -hydroxysteroid dehydrogenase, that is enzyme that controls mutual transformations of testosterone and androstenedione, estradiol and estrone, were elucidated in several cell lines of human PC (Castagnetta et al., 1997). 5 α -Reductase type I expression in prostate cancerous tissue is increased (Lehle et al., 1999).

Possible relationship between vitamin D and risk of PC development is under discussion. Vitamin D active form (D₃) acts in a cell through a specific receptor that belongs to steroid receptor family. Like steroid hormones, vitamin D₃ regulates gene expression and effects cell proliferation and differentiation. In PC cell culture, it increases cytokeratin contents and PSA formation, i.e. promotes their differentiation. Perhaps, this effect is due to an increase in androgen receptor synthesis under the effect of 1 α -25-dihydroxyvitamin D₃ (Zhao et al., 1997). It was noted that PC is less often in regions where insolation is high. As D.M. Peehl et al. (1994) reported at the symposium in Milan, 10-year prospective study resulted in establishing negative correlation between PC incidence and blood vitamin D₃ content.

Hormonal modulators of PC growth. As it has already been mentioned, androgens and especially DHT, most active of them, are undoubtedly major hormonal factors, which support PC growth. At the early stages of the disease about 85 % of cells belong to androgen-dependent clones which later are substituted with androgen-resistant cells (Fig. 1.8). Somatotropin stimulatory activity in PC is possible. Hyperprolactinemia occurs frequently in metastatic PC and it is associated

with poor prognosis and low efficacy of the treatment (Costello, Franklin, 1994), presumably due to a direct stimulatory effect on cancer cell proliferation (Welsch, Nagasawa, 1997). That is why pharmacological control of cancer-related hyperpolactinemia seems to be important in the management of PC patients (Lissoni et al., 2000). On the contrary, other hormones inhibit PC development. These include, first of all, estrogens, both natural and their active synthetic analogues. As well as in a healthy organism, estrogen antitumoral effect is mediated by inhibited secretion and decreased bioavailability of male sex hormones. This is achieved through inhibition of LHRH-synthesizing neurons, Leydig cells and an increase in hepatic SHBG synthesis.

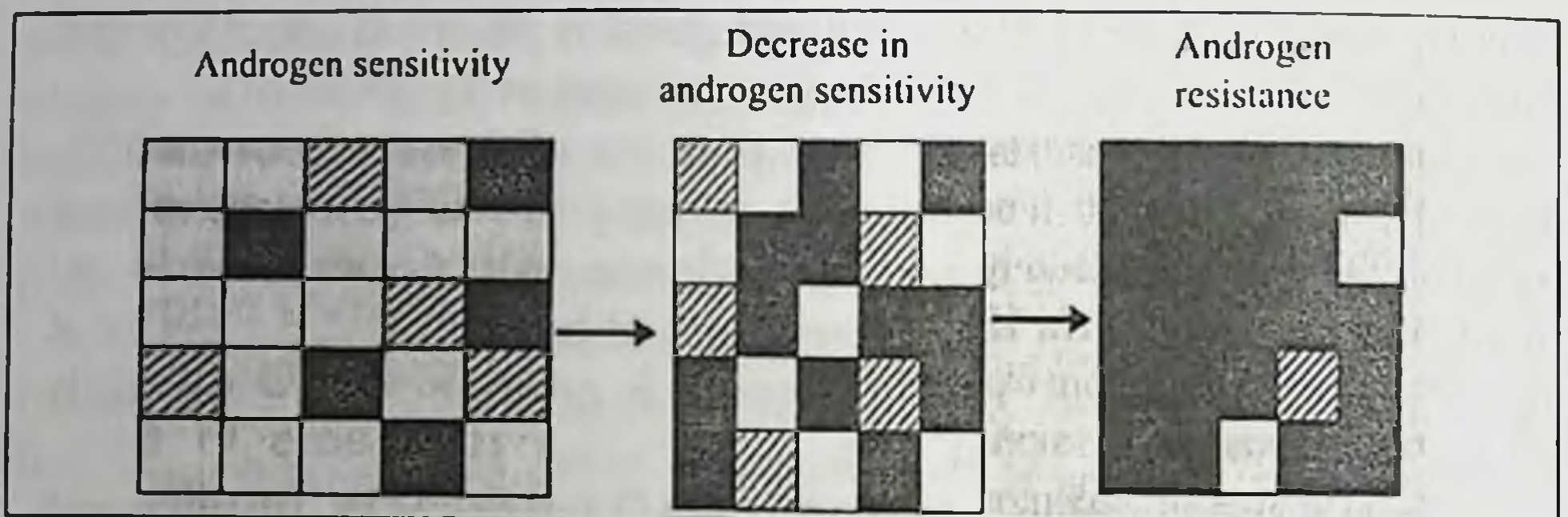


Fig. 1.8. Formation of androgen resistance in PC development. The diagram illustrates the tumorous tissue distribution of androgen-dependent cells (open squares), androgen-responsive cells (shaded squares) and androgen-resistant cells (black squares)

Somatostatin (hypothalamic inhibitor of growth hormone secretion) also inhibits PC growth. This effect is caused by inhibiting growth hormone secretion and also by a direct action on a tumoral tissue. Reassuring results of somatostatin clinical use for PC treatment were obtained (Calais de Silva, 1994) It is known, however, that somatostatin cellular receptors, which are always found in rat prostatic adenocarcinoma (Dunning R 3327), are not always present in human PC tissues. That is why the mechanism of somatostatin antiproliferative action on malignant cells needs further study. Possibly, it is related to dephosphorylation of epidermal growth factor receptor (Brevini et al., 1994).

Paracrine and autocrine regulators. Nowadays oncologists pay special attention to the factors of intercellular interaction (paracrine) and autocrine regulation. In this respect PC is not an exception. These factors

produced by stromal or epithelial cells of the prostate inhibit or stimulate tumor growth. Fibroblast growth factor, insulin-like growth factor, epidermal growth factor, transforming growth factor, TGF α , exert stimulatory effects (Marelli et al., 1994; Limonta et al., 1995). Transforming growth factor, TGF β , and, possibly, LHRH of local origin (Azad et al., 1993; Dondi et al., 1994; Limonta et al., 1995) produce antiproliferative effect. IGF-1 level is thought to be a risk factor for prostate cancer (Pollak et al., 1998).

Recent study by Okamoto et al. (1997) showed possible cytokines involvement in androgen-induced proliferation of prostatic cancerous cells. In the presence of DHT, LNCaP cells start to express interleukin-6, which stimulates proliferation of this androgen-dependent cell line.

Androgen receptors. The status of androgenreceptor system in PC has been studied for many years already because cellular receptors of male sex hormones play a very important role in androgen action on normal and malignant prostatic tissues. For several reasons this question turned out to be very complicated. These include a considerable individual variability, uneven distribution of receptors in stromal and epithelial cells, possible dependence on the PC stage, differentiation of malignant cells etc. However, it is obvious that being androgen-binding transcription factors, these protein molecules directly regulate expression of those genes, which are responsible for cell proliferation and some specific functions of prostatic epithelium, both normal and malignant (Trapman, Brinkmann, 1991, 1996). It is believed that high «saturation» of prostatic tumoral tissue with androgen receptors may prove persistence of androgen sensitivity and advantageous therapy with androgens (Ekman, 1980; Mobbs et al., 1980; Ghanadian et al., 1981; Pertschuk et al., 1982; Fyodorov et al., 1983; Bassalyk, 1987). In practice, measurements of androgen receptors in PC tissues sampled during prostatectomy, transurethral resection or by means of transrectal puncture biopsy may serve a reference-point when choosing a suitable treatment for the initial tumor and metastases, making prognosis and evaluating the effectiveness of hormonal therapy. Concentration of functionally active androgen receptors in the glandular tumoral tissue (found in 11 of 18 newly diagnosed patients) is within a wide range from 26 to 238 fmol ^3H -DHT/mg protein (Kushlinsky et al., 1983, 1984).

In the study that was carried out by Dr. S. Varga together with the authors, high variability of receptor concentrations was shown. Tumor

samples were obtained during radical prostatectomy. Concentrations of androgen receptors were assayed in cytosol fraction obtained by ultracentrifuging of 20 % homogenate at 105 000 g during one hour. ^3H -DHT was used as a ligand. Non-specific binding of radioactive ligand was measured in similar samples with 400-fold excessive unlabeled DHT.

Free and bound ^3H -DHT fractions were separated by a solid phase adsorption on dextran- and gelatin-coated activated charcoal.

Cytoplasmic androgen receptors were found in tumoral tissues in all 18 patients who were operated on. Their contents ranged (fmol ^3H -DHT/mg protein): from 7.7 to 44.0 in 4 patients, from 75.1 to 160.4 in 11 patients, from 205.5 to 332.8 in 3 patients. Thus, in the majority of cases high level of androgen receptors was observed. Different ratio of stromal and epithelial cells in studied PC samples contributes greatly to the data variability. This statement is supported by F. Markland and L. Lee (1979) who found direct dependence of androgen-receptor protein concentrations on the ratio of connective tissue and epithelial cells in the rat prostate adenocarcinoma (Dunning R 3327). Tumor cells with abundant stroma, as a rule, showed few low receptor level while their high level corresponded to prevailing neoplastic epithelial cells.

As to the frequency of detecting androgen receptors in prostate malignant tumors, literature analysis gives contradictory findings: some authors found them in all samples of tumor tissue as we did, others only in 60-80 % of cases (see P. Bassalyk, 1987). This monograph gives opposing opinions of different authors who studied correlation between the level of cytoplasmic androgen receptors and degree of tumor cytodifferentiation.

N. Kushlinsky et al. (1983, 1996) showed that in highly differentiated prostatic adenocarcinomas cytosol androgen receptors were found rather often (72.9 % of cases). And it determined their positive response to castration and estrogen therapy. In moderately and poorly differentiated adenocarcinomas (cribriform and solid-trabecular) these receptors were found only in 39.5% of cases. In highly differentiated receptorpositive prostate tumors cytosol receptor contents measured by radioligand assay ranged 10-100 fmol/mg protein. In moderately and poorly differentiated receptor-positive tumors it exceeded 100 fmol/mg protein. In our opinion, the latter may be related to amplification of androgen receptor gene (Koivisto et al., 1997).

It should be mentioned that the role of androgen receptors in PC development needs revision after the study by Kokontis et al. (1998) was published. An increase in cellular androgen receptor levels may be associated not with acceleration of cellular proliferation but on the contrary, with its inhibition. This paradoxical effect was found in long-term cultivated LNCaP 104S cells following their transition to a decelerated or accelerated growth stage. Addition of androgens to the culture medium inhibited tumor cells proliferation and restored their androgen-dependent status. It was established that androgen inhibition of cultivated human PC cells proliferation was mediated by inducing cellular inhibitory factor Cdk2, which was required for normal cellular division cycle.

According to immunohistochemical studies (Ruizeveld de Winter et al., 1990), in moderately and highly differentiated sites of human PC all tumor cells have androgen receptors while they are not found in poorly differentiated parts or their amounts vary greatly. Using the same assay androgen receptors were found in lymph nodes involved as well as in bone and brain metastases (Hobisch et al., Smith, 1995; Klocker et al., 1996), i.e. in advanced disease. Immunohistochemical analysis of androgen receptors in PC tissues from 90 patients showed their absence in 15 cases, which correlated with the disease development (Pertschuk et al., 1995). The risk of fatal outcome in these 15 cases was 2.5-fold that in patients with positive immunohistochemical staining for androgen receptors. The authors conclude that this assay allows making a prognosis as to survival and response to endocrine therapy.

1.3. Molecular mechanisms of prostate cancer progression and resistance to endocrine therapy

As it has already been mentioned at a disease onset in a heterogenous population of PC cells the majority of tumor cells are androgen-dependent. However, suppression of their proliferation through androgen deprivation (castration, antiandrogens, estrogens, LHRH agonists) makes a situation when androgen-independent cell clones have relative priorities. Using an experimental model of androgen-dependent breast tumor (Shionogi carcinoma), which was transplanted to male mice, accelerated increase of tumorigenic stem cells following castration was shown. This process is observed in intact human prostatic adenocarcinoma without endocrine therapy. As a result, the tumor

becomes hormone-resistant and this is manifested in a relapse and metastatic spreading with hormonal treatment getting on. It should also be mentioned that even in early diagnosis only 80 % of patients respond positively to androgen deprivation, the rest 20 % demonstrate no effect. That is why molecular mechanisms of complete or partial loss of hormonal dependence by PC cells are carefully studied (Reznikov, 1998).

Mutation of androgen receptor gene. Loss of androgen sensitivity by PC cells may result from a decrease in the number of receptor molecules, disturbances in their kinetics, gene transcription and translation of androgen-inducible proteins, activation of androgen-independent mechanisms, which regulate prostate growth and, finally, receptor gene mutations, which change functional activity of the receptor molecule, i.e. specificity and kinetic parameters of interaction with a ligand. Since the gene that encodes synthesis of androgen receptor is located in the X-chromosome, its mutation in males is inevitably manifested by changing the amino acid structure of the receptor protein.

Using molecular biology methods point mutations of androgen-receptor gene were found in human PC biopsies, bone metastases, inoculated human PC and its cell lines. Many authors report mutations in androgen-binding domain of the receptor. In tumoral LNCaP cells originating from human PC, mutant substitution of adenine with guanine in DNA codon 868 of the receptor ligand-binding domain was discovered. It is manifested by a substitution of threonine residue with alanine residue (Trapman, Brinkmann, 1991, 1996). Recently a similar mutation was found in human PC bone metastases (Brinkmann, 1996). In inoculated human prostate tumor CWR22, substitution of cytidine with thymine in codon 874 was found. As a result, histidine is substituted with tyrosine in the ligand-binding domain of the receptor molecule (Tan et al., 1997). Other similar mutations were described (Harper et al., 1994).

Possible consequences of these mutations include changes in the spectrum of ligands, which interact with androgen receptor, resulting in insusceptibility to androgen deprivation and further tumor growth (Culig et al, 1998; Jenster, 1999). Indeed, PC whereof cancerous LNCaP cells originated progressed in a patient despite estrogen therapy (Horoszewicz et al., 1980).

Conclusions that were made by the authors mentioned as well as by other researchers (Berrevoets et al., 1993) are of great interest and importance. According to them, not only testicular androgens but also

progesterone, adrenal androgens (dehydroepiandrosterone, androstenedione), androgen metabolites (androsterone, androstanediol) and even antiandrogens (cyproterone acetate, hydroxyflutamide, nilutamide) may bind and activate mutant receptors. Presumably, this bypass of androgen receptor activation is accomplished when testicular androgen levels are low following castration, PC therapy with estrogens, LHRH agonists and when antiandrogen therapy (with cyproterone acetate, flutamide etc.) is applied.

Mutant androgen receptors are seldom found in PC tissues. The question arises: are there mechanisms in the tumoral cell, which activate normal androgen receptors when androgen levels are low? Klocker et al. (1994, 1996) showed that intracellular processes involving epidermal growth factor, insulin-like growth factor IGF-1, LHRH and cyclic AMP might be such alternative routes. These local regulators are able to activate androgen receptors in the cell culture even in the absence of androgenic hormones. Hence, it may be assumed that the signal cascade, which is usually initiated by androgens, is activated under androgen deprivation as well. In this case androgen deprivation as a way to treat PC turns out to be ineffective.

It is possible that an increase in androgen receptor synthesis with a consequent hypersensitivity of androgen-dependent cells to androgen steroids despite the continuous expansion of androgen-independent cell clones are even more important for PC progression under endocrine therapy (Taplin et al., 1999). As Koivisto et al. (1997) showed, amplification of androgen receptor gene and its increased expression in human PC tissues are observed in 28 % of patients who relapsed after endocrine therapy but in none of untreated tumors. In all cases, with one exception, gene structure was normal. Its amplification was accompanied by an increase in the respective mRNA level, which was established by *in situ* hybridization. Survival in patients with gene amplification was significantly higher than in patients without gene amplification who demonstrated resistance to endocrine therapy.

It is possible that on the one hand increased expression of androgen receptors suppresses transformation of tumor cells towards dedifferentiation and independence from androgens. On the other hand, it is the cause of ineffective endocrine therapy since there appears increased sensitivity of tumor cells to persistent low androgen levels, which promote cell proliferation. The further tumor progression and metastatic spreading

are associated with the transition to the stage of hormoneindependent malignant growth, its mechanisms will be discussed below.

Chromosome aberrations. One of principal postulates of molecular oncology says that malignant transformation of tissues is a multi-stage process in which accumulation of genetic changes results in uncontrolled cell proliferation. Further selection of cells with most aggressive phenotype explains the occurrence of metastatic tumors.

About 85 % of human and animal PC biopsies demonstrate signs of histological heterogeneity which is reflected in increased genetic instability (Isaacs, 1998). In PC progression loss of chromosome 8p, 10p, 10q and 16q segments is found frequently. It is loss of 16q segment which is associated with loss of function by E-cadherin - tumor growth suppressor which restrains its aggressive growth (Schalken, 1994). This process is accompanied by mutant inactivation of another allele. Further study of heterozygosity loss in PC cells may result in a discovery of a new tumor suppressor gene(s) whose loss or inactivation causes accelerated tumor growth (Romin, 1991). Possibly, loss or low expression of p27 (protein, which inhibits cyclin-dependent kinase of the S-phase cellular division) is associated with chromosome aberrations in PC with aggressive phenotype (Macri, Loda, 1998).

In hormone-independent PC cell subpopulations of LNCaP culture, deletion of chromosome 8p segment was found while in androgen-dependent subpopulations no abnormalities of chromosome 8 were revealed (Konig et al. 1989). It is believed that specific deletions may activate cell oncogenes and, as a result, the tumor becomes androgen-independent.

Chromosome aberrations always accompany formation of hormonal independence in human PC (Verma et al., 1999) and in inoculated Dunning R 3327 in rats (Isaacs et al., 1982).

As a result of these and other cytogenetic studies there appeared an idea that genetic instability in PC (as well as in other tumors) caused an increase in tumor cell clones with various phenotypes. An unfavorable consequence of this process is an appearance of a clone that is characterized by hormonal autonomy and super aggressiveness. Clonal selection is accompanied by reduced histological heterogeneity of PC and its metastatic spreading, i.e. increase of its malignancy.

A question about possible genetic predisposition to PC is of special importance. Analysis of data available (Isaacs et al., 1996) shows that

according to familial heredity prostate cancer yields only to carcinoma of the lip, skin melanoma and ovarian cancer but is more frequent than cancer of the large intestine and breast cancer. In 15 % of PC patients their father or brother suffered the same disease. Inheriting predisposition to PC corresponds to Mendel law of transmitting features according to a dominant pattern. Though cases with such inheritance make less than 10 % of PC cases, which are registered at the age of 85, they make 40 % among patients under 55 (early onset of the disease).

Cell oncogenes. One of the most important mechanisms of carcinogenesis is cell oncogenes activation, which is induced by carcinogens or retroviruses. They are supposed to be involved in synthesis and/or secretion of cell growth factors, which control cell proliferation. When native PC and its cell lines were examined increased expression of various oncogenes, especially *ras* oncogenes, was found. In addition, *myc* and *sis* oncogenes demonstrate high level of expression (Roehrborn, 1991). It is interesting that expression products of these genes are able to modulate the process of apoptosis (programmed cell death). It is not clear yet to what extent oncogenes are involved in transformation of androgen-dependent PC into androgen-independent form.

Apoptosis. A body of evidences proves that disturbances in apoptosis are associated with carcinogenesis and tumor progression (Filchenkov, Stoyka, 1999). Decrease in PC sensitivity to androgens results in recurrences and accelerated malignant growth despite endocrine therapy. At the same time the apoptosis rate is decreased, it is promoted by gene p53 mutations and increased expression of bcl-2 (Lara, Meyers, 1999). In androgen-independent PC cell line (AT-3) expression of TRPM-2 gene, which is called apoptosis gene, is at a low level (Kyprianou, Isaacs, 1989). However, all components of biochemical cascade of programmed cell death are preserved. Searching for possibilities of direct apoptosis stimulation is an urgent task because it may lead to novel methods of treatment of androgen-independent PC (Steenbrugge, 1991, 1994; Tenniswood, Michna, 1995). In particular, mitogen-activated protein kinase 1 (MAP kinase 1) stimulates apoptosis in prostate cancer (Abreu-Martin et al., 1999).

PHARMACOLOGY OF HORMONAL DRUGS FOR TREATMENT OF PROSTATE CANCER

2.1. Strategy and methods of androgen deprivation

Since the forties of the XX century androgen deprivation for treatment of prostate cancer has become usual in the world oncurologic practice. Castration and estrogen therapy, which opened a new era in PC treatment (Huggins, Hodges, 1941; Huggins et al., 1941 a, b; Huggins, 1946), have preserved their significance till now but often they give place to novel methods of endocrine therapy. A main theoretical prerequisite of endocrine therapy of PC lies in the fact that tumoral cells proliferate in response to androgens just as normal cells do.

In the opinion of many experts, endocrine therapy (orchi-epididymectomy and/or hormonal drugs) is indicated in all PC cases including those following radical prostatectomy (Marinbach, 1980; Portnoy, Grodzovskaya, 1984). Positive response to endocrine therapy was registered in 60-80 % of newly treated patients.

Proceeding from existing ideas on endogenous sources of male sex hormones, regulation of their secretion, metabolism and biological availability for target organs as well as about molecular mechanisms of androgen regulation of proliferation and apoptosis in normal and malignant prostate, there exist various methods of androgen deprivation. They include castration, hypophysectomy, adrenalectomy, suppression of synthesis and secretion of pituitary gonadotropic hormones, testicular and adrenal androgens, decrease in free testosterone concentration in the circulating blood by increasing SHBG level, pharmacological blockade of androgen cellular receptors in tumors, lessening the formation of testosterone active metabolites. In this book we will not touch upon such methods as hypophysectomy, adrenalectomy, inhibitors of prolactin secretion, which are not used currently because of their low effectiveness, intolerance and high traumatic effect. Drugs that

suppress androgen biosynthesis - ketoconazole, aminoglutetimide - are seldom used because of their side effects.

As to castration, about one third of patients do not agree to surgery though according to survival criterion it does not yield other methods of androgen deprivation (Balducci et al., 1990; Dalesio et al., 1995b; Denis, 1995). For the majority of patients it remains a serious psychological trauma. That is why such drugs as natural and synthetic estrogens, LHRH agonists, blockers of androgen cellular receptors take on special significance. These drugs differ in their chemical structure, mechanism of pharmacological action, side effects and effectiveness. Below a short description of these features for well-known and prospective hormonal drugs is given. The term «hormonal drug» applies both to the drugs with their own hormonal activity and to those which demonstrate antihormonal effect, for example non-steroid antiandrogens.

Hormonal means of androgen deprivation are used independently (monotherapy), in combination with each other or with surgical or pharmacological castration (combined therapy). Combined therapy, which was first proposed by Giuliani et al. (1980), has obtained recognition as it is aimed at maximum androgen blockade. A concept of maximum (also called total) androgen blockade prevails in modern strategy of drug therapy of advanced and metastatic PC (Labrie et al., 1983b, 1987, 1988; Balducci et al., 1990; Denis, 1995). Elimination of the main source of male sex hormones, i.e. surgical or pharmacological castration, is combined with a decrease of their bioavailability and blockade at the level of androgen cellular receptors in tumoral tissues. The latter is important because after castration another source of androgens - the adrenal cortex - is preserved. Androgens of the adrenal origin, having transformed in PC tissues into DHT and other active metabolites, contribute greatly to PC progression in men (Labrie et al., 1993 c, d). In addition, blockade of androgen receptors allows neutralization of stimulatory effects of residual blood testosterone, which is left after orchiectomy (5 % of the initial level), on the tumoral cells.

Till now there is no unanimity as to benefits of combined endocrine therapy of PC at the D2 stage (metastases) regarding its effectiveness, which is judged upon by the duration of remission and effect on survival as compared to castration or hormonal monotherapy. Despite the acquired vast material including multi-central clinical trials conducted in accordance with double blind control standards, opinions vary from positive

(Labrie et al., 1988 a; Balducci et al., 1990) to negative (Dalesio et al., 1995 b). However, all authors unanimously keep to the same idea that, first, combined treatment does not yield to castration, second, it has obvious advantages, which include less grave complications and adverse effects as compared to estrogen therapy. If a patient does not agree to orchiectomy, then combined therapy is the method of choice.

Combined hormonal therapy of PC, which is applied at early stages of the disease as neoadjuvant therapy, allows to lessen the volume of the malignant tissue and, consequently, to decrease the traumatic effect of surgery (radical prostatectomy) and to decrease the dose of radiation.

2.2. Estrogens

In order to treat PC natural and synthetic compounds with estrogenic activity are used. The task of synthetic analogues of estrogens is to increase their ability to suppress testosterone secretion, decrease androgen bioavailability for prostate tumoral cells, optimize pharmacokinetic parameters, facilitate new dosage forms and to minimize intrinsic estrogenic activity. The latter is especially important for minimizing the risk of grave complications of estrogen therapy.

Among non-steroid synthetic estrogenic drugs diethylstilboestrol and its diphosphoric ether (Honvan, fosfestrol), Synestrol (hexestrol), chlorotrianisene etc. are most popular. Steroid group is presented by ethinylestradiol (Microfollin), polyestradiol phosphate (Estradurin), Premarin (urinary estrogens conjugates). The active ingredient in these drugs is natural estrogen. In some cases when PC patients cannot endure treatment with synthetic non-steroid estrogenic drugs, natural estrogens might be helpful and well tolerated.

The main mechanisms of pharmacological action of estrogens as male sex hormone antagonists are given in Chapter 1. In addition it should be mentioned that estrogens increase apoptosis in prostate adenocarcinoma. This is possibly realized through stimulating formation of TGFp, antiproliferative autocrine factor in tumoral cells (Landstrom et al., 1996).

It was thought that estrogen-induced increase in blood prolactin level should counteract their therapeutic effect in PC because of prolactin ability to effect prostatic growth. Prolactin level increases considerably

under the effect of Honvan, to less degree under stilboestrol effect. However actual significance of this factor as counteracting to effectiveness of estrogen therapy in PC has not been proved so far.

Use of estrogens for PC treatment is justified by their effectiveness. According to results of comparative multicentral clinical trials, which were summarized in a review by Balducci et al. (1990), estrogenic drugs (diethylstilboestrol, Estradurin) are more effective than castration, they slow down the tumor growth but they have no benefits as to patients' survival.

The most problematic question of PC estrogen therapy is associated with drug intolerance because of their toxicity, feminizing and psychological effects. Such accompanying manifestations as gynecomasty, breast tenderness, decreased libido, impotence and others are explained by intrinsic estrogen activity. As to side toxic effects and complications, unfortunately, they are observed even when minimal therapeutic doses of estrogens are prescribed. These include angina pectoris, myocardial infarction, thromboembolism, arterial hypertension, edema, cerebrovascular disorders and cholestasis. Many cardiovascular and other complications are associated with estrogen-induced hypercholesterolemia, changes in lipoprotein fraction ratio, water retention and impairment of blood rheologic parameters. Toxicological characteristics mentioned are typical for all estrogenic drugs. They are not indicated to patients with hepatic and renal disorders, thromboembolism, decompensated diabetes mellitus and grave cardiovascular diseases.

Diethylstilboestrol - *trans*-3,4-di-(para-hydroxyphenyl)-hexene-3 (Fig. 2.1). White crystalline powder, well soluble in ethanol, diethyl ether, fatty oils, poorly soluble in water.

Diethylstilboestrol has high estrogenic activity, which is twofold that of estrone and Synestrol (1 mg preparation has 20 000 U of estrogenic activity). Its direct cytotoxic effect on PC cells is suggested. In blood it is found in its free form, not SHBG-bound. It is produced as 3% oil solution in 1 ml ampoules (30 mg per an ampoule) for intravenous administration. The highest single and daily dose for PC patients is 60 mg. The drug is also effective when administered per os. The conventional daily dose for

ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER
DIETHYLSTILBOESTROL

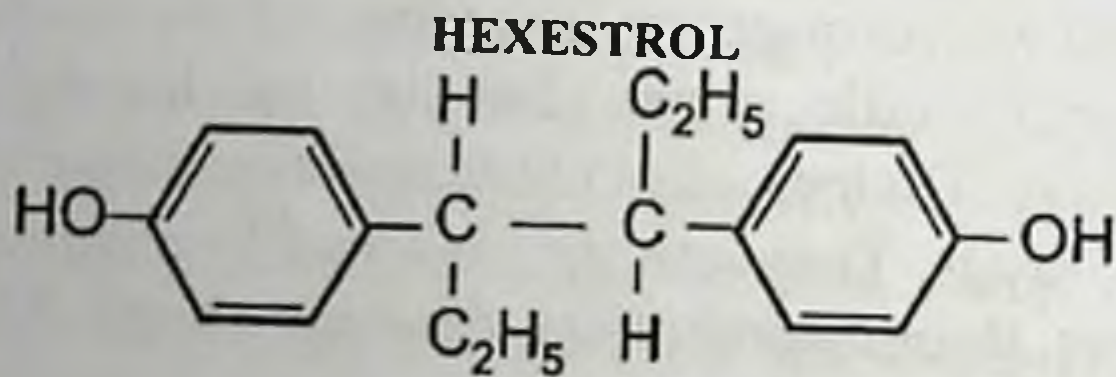
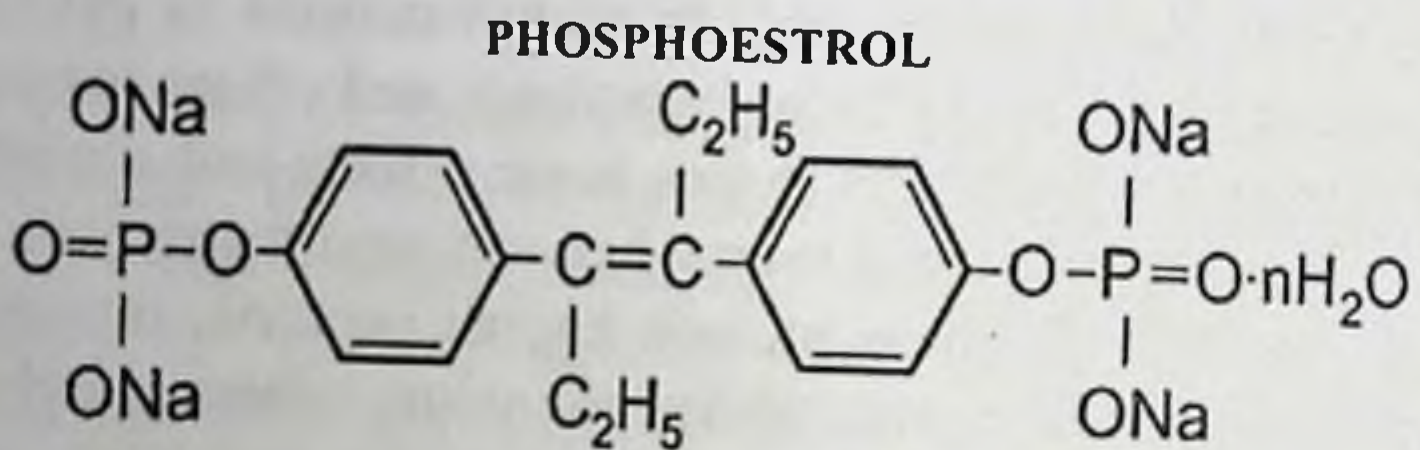
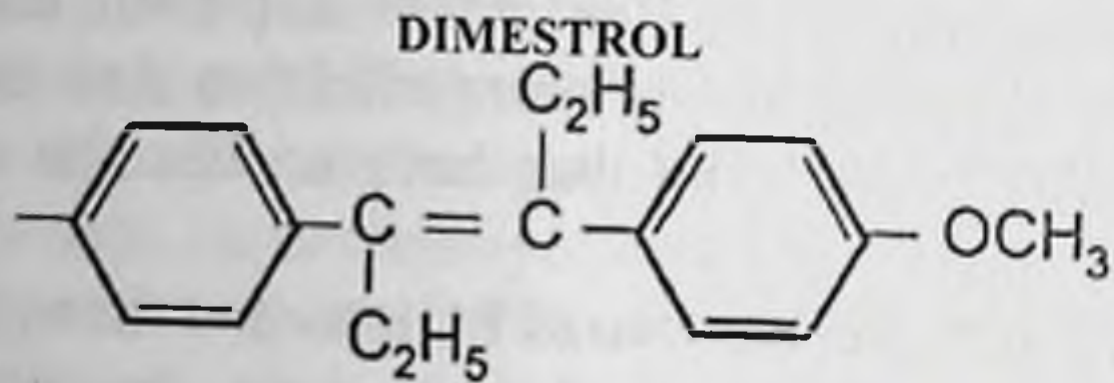
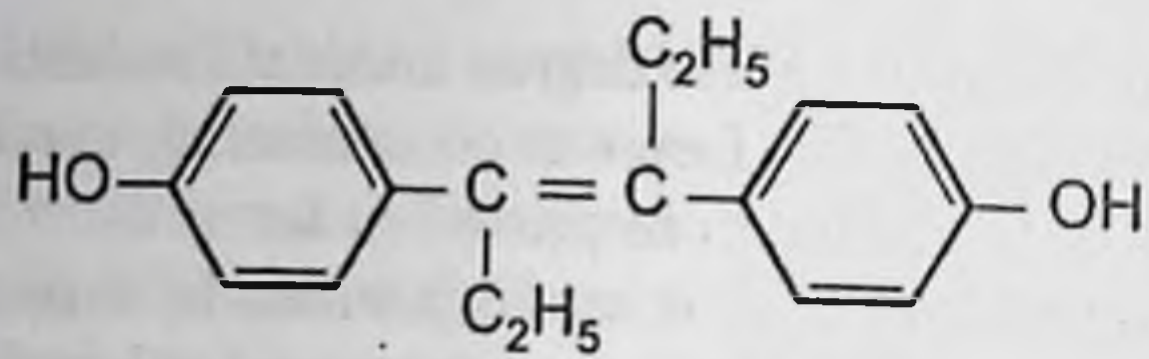


Fig. 2.1. Non-steroid estrogenic drugs which are used to manage prostate cancer

PC treatment is 3 mg (1 mg 3 times a day). It facilitates a decrease of blood plasma testosterone concentration to postcastration level. Dose reduction to 1 mg/day gives variable results though toxicity is decreased. In 33% of patients grave cardiovascular and thromboembolic complications are observed (in a daily dose of 3 mg).

Dimestrol is diethylstilboestrol dimethyl ether, 3,4-dimethoxy- α , β -diethylstiiben (Fig. 2.1). White crystalline powder, essentially insoluble in water, difficulty soluble in ethanol.

Its estrogenic activity is less than that of Synestrol and diethylstilboestrol (1 mg = 2000 U) but its effect is more prolonged, this allows less frequent administration. The effect persists for 1-2 months following the administration. It is produced as 0.6% oil solution in 2 ml ampoules. As a rule, dimestrol is administered intramuscularly once a week in a dose of 12 mg (2 ml of 0.6 % oil solution). An average treatment dose is 24- 36 mg (2-3 injections).

Diethylstilboestrol dipropionate is diethylstilboestrol dipropionic ether. White crystalline powder, soluble in diethyl ether and chloroform, poorly soluble in ethanol, insoluble in water.

It is a drug with a prolonged action. It is produced as 0.1% oil solution in 1ml ampoules for intramuscular administration.

Fosfestrol (Phosphoestrol, Honvan) is tetrasodium salt of diethylstilboestrol diphosphoric ether (Fig. 2.1). White or creamy white finely crystalline powder, easily soluble in water, essentially insoluble in ethanol.

When circulating in blood in its native form fosfestrol does not show any estrogenic activity. In prostatic tissue, under the effect of acid phosphatase, its content being especially high in tumor cells, fosfestrol is hydrolyzed with diethylstilboestrol release. In such a way a purposeful estrogen delivery to the target is accomplished. Under high local diethylstilboestrol concentration its antiproliferative effect on PC cells should be enhanced. When large doses of phosphoestrol are infused (1,2 g a day) its concentration in blood plasma reaches 3.6 mg/ml. *In vitro* experiments showed that under drug concentration of 1 mg/ml protein and DNA synthesis is inhibited in prostate tumor cells, antimitotic activity is demonstrated which is 30-fold that of colchicine. However, absence of fosfestrol therapeutic effect in case of estrogen resistance of the tumor casts doubts as to its local antimitotic activity under systemic administration. To

demonstrate such activity much time is required. However, pharmacokinetic studies showed that in the rabbit prostate 70 % of fosfestrol was completely hydrolyzed 15 min after its intravenous administration. Free diethylstilboestrol passes to circulation, hence an increase of estrogen local concentration in the tumor is of short duration.

The main mechanisms of fosfestrol therapeutic effect include anti-gonadotropic effect, direct suppression of testicular testosterone secretion, increase of blood SHBG level and decrease of free testosterone fraction, i.e. they are the same as for Synestrol, diethylstilboestrol and some other estrogenic drugs. Domer and co-authors (1975) demonstrated that intravenous fosfestrol administration for 20 days in a total dose of 12 mg resulted in a decrease of blood plasma LH concentration by 50 %, that of total testosterone by 95 %, free testosterone by 98 %.

According to Ackerman et al. (1991), the mechanism of fosfestrol action may be divided into several effects.

1. Hormonal effect: under low doses (2 mg/day) blood plasma fosfestrol concentration reaches 2.4 ng/ml and it acts as an estrogen. By effecting the hypothalamic-pituitary-testicular system it suppresses androgen formation. The estrogen increases SHBG binding capacity of blood plasma and may directly effect testicular androgen synthesis. Testosterone utilization may also change under fosfestrol effect.

2. Cytostatic effect: under large doses (1200 mg/day) fosfestrol concentration in blood plasma reaches 3.6 mg/ml, it directly suppresses DNA and protein synthesis. In concentration of 1 mg/ml, fosfestrol induces a pronounced antimitotic effect.

3. Alleviation of pain in PC bone metastases is connected neither with hormonal nor with cytotoxic phosphoestrol effect and is often observed when there are no objective signs of improvement. This effect may be explained by the fact that phosphate groups of fosfestrol molecule protect bones from osteolytic damage. The same positive effect is observed in primary osteoblastic metastases.

4. Antibacterial and antimycotic effects.

Fosfestrol is used at all stages of PC both intravenously and orally in tablets. Even in estrogen resistance in some cases it produces positive effect alleviating pain associated with bone metastases, reducing symptoms of urinary tract obstruction. Treatment with fosfestrol is effective in all morphological types of PC with the exception of transitional cell carcinoma and squamous cell carcinoma.

Phosphoestrol and Honvan are produced as 6 % solution in 5 ml ampoules and as 0.1 g tablets.

The treatment should be given taking into consideration how the drug is tolerated and also the general state of a patient. If the drug is well tolerated and the general state is satisfactory then the treatment begins with daily intravenous administration of 0.9-1.2 g (3-4 ampoules of 0.3g). The drug is infused slowly or by drops, fosfestrol solution is diluted in 150-200 ml of 5 % glucose solution or isotonic solution of sodium chloride (fosfestrol solutions should not be mixed with infusion solutions, which contain calcium or magnesium salts). Following a 10-day course the dose is reduced to 0.3 g (1 ampoule a day) and the treatment goes on for the next 10-20 days. In patients with cardiovascular insufficiency, hepatic and renal dysfunction, asthenic patients and those with a great body mass the treatment begins with a dose of 0.6 g/day for 10 days followed by a dose of 0.3 g for the next 20 days.

If intravenous fosfestrol administration is impossible then 3-4 tablets 3 times a day are prescribed (a daily dose of 0.9-1.2 g) before meal with some liquid. Then maintenance fosfestrol doses are taken: 1 tablet 2-3 times a day or 1-4 intravenous injections (0.3 g each) a day, 1-4 times per week.

The second common treatment protocol is the following. A patient is administered 0.6 - 0.9 g fosfestrol intravenously over 30-35 days, in some cases this dose makes 1.2 g. After a 3-4-week interval the drug is taken in a dose of 1 tablet 3 times a day for a one-month period. Then the treatment course is repeated, when indicated, but intravenous fosfestrol administration is cut down to 20-25 days.

As a rule, fosfestrol treatment is well tolerated. Side effects are the same as for other estrogenic drugs. At the beginning patients may complain of nausea, vomiting, depression, worsening of health state, pains in metastatic areas as well as anal, genital, facial and cervical pruritus. Blood coagulability diminishes, hemorrhage is possible.

If fosfestrol injections are badly tolerated it is possible to reduce the dose under the control of clinical and biochemical parameters, especially acid phosphatase and PSA levels. If there are dyspeptic manifestations during tablet administration then it is recommended to keep tablets under the tongue or behind the cheek till complete resorption. In case of skin pruritus antihistaminic drugs are prescribed, in hemorrhages - intravenous injections of calcium chloride solution.

In addition to contraindications, which are common for estrogenic preparations (hepatic, cardiac, vascular diseases), fosfestrol is not indicated in diminished blood coagulability.

Hexestrol. Synonym: Synestrol. Hexestrol is a synthetic derivative of stilben - *meso*- 3,4-di- (para-hydroxyphenyl)-hexane (Fig. 2.1). White or whitely yellowish powder. Easily soluble in ethanol, chloroform, poorly soluble in oil (1:50), insoluble in water.

As to its estrogenic effect, Synestrol is equivalent to estrone (1 mg Synestrol corresponds to 10 000 U of estrogenic activity) but yields to diethylstilboestrol. It is active in parenteral and oral administration. Synestrol is effective in highly differentiated adenocarcinoma, solid-trabecular carcinoma with a preserved glandular structure, undifferentiated carcinoma but it is hardly effective in cribriform and solid-trabecular carcinoma with solid structures prevailing.

Synestrol is produced as 0.1 or 0.2% oil solution in 1ml ampoules for intramuscular or subcutaneous administration and in 0.0001g tablets. For PC treatment, Synestrol 2 % solution is used (20 mg in 1 ml). When administered per os Synestrol is easily absorbed in the gastrointestinal tract without decomposing.

When treating malignant neoplasms the highest single dose for injection is 60 mg (3 ml of 2 % solution), the largest daily dose is 100 mg (5 ml of 2 % solution). For PC treatment Synestrol is administered daily intramuscularly in a dose of 3-4 ml of 2 % solution (60-80 mg) a day over a two-month period, then maintenance doses are taken - 10-20 mg/day intramuscularly (0.5-1.0 ml of 2 % solution) and in tablets. A total dose and treatment duration vary depending on the gravity of the disease, metastatic spreading, patient's state and drug tolerance.

Sometimes patients may complain of nausea, vomiting, dizziness, hepatic dysfunction and other adverse reactions. Hepatic and renal disorders are limiting factors for the use of Synestrol.

Chlorotrianisene (TACE) - 1, 1,2-trianisil-2-chloroethylene (Fig. 2.1). White crystalline powder, difficulty soluble in ethanol, insoluble in water.

Chlorotrianisene is effective when administered per os. It has prolonged estrogenic activity, which persists longer than under treatment with diethylstilboestrol or Synestrol. Its low toxicity, minimal feminizing effect and adverse reactions facilitate long-term use.

Chlorotrianisene decreases testosterone level to less extent as compared with other estrogenic drugs. According to our experimental studies, in rats a decrease in LH and testosterone levels is pronounced enough. It is thought that curative effect of chlorotrianisene in PC patients is associated with its direct action on tumoral cells and also with the absence of stimulating androgenic activity of the adrenal cortex, which is typical for other estrogens. Experimental and clinical studies showed that chlorotrianisene inhibited castration-induced compensatory hypersecretion of adrenal androgens (Popova, 1971). According to some authors, who keep to the opinion that post-castration PC relapse is associated with increased adrenal androgen secretion, the use of chlorotrianisene instead or after castration seems preferable than the use of other estrogenic drugs.

Chlorotrianisene is produced in 0.012 g tablets. It is prescribed to PC patients per os in a dose of 1 tablet 2-3 times a day. It is recommended to take 0.012 g 3 times a day during first 3 days, 0.012 g 2 times a day on days 4 and 5, then 0.012 g a day over the next 7 days, starting from day 15 - 0.006 g a day (half a tablet) for a 40-day period; treatment courses are taken 1-2 times a year (Portnoy, Grodzovskaya, 1984).

The highest single chlorotrianisene dose is 0.012 g, a daily dose - 0.048g.

Chlorotrianisene is well tolerated, without nausea, vomiting, dyspepsia or edema. Sometimes transitional gynecomasty and tactile breast tenderness are observed.

Ethinylestradiol (Microfollin, Microfollin Forte) - ethinylestradiol-17 β . A synthetic analogue of the natural estrogen, estradiol -17 β .

It is active when administered per os due to good absorption from the gastrointestinal tract. Its pharmacological properties are similar to those of estradiol-17 β but its activity is 15-fold that of estradiol-17 β . It allows curative effect in patients' who are ineffectively treated with other estrogenic drugs. In a dose of 0.05 mg twice a day it facilitates a decrease of blood testosterone level similar to that produced by diethylstilboestrol in a daily dose of 3 mg.

After oral ethinylestradiol administration its maximum concentration in blood is achieved 0.5-1 h later. The further changes of concentration are characterized by a two-phase decrease with a half-life in blood of 1-3 hours or 24 hours. There is no cumulative effect. 40 % of

ethinylestradiol is excreted through the kidneys, 60 % through the liver. A half-life in the body is about 24 hours.

It is produced as 0.00001 g tablets (Microfollin) or 0.00005 g tablets (Microfollin Forte). The treatment course begins with small doses rising them up to 0.00005 g (50 μ g) twice a day.

During treatment with ethinylestradiol adverse reactions manifested in nausea, vomiting, edema etc. are possible. Feminizing effects - gynecomasty, decreased libido - are pronounced.

Polyestradiol phosphate (Estradurin) - is a polymerized estradiol-17 β phosphate. Lyophilized white porous water-soluble substance.

The drug is prescribed for parenteral administration. As a result of consecutive hydrolysis of the phosphate groups the active substance - estradiol 17 β - is released. Due to it a sound and prolonged estrogenic effect is produced. In long-term use blood testosterone level decreases by 80-85 %. The drug is used independently and also for maintenance therapy following fofestrol (Honvan) and other quick-acting drugs. It is used to treat all PC stages.

It is produced in flasks with 40 or 80 mg of lyophilized substance, a solvent is produced in 2 ml ampoules. The drug contains carbocaine as a local anesthetic.

The drug solution is prepared immediately before the injection and is administered intravenously. For PC treatment 80-160 mg is prescribed once a month or 40-80 mg twice a month. After 2-3-month treatment the dose is reduced to 40-80 mg per month. The treatment is prolonged.

The drug is relatively low toxic and well tolerated. Side effects are typical for other natural estrogenic drugs. Gynecomasty is frequently observed. Contraindications: thromboembolic disease, thrombophlebitis, hepatic disorders etc.

Estradiol dipropionate (Proginon-depot, Proginon-retard) - a prolonged preparation of estradiol-17 β . It is produced in ampoules containing 100 mg of preparation in 1 ml oil solution.

For PC treatment the drug is administered intramuscularly in a dose of 100 mg with an interval of several days to two weeks.

Estramustine phosphate (Estracyt) - estradiol-3-[bis(2-chloroethyl)carbamate]17 β -dihydroxyphosphate. A combination of phosphorous ether of the natural estrogen with a cytostatic agent (Nitrogen mustard) facilitates hormonal and cytostatic activities of the drug. Estradiol being a part of estramustine acts as a carrier of the

alkylating agent of the molecule (Nitrogen mustard) to the prostate. In the cytoplasmic fraction of the rat prostate homogenate a specific protein, which binds estramustine, was found. Following intravenous infusion estramustine is primarily accumulated in the glandular epithelium and then is secreted into the lumina of the gland lobes. Dephosphorylated isomer of estramustine is its main metabolite, which is found in the prostate and blood plasma.

Estramustine exerts antigonadotropic, antiestrogenic, antiandrogenic and weak estrogenic effect - it is 100 times less active than estradiol-17 β . As to its antigonadotropic activity it is more potent than estradiol-17 β . Estramustine inhibits testosterone formation, testosterone conversion into DHT in the prostatic tissues, decreases zinc absorption by these tissues. PC metastatic nodules accumulate estramustine like primary tumor does, that is why the drug is recommended for treatment of disseminated tumors. Due to cytostatic activity of the alkylating agent this drug has curative effect when tumors are estrogen resistant. Owing to low toxicity, satisfactory tolerance, rare hemopoietic complications, absence of cumulative and toxic effects estramustine may be applied at all stages of PC.

Estramustine is effective when administered intravenously and orally. It is produced in 10 ml ampoules containing 1.5 % (150 mg per an ampoule) or 3 % (300 mg per an ampoule) solution with a solvent and also in 140 or 280 mg capsules.

For PC treatment estramustine is administered intravenously in a dose of 300 mg a day (sometimes 450 mg) for a maximum period of 3 weeks. The drug solution is administered slowly, for 3-5 min, to decrease the risk of phlebitis. Estramustine may be infused after it is diluted in 250 ml of 5 % glucose solution (not isotonic solution of sodium chloride). Maximum duration of the infusion is 3 hours. If the positive effect is observed then the maintenance therapy is given, 300 mg intravenously twice a week with a 7-day interval. The total treatment duration is up to 3 months.

The maintenance therapy may consist of 2-3 capsules (140 mg each) of estramustine twice a day. Estramustine in capsules is indicated for PC main treatment course because of relatively high incidence of thrombophlebitis in the injection sites and also in patients who are susceptible to thrombophlebitis.

Positive curative effect of estramustine in patients with estrogen resistant metastatic PC is 35-55 %. Up to 80 % of patients who were primarily treated with estramustine responded with long-lasting remission.

Side effects of the drug may be manifested by gastrointestinal disorders (nausea, vomiting, diarrhea), leukopenia, allergic reactions, heart pains. Thromboembolism and gynecomasty are sometimes observed. Acute cardiac insufficiency, edema, depression, suppression of medullary hemopoiesis are less frequent than in other types of estrogen therapy.

Estramustine is contraindicated in grave hepatic and cardiac disorders, thrombophlebitis, thromboembolic disease.

Estrogens conjugates (Premarin) are conjugated estrogens of pregnant mares. They are produced in 0.000625 g and 0.00125 g tablets. In PC the drug is prescribed in a dose of 3.75- 7.5 mg a day. Care should be taken when prescribing this drug to patients with diabetes mellitus, arterial hypertension, epilepsy and disseminated sclerosis.

2.3. LHRH agonists

LHRH effect on LH secretion and, consequently, on testicular hormonal activity depends on the amount of the releasing hormone, duration and pattern of its action. Under physiological conditions hypothalamic LHRH is released in the portal system of the hypophysis in the pulsatile pattern (with a period about 90 min) inducing gonadotropin pulsatile secretion. The intensity of such stimulation is determined by physiological needs of an organism. Under such conditions LHRH induces synthesis of its own receptors on membranes of pituitary gonadotropocytes («up-regulation») and preserves pituitary sensibility to this regulator.

At the same time a prolonged continuous pituitary stimulation, especially an intensive one, with a preparation of hypothalamic LHRH results first in activation and then in a decrease of the number of LHRH membrane receptors («down-regulation»). Finally, desensitization of gonadotropocytes occurs (tachyphylaxis), and LH secretion decreases (Clayton, Catt, 1981; Marian et al., 1981). The initial stimulation brings about a maximum increase of blood plasma LH during 24-48 h, then LH level lowers gradually. 2-3 weeks later maximum desensitization of the hypophysis is observed. Basal blood LH and testosterone concentrations decrease to their lowest values.

Similar, though even more pronounced changes in the hormonal profile are observed when superactive LHRH analogues are used. In this case blood testosterone level corresponds to postcastration values, this allows speaking about «pharmacological castration». The main biochemical mechanisms, which determine such effect, are similar to those described above (Coy et al., 1975; Tolis et al., 1981; Bhasin, Swerdloff, 1986; Swanson et al., 1988).

A decrease in the number of pituitary LHRH receptors is explained in the following way. After binding to LHRH the receptor molecules disappear from the surface of gonadotropocytes and are internalized, i.e. uptaken by a cell through pinocytosis. In case of pulsatile inflow of LHRH and its agonists to the hypophysis the peptide occupies only part of available receptors. Due to it there is enough time before the next pulse to substitute the «exhausted» receptor molecules and to preserve gonadotropocyte responsiveness to LHRH.

At the same time a continuous effect of LHRH and its analogues results in complete occupation of all receptors available and their simultaneous internalization. The cell «does not manage» to make up a number of LHRH membrane receptors, which is required for a normal response.

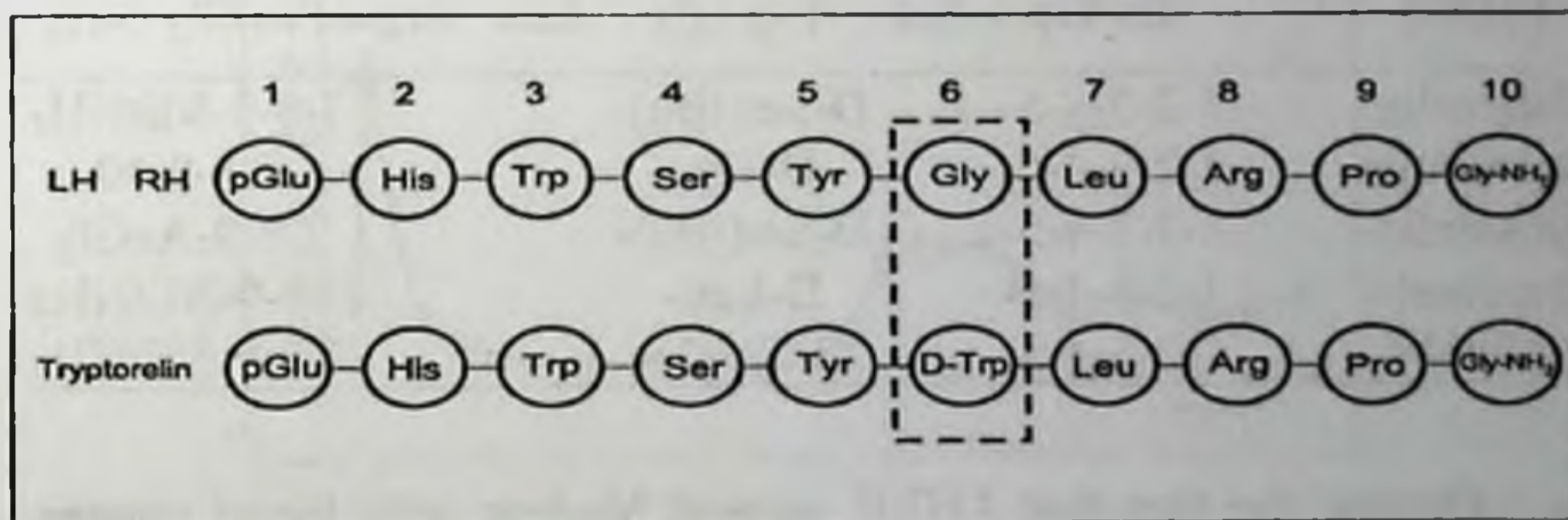


Fig. 2.2. The primary structure of hypothalamic LHRH and its synthetic agonist, triptorelin

The chemical structure and pharmacological activity of LHRH analogues, which are widely used in medicine are described by many authors (Rivier et al., 1983, Bex, Corbin, 1984; Sandow, 1987; Shparyk, Bilynsky, 1994; Nizharadze, 1996). Synthetic agonists differ from natural LHRH, first, by much greater (10-fold and more) activity in stimulating (or inhibiting) gonadotropin secretion due to their great affinity for

receptors and, second, by a much lower rate of degradation in a body. Modifications of the chemical structure of natural LHRH, which facilitates these properties, consist in changing the amino acid sequence of the peptide, substitution of L - amino acid with D - amino acid, for example, substitution of L - glycine with D - tryptophane (Fig 2.2). This substitution occurs in position 6 or 10, or both, in natural LHRH molecule since that is the point where peptidases «break» peptide bonds during LHRH metabolic degradation. Often ethylamide is introduced in position 10 (C-terminal) instead of glycine residue (Table 2.1).

The ability of LHRH analogues to inhibit LH and testosterone secretion to postcastration level has been demonstrated in many laboratory animal species. For example, high inhibitory activity of surfagon was shown in monkeys (Surfagon D-Ala⁶, des-Gly¹⁰-ethylamide LHRH, was synthesized at the Russian research Center of Cardiology, Moscow (Fig. 2.3).

Table 2.1. Chemical structure of hypothalamic LHRH and its superactive agonists

Peptide	Amino acid position									
	1	2	3	4	5	6	7	8	9	10
LHRH	pGlu	His	Trp	Ser	Typ	Gly	Leu	Arg	Pro	Gly-NH ₂
Buserelin		1-2-3-4-5-			D-Ser(tBu)-				7-8-9-NEtNH ₂	
Tryptorelin		1-2-3-4-5-			D-Trp-				7-8-9-10	
Goserelin		1-2-3-4-5-			D-Ser(tBu)-				7-8-9-AzGly	
Leuprorelin		1-2-3-4-5-			D-Leu-				7-8-9-NEtNH ₂	
Naferelin		1-2-3-4-5-			D-Nal(2)-				7-8-9-NEtNH ₂	

Despite the fact that LHRH agonist binding with blood plasma proteins varies greatly (25-80 %) this is not actually reflected on their metabolic clearance, which to a large extent determines the pharmacokinetic characteristics. Half-life of these compounds in blood is 4-12 times greater than for natural LHRH, which makes 10-15 min in humans (Fig. 2.4). Some of basic pharmacokinetic features of widely known LHRH agonists are given in Table 2

Table 2.2. Pharmacokinetics of hypothalamic LHRH and its agonists in humans

Peptide	Metabolism: point of hydrolysis	Binding to plasma proteins, %	Half-life in blood, min
LHRH	5-6, 1-2, 9-10	20-25	10-15 (i.v.)*
Buserelin	4-5	<20	80 (s.c.)
Tryptorelin	4-5, 9-10	20-25	50 (i.v.)
Goserelin	4-5, 7-8, 9-10	20-28	252 (s.c.)
Leuprorelin	No data	15	174 (i.v.)
Naferelin	5-6, 7-8	78-84	258 (s.c.)

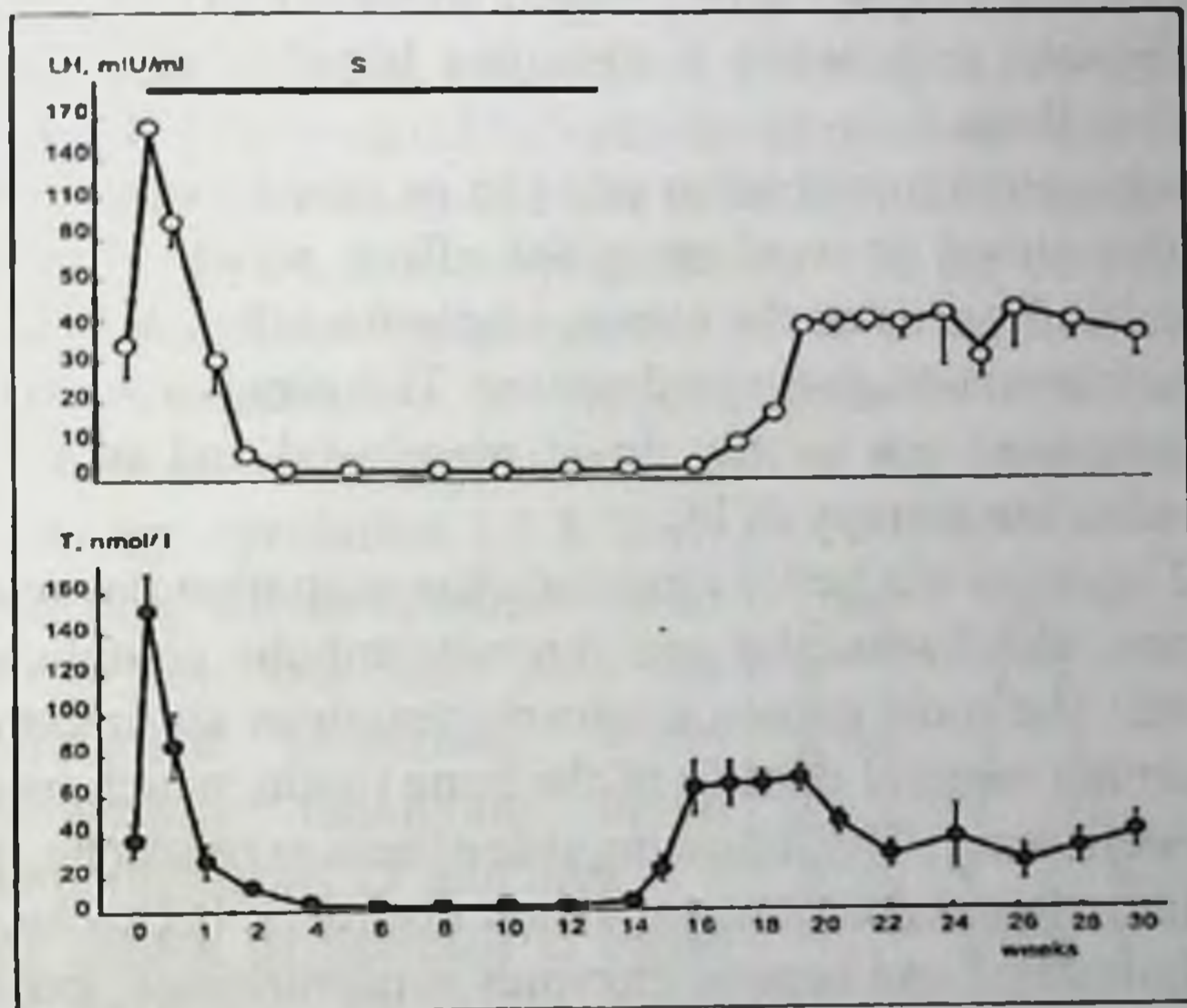
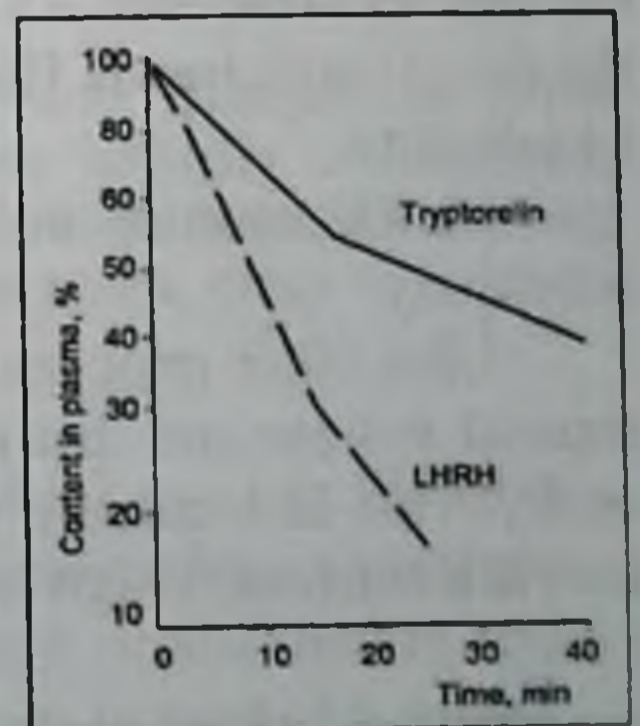


Fig. 2.3. Changes in blood plasma LH and testosterone contents in baboon hamadryad males under the effect of Surfagon (S) and their recovery following the drug withdrawal (From Goncharova et al., 1992)

Fig. 2.4. Elimination of hypothalamic LHRH and tryptorelin from blood after intravenous administration



* Here and further in the text the administration route is given in the parentheses: s.c. - subcutaneously, i.v. - intravenously.

In their antineoplastic activity in PC patients LHRH agonists are comparable to orchiectomy and estrogenic drugs. They are indicated as the initial hormonal therapy of PC and are less effective in previously treated patients. Since therapeutic effect of LHRH agonists is accomplished through inhibition of testicular androgen secretion, their use in castrated patients has no sense.

A rapid and considerable increase of blood testosterone level in the first days and weeks after treatment may accelerate the tumor growth (Kahan et al., 1984). In 10-30 % of patients it may cause delayed urination, pains in the sites of bone metastases. That is why it is recommended to take simultaneously blockers of androgen cellular receptors - flutamide (Niftolide, Flucinom), cyproterone acetate (Androcur) etc. Antiandrogens may be withdrawn only when testosterone blood level is at its initial values or below them.

Antiandrogen administration prior to or simultaneous with LHRH agonist is also aimed at weakening the effect, which is produced by adrenocortical androgens on the tumor. Under the effect of LHRH and its analogues their secretion does not decrease. This aim is achieved through prolonged combined use of the drugs mentioned and is a variant of combined endocrine therapy of PC.

LHRH agonists are better tolerated than castration or monotherapy with estrogens. Cardiovascular and thromboembolic complications are rare or absent. The most common adverse reactions are impotence, hot flushes, lessening mineral density of the bone tissue, which results from testosterone deficiency. The following side effects as headache, dizziness, tinnitus aurium, depression, nausea, vision disorders, backache, increase of plasma cholesterol and hepatic enzymes concentrations, gynecomasty etc. are less frequent. As a rule, all these manifestations disappear when the drug is withdrawn. Hot flushes may be stopped by cyproterone acetate (Androcur).

LHRH agonists in PC are contraindicated in case of drug hypersensitivity.

Like other peptides, LHRH agonists are digested in the gastrointestinal system and that is why they are ineffective when administered orally. This fact and also the necessity to maintain their blood concentration at a constantly high level makes the drug formulation very important.

More often they are employed for subcutaneous and intramuscular administration. As solutions these drugs are used daily as injections or intranasally by spraying.

Injections of LHRH agonist, which is deposited in biodegrading polymer microspheres, once a month are more convenient (but also less controlled).

Buserelin (Suprefact).

The chemical formula for buserelin is as follows:

5-oxo-L / Pro-L / His-L / His-L / Trp-L / Ser-L / Tyr-O-tert-butyl-D / Ser-L / Leu-L / Arg-N-ethyl-L / Pro-amide acetate.

It is white or yellowish amorphous powder, soluble in water and diluted acids. When used continuously Suprefact diminishes testosterone concentration to postcastration values for 2-3 weeks. It is manufactured in 5.5 ml flasks, which contain 0.3% buserelin aqueous solution (3 mg/ml) for subcutaneous administration, and also in the form of dosed nasal spray (200 doses per flask, one dose corresponds to 100 µg buserelin). The flasks are supplied with dosing sprayers.

Maximum concentration in blood plasma is easily achieved following subcutaneous administration, a half of the administered dose eliminates from the circulation 1.5 h later. That is why the drug should be administered several times a day. Buserelin does not possess cumulative properties. When sprayed intranasally maximum blood concentration is registered 15 min later, 2 h later the drug cannot be detected in blood plasma (Fig. 2.5). Aerosol Suprefact is well absorbed by the nasal mucous membrane even when a patient gets a cold.

For the initial endocrine therapy of PC Suprefact is administered subcutaneously in a dose of 500 µg 3 times a day with an 8h interval over a 7-day period. On day 8 the drug is administered intranasally in a daily dose of 1.2 mg, i.e. 12 doses of the spray. One dose of the spray is administered into each nasal passage before and after breakfast (which makes a total of 4 doses), before and after lunch (a total of 4 doses), before and after dinner (a total of 4 doses),

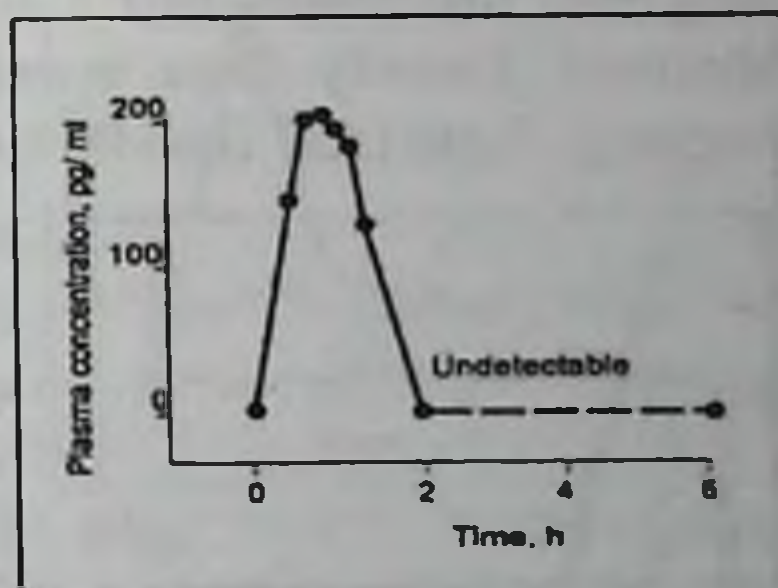


Fig. 2.5. Changes in blood plasma buserelin concentration after a single intranasal spraying (From Adam, 1992)

which makes all in all 12 doses a day. Aerosol Suprefact may be used following another scheme, when it is administered with equal intervals over a day not exceeding a daily dose (1.2 mg).

In order to prevent a short-term relapse and side effects antiandrogen therapy is recommended. Antiandrogen administration (flutamide, cyproterone acetate etc.) 5-7 days before treatment with Suprefact is recommended. Later on antiandrogen is taken for 3-4 weeks together with Suprefact. As a rule, after such treatment the level of sex hormones decreases considerably.

Treatment with Suprefact is of long duration; it might be used for the whole life of a patient with confirmed diagnosis of PC. Measuring blood plasma testosterone concentration should check the effectiveness of Suprefact as a drug that induces pharmacological castration: every 5 weeks at the beginning, then every 3 months or more often.

As a rule, Suprefact is well tolerated. Interactions with other drugs have not been reported. Side effect of Suprefact, which is used without antiandrogen therapy, is manifested in transient activation of the tumor growth, bone pains or their aggravation in approximately 10 % of patients with bone metastases. In 2-3 % of patients dysuria and lymphostasis are observed. Usually these symptoms disappear spontaneously, without stopping Suprefact. Hot flushes, gynecomasty (rare), depression, decreased libido and impotence are faced

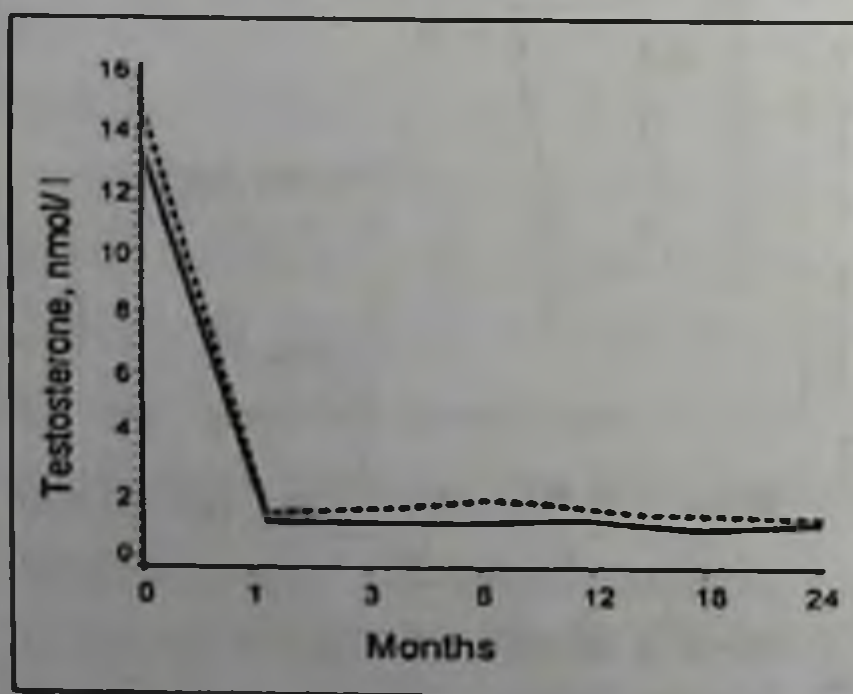


Fig. 2.6. Effect of Decapeptil (solid line) and castration (dotted line) on blood plasma testosterone level in PC patients (From Parman et al., 1988)

in some patients. As mentioned above, cyproterone acetate (Androcur) successfully fights hot flushes. Some patients complain of irritation of the nasal mucous membrane and rare nasal hemorrhages.

There are no contraindications as to the drug use except for hypersensitivity to buserelin or benzalconium chloride (a preservative). It is not reasonable to prescribe Suprefact to PC patients who have undergone orchiectomy or those

with tumors unresponsive to endocrine therapy.

Tryptorelin (Decapeptil).

The chemical formula for tryptorelin is as follows:

Pyro-L / Glu-L / His-L / Trp-L / Ser-L / Tyr-D / Trp-L / Leu-L / Arg-L / Pro-L / Gly-NH₂

Decapeptil 3.75 mg is an injection form with prolonged action. The acting component (tryptorelin) is adsorbed on the surface of biodegrading polymer (polylactide coglycolide), which consists of microspheres of different size. In the body, these microspheres disintegrate thus facilitating a prolonged tryptorelin release in blood following a single intramuscular injection. That is why the drug is administered once in 4 weeks. This results in a decrease (following an initial increase) of blood testosterone level to minimal value comparable to hormone content in castrated patients (Fig. 2.6).

In a test under challenge with chorionic gonadotropin testicular hormonal response is weakened. During Decapeptil treatment the response of pituitary LH and FSH secretion to stimulation with natural LHRH is suppressed completely, spermatogenesis discontinues and the number of Leydig cells decreases (Roger et al., 1986; Fretin et al., 1987; Rolandi et al., 1988).

Detailed studies of pharmacokinetics of a prolonged form of Decapeptil in dogs (3.0 mg) showed that tryptorelin was released at a rate of approximately 200 µg/kg b.w. a day for a period of up to 31 days (average plasma level 0.37 ± 0.12 µg/ml). A maximum concentration of the acting substance was achieved during 24 h after intramuscular injection. Blood plasma testosterone level decreased to postcastration values and was minimal between day 4 and day 7 following the injection (Redding et al., 1984).

Similar studies in PC patients (Drieu et al., 1987) showed that the initial peak of tryptorelin concentration (on average, 1.28 ± 0.24 ng/ml) gives place to a permanent elimination at a rate of 46.6 ± 7.1 mkg/day

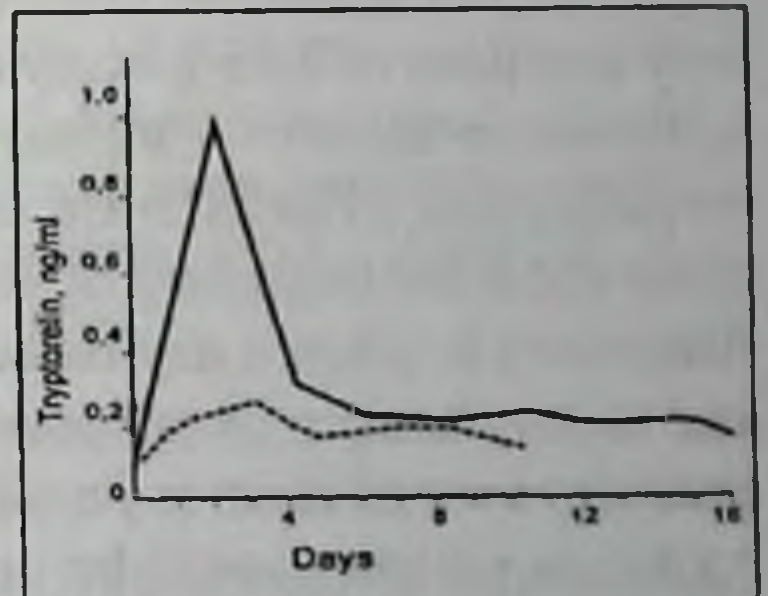


Fig. 2.7. Tryptorelin concentrations in blood plasma under daily subcutaneous injections of tryptorelin solution in a dose of 0.1 mg (dotted line) and following a single intramuscular injection of Decapeptil 3.75 g (solid line)

during an interval between the injections (28 days). Mean blood level is 0.32 ± 0.12 ng/ml. Half-life period in blood is 11.7 ± 3.4 h, distribution volume -113.4 ± 21.6 l, blood clearance -188.1 ± 32.0 ml/min. A half of administered dose is eliminated from the body a month later. For maintaining a relatively constant blood tryptorelin level daily injections of the drug (non-prolonged form) are required (Fig. 2.7).

Experts from «Beaufour Ipsen Int.» studied local tissue response to intramuscular Decapeptil administration to laboratory animals. It corresponded to a typical response to an alien body with macrophagal participation. Following resorption of the microspheres tissues acquired the initial histological outlook without any signs of inflammation.

Decapeptil 3.75 mg is produced in flasks, which contain microspheres for making suspension (one flask contains 3.75 mg tryptorelin). Each flask is supplied with an ampoule containing 2 ml of solution for microsphere diluting. An advantage of Decapeptil 3.75 mg as compared to similar drugs is its stability when the drug is stored at room temperature.

For PG treatment Decapeptil 3.75 mg is administered intramuscularly in a dose of 3.75 g every 4 weeks. It is recommended to check blood testosterone level (< 1 ng/ml) regularly. In order to prevent undesirable consequences of an increase in blood testosterone level, which is usually observed at the beginning of treatment, an antiandrogenic drug (flutamide, Androcur) is taken a day before the first injection of Decapeptil 3.75 mg and then it is taken over a month period. Taking into consideration that a transient exacerbation is possible at the beginning of Decapeptil 3.75 mg course, a patient should be under careful medical control especially in cases of hematuria, obstruction of urinary tract and bone metastases.

Decapeptil - Depot is produced as a set consisting of a disposable syringe with «retard» microcapsules which contain tryptorelin acetate in a dose of 4.12 mg (which corresponds to 3.75 mg of tryptorelin). The set is also supplied with a solution to prepare a suspension in a syringe. The drug is administered intramuscularly.

Decapeptil - Depot should be stored in a refrigerator since it is not stable under room storage conditions. This should be kept in mind when the drug is transported.

The dosage in PC treatment is the same as for Decapeptil 3.75 g. Studies of Decapeptil - Depot pharmacokinetics showed that blood

plasma tryptorelin concentration is within 0.3-0.5 ng/ml, half-life in blood in the distribution phase is 4.2 h, in the elimination phase is 13.6 days.

Under repeated administration blood tryptorelin concentration remains at a level of approximately 0.4 ng/ml (Happ et al., 1987).

Decapeptil preparations are not toxic. Side effects - hot flushes (about 35 % of cases), sweating, osteoporosis etc. - are directly associated with pharmacological properties of Decapeptil. They are predictable and may be stopped or prevented by symptomatic treatment. That is why Decapeptil is regarded to be a well tolerated drug. A decrease of libido, impotence (6 % of cases), gynecomasty are possible because of LHRH agonist - induced suppression of testosterone secretion. In 3 % of patients transient arterial hypertension was observed, in 2 % - pain and hyperemia in the injection site. Increase of general clinical manifestation or some particular symptoms, pains in local bone metastases for example, disappear usually during 1-2 weeks of the treatment course.

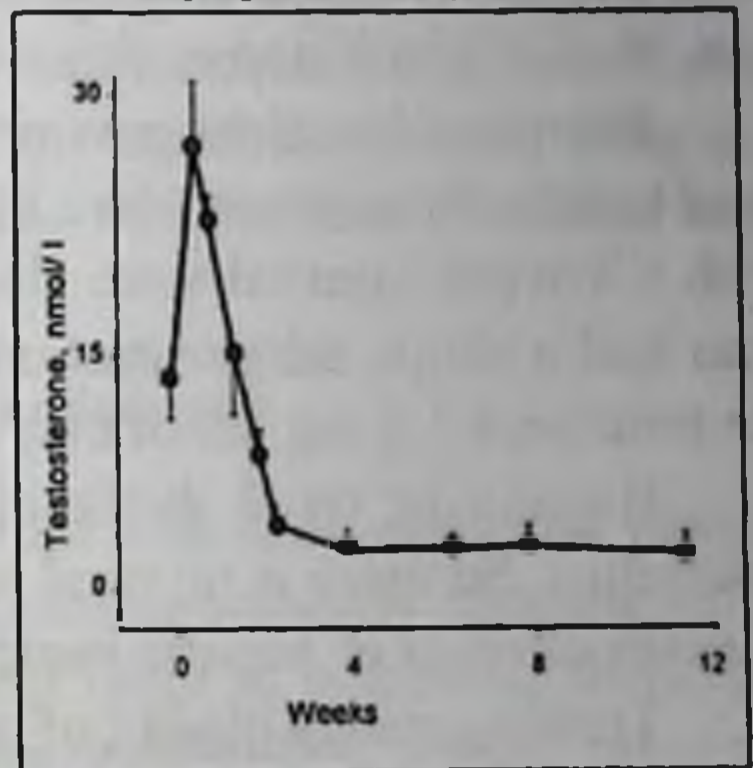


Fig. 2.8. Effect of goserelin (Zoladex) on blood plasma testosterone concentration in PC patients (From Allen et al., 1983)

Goserelin (Zoladex). The chemical structure of goserelin is as follows:

Pyro-L / Glu-L / His-L / Trp-L / Ser-L / Typ-D / Ser-O-tert-butyl-L / Leu-L / Arg-L / Pro-Az-L / Gly.

The drug active ingredient is goserelin acetate, LHRH agonist. When used continuously it increases and then decreases blood testosterone level in men. Three weeks after the first injection of the depot preparation blood testosterone level reaches postcastration values (Fig. 2.8). Repeated Zoladex injections with 4-week or 12-week intervals (depending on a dose - 3.6 or 10.8 mg) provide permanently low testosterone concentration in blood plasma.

Zoladex is produced in the form of sterile whitely creamy depot where goserelin acetate is dispersed in a matrix, which undergoes bio-

logical degradation. It is stored at a temperature below 25° C. An applicator syringe contains a single dose of goserelin (3.6 or 10.8 mg). The drug is administered subcutaneously in the abdominal area. Local anesthesia may be applied, if necessary.

Zoladex is characterized by high, near total bioavailability. It has no cumulative properties. It hardly binds to blood plasma proteins. A peak of goserelin serum concentration is observed 2 h after Zoladex administration. Half-life in blood is about 4 h.

Pharmacokinetical parameters for 10.8 mg depot in patients who used to take three consecutive Zoladex injections in a dose of 3.6 mg each with a 4-week interval were similar to respective parameters in patients who had a single administration of 10.8 mg depot. It means that during the treatment 3.6 mg depot may be substituted with 10.8 mg depot.

Hepatic or renal dysfunction does not impact goserelin pharmacokinetics. So there is no need in dose adjustment in elderly patients and in cases of renal or hepatic insufficiency.

Treating with Zoladex of hormone-sensitive metastatic PC requires time. Zoladex may be combined with antiandrogenic drugs (blockers of androgen receptors). Zoladex is well tolerated. Cutaneous eruption is observed sometimes but usually it disappears without drug withdrawal. There are some cases of urinary tract obstruction or spinal compression, transient aggravation of bone pains in case of metastases and other complications and side effects typical for LHRH agonists. The figures given below describe the frequency of reactions to Zoladex as compared to similar reactions following surgical castration (in parentheses): decreased libido - 73 % (79 %), erectile dysfunction - 84 % (85 %), hot flushes - 63 % (58 %), gynecomasty - 5 % (5 %). No overdose has been reported.

Leuprorelin (Lucrin-depot). The chemical structure of Leuprorelin is given in Table 2.1.

It is a superactive LHRH analogue. In its pharmacological effect it is similar to other LHRH agonists.

For palliative treatment of metastatic PC combined therapy with non-steroid antiandrogen bicalutamide is recommended. A dose should be established individually. The drug is administered subcutaneously in the brachial, abdominal or gluteal area or intramuscularly in a dose of 3.75

mg or 7.5 mg once in 4 weeks. The drug should not be administered in the same body site. The duration of treatment course does not exceed 6 months. After the drug withdrawal physiological secretion of hormones is recovered.

During treatment with leuprorelin an increase of serum level of hepatic enzymes - LDH, AST, ALT - is possible. Hot flushes, sweating decreased libido, impotence, gynecomasty, atrophy of testes, feeling of discomfort in the perineal area, pains in bones and joints, ischuria, hematuria, changed ECG, diarrhea, nausea, vomiting, anorexia, general fatigue, paresthesia, impairment of hearing, tinnitus aurium, skin reactions are observed sometimes.

2.4. Non-steroid antiandrogens

Nowadays pharmacological preparations with antiandrogenic effect are widely used to treat PC. These preparations successfully compete with estrogens or LHRH agonists or supplement them in combined therapy. According definition, «antiandrogens are substances which prevent androgens from expressing their activity at target sites. The inhibitory effect of these substances, therefore, would be differentiated from compounds which decrease the synthesis and/or release of hypothalamic (releasing factor) and anterior pituitary hormones (gonadotropins, particularly luteinizing hormone) and materials which act directly on the gonads to inhibit biosynthesis and/or secretion of androgens» (Dorfman, 1970). Blockers of cellular receptors of male sex hormones correspond to this definition most of all.

An interest to antiandrogens aroused in the middle of sixties of this century when experts from «Schering AG» (Germany) discovered antiandrogenic activity of cyproterone acetate, a synthetic progestin with high potency. At the beginning of seventies the first non-steroid antiandrogen Sch 13521 (the international name «flutamide») was synthesized and introduced in the USA («Schering Plough»).

In the former USSR the work on synthesis, studies of the mechanism of action and implementation in the medical practice of antiandrogenic drugs (substituted carboxanilides) was initiated by A. Reznikov at Kiev

Institute of Endocrinology and Metabolism. For more details about antiandrogens please refer to the related monographs (Eichler et al., 1974; Reznikov, Varga, 1988) and reviews (Reznikov, Varga, 1979, 1982; Neumann, 1980, 1989; Reznikov, 1986).

According to the chemical structure steroid and non-steroid antiandrogens are distinguished. The antiandrogenic activity is assayed by a decrease in the weight of the ventral prostate under the effect of the tested drug, which is administered to castrated immature rats over a week together with testosterone propionate (Dorfman, 1962). In general, mechanism of antiandrogenic effect of steroid compounds lies in competitive antagonism with endogenous androgens for binding with cytoplasmic receptors. For non-steroid antiandrogens their ability to block translocation of hormone-receptor complex from the cytoplasm to the cell nucleus is an essential feature.

According to W. Mainwaring (1977), an ideal antiandrogen should meet the following requirements: safety, high affinity for androgen receptors and minimal accompanying hormonal activity. The so-called pure antiandrogens with nonsteroid structure, flutamide for example, meet the latter requirement. However, hormonal activity in progesterone derivatives sometimes imparts them with properties highly desirable in PC treatment. In this respect cyproterone acetate seems to be the most adequate example since it is characterized by antiandrogenic and antigonadotropic activities, the latter strengthening its antiandrogenic effect.

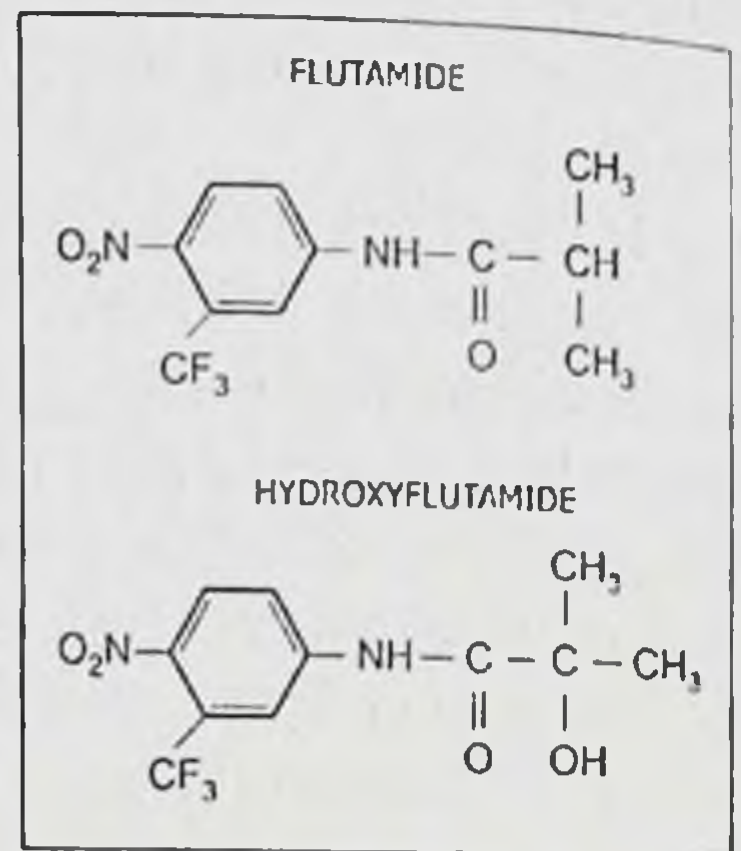


Fig. 2.9. Chemical structure of flutamide and its active metabolite

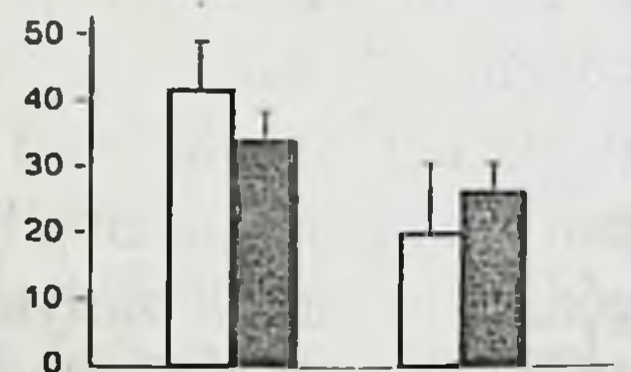


Fig. 2.10. Weights of the ventral prostate (white bars) and seminal vesicles (black bars) in adult rats following 10-day administration of flutamide or hydroxyflutamide in a daily dose of 10 mg/kg b.w. (percentage relative to its values in intact animals)

At the same time steroid antiandrogens often cause impotence, liquid retention and thromboembolic complications (de Voogt et al., 1986) while non-steroid antiandrogens very seldom result in such complications (Sogani et al., 1984).

Flutamide. Synonyms: Niftolide, Flutapharm, Flucinom, Flutakan, Flugil, Flulem, Euflex, Eulexin, Fugerel, Norex etc.

Flutamide is a substituted carboxanilide - 4'-nitro-3'-trifluoromethylisobutyranilide, or 2-methyl-N (4-nitro-3-trifluoromethyl-phenyl)propanamide (Fig. 2.9).

It prevents binding of endogenous androgens (testosterone, DHT, androstenedione etc.) to cellular receptors and translocation of cytoplasmic hormone-receptor complex to the nucleus of target cell. As a result, DNA replication and proliferation of PC cells are disturbed. It neither produces any hormonal, that is androgenic, estrogenic progestational, glucocorticoidal, gonadotropic side effects, nor manifests antagonistic properties towards mentioned hormones (except androgens). It is supposed that antiandrogenic effect of flutamide is mediated by its active metabolite, hydroxyflutamide, which is produced in the liver (Katchen, Buxbaum, 1975).

The ability of flutamide to cause atrophy of the normal and malignant prostate gland was established in numerous experiments in animals (Fig. 2.10). In intact rats, according to our data, a significant regression of accessory sexual glands was found when flutamide was administered orally in a dose of 5-25 mg/kg b.w. In castrated animals that were given testosterone propionate it persisted even under minimal (2.5-fold) increase of flutamide (Niftolide) dose over the amount of testosterone, which was administered parenterally.

Flutamide-induced morphological changes in the prostate gland are characterized by a decrease in the height of the epithelial cells (Fig. 2.11), decrease of cytoplasm volume, lumina of the terminal departments of the gland, spreading of the connective tissue. Atrophic changes are accompanied by a decrease of DNA and RNA synthesis, total

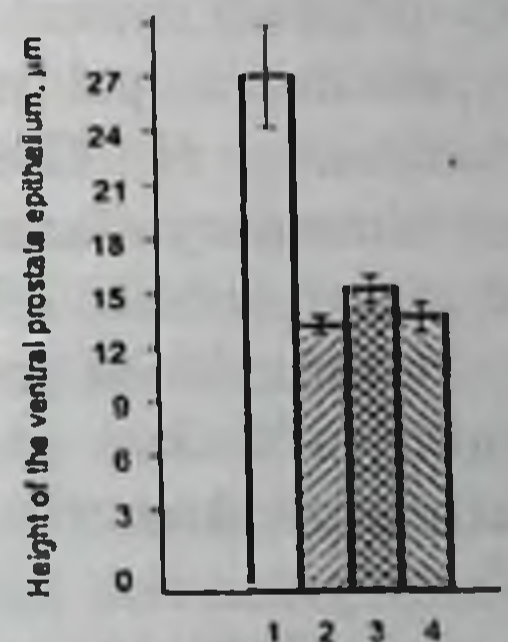


Fig. 2.11. Effect of flutamide on the height of the epithelium of the ventral prostate in adult rats: (1) testosterone propionate (TP, 200 µg/kg a day); (2) solvent (kernel oil); (3) TP + flutamide (25 mg/kg a day). All preparations were given during 7 days

biopolymer contents, discontinuance of exogenous secretion, suppression of acid phosphatase activity, low fructose content. At the same time catabolic processes, in particular RNA degradation, are intensified.

Antiandrogenic effect of flutamide in the prostate is potentiated due

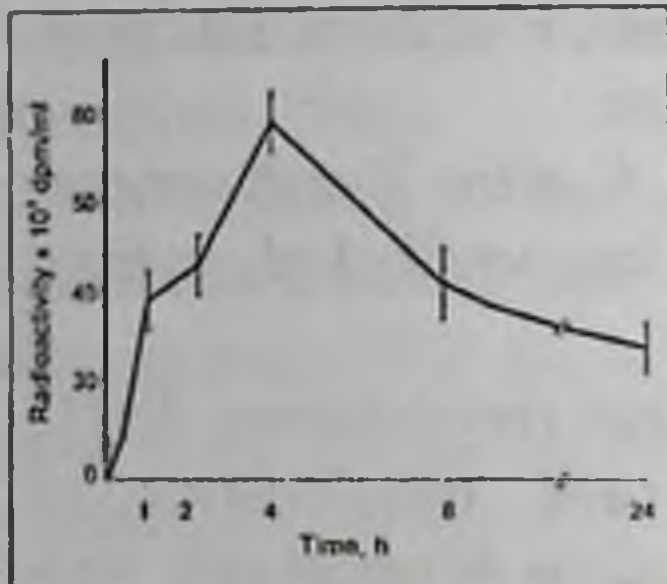


Fig. 2.12. Changes of rat blood radio activity following oral ^3H -flutamide administration

to the inhibitory effect of the drug on DHT formation in the gland tissues (Reznikov, Korpacheva, 1990). It seems to be connected with attenuation of inductive effect of endogenous androgens on steroid- 5α -reductase activity.

A typical feature of flutamide, common for all «pure» antiandrogens, is stimulation of the activity of hypothalamic-pituitary-testicular axis (Reznikov, 1990). The reason for this stimulation is attenuating by flutamide the inhibitory effect of circulating testosterone

on pituitary gonadotropin secretion because of the blockade of hypothalamic and pituitary androgen receptors. Besides, an active metabolite of flutamide, hydroxyflutamide, increases pituitary gonadotropocyte sensitivity to stimulating effect of hypothalamic LHRH (Reznikov et al., 1987). Resulting from increased gonadotropocyte stimulation blood total testosterone increases. It hampers maximum androgen blockade under monotherapy with flutamide and justifies its use for combined treatment of PC together with LHRH agonists or low doses of estrogens.

As showed by experiments in rats (Reznikov, Varga, 1988), following administration in the stomach of tritium-labeled flutamide radioactivity in blood reaches its maximum 4 h later and keeps rather high within first 8 h (Fig. 2.12). During at least 16 h following flutamide administration antiandrogen displaces ^3H -testosterone in the prostatic tissues.

Main parameters of pharmacokinetics and metabolism of ^3H -flutamide in men were studied by B. Katchen and S. Buxbaum (1975). Flutamide is well absorbed in the gastrointestinal tract and its metabolites are excreted mainly through the kidneys. During 2 days following a single oral administration of 200 mg 91 % of flutamide and its metabolites is excreted with urine and feces, following 3 days - 98 %. Neither flutamide nor its metabolites have cumulative properties.

Following 1 h after oral administration only 2.4 % of native antiandrogen is found in the blood. By that time 23 % of flutamide is transformed into hydroxyflutamide with higher antiandrogenic activity. Maximum concentration of this antiandrogen in men is achieved in 2 h following oral administration and decreases considerably in 8 h.

All companies produce flutamide in 250 mg tablets.

For palliative treatment of advanced PC (with metastases or without them) flutamide is taken for a long time, 1 tablet three times a day (a daily dose is 750 mg). The therapeutic effect is better in PC patients who have not been treated previously. In some cases a positive result is observed in patients with hormonal drug resistance.

When flutamide is prescribed for primary endocrine therapy positive therapeutic effect is found in 50-80 % of patients. In its effectiveness it does not yield to diethylstilboestrol while the latter evokes cardiovascular complications and thrombophlebitis twice as often as flutamide (Neri, Kassem, 1982; Boccon-Gibod, 1993; Chang et al., 1996). As compared to estrogen therapy and castration flutamide does not increase the survival rate in patients with metastatic PC but it facilitates better quality of life.

Flutamide administration in combination with LHRH agonists or low doses of estrogens and also its administration after castration is considered to be most effective. In these cases flutamide administration is aimed at suppressing the residual amounts of androgenic hormones, in particular of the adrenal origin.

Some authors report that combined therapy of PC with flutamide included (together with castration or LHRH agonists) decreases annual mortality rate by 9% (Waxman, Pandha, 1995; Quartey, 1995). Other authors who also use the results of meta-analysis do not confirm this conclusion (Dalesio et al., 1995b). However, all authors agree that supplementary use of flutamide alleviates symptoms of the disease and improves the quality of life, though in some patients side effects are observed.

Flutamide is well tolerated by the majority of patients. 30 % of patients demonstrate gynecomasty or breast tenderness, less often galactorrhea is found. These manifestations disappear when the dose is reduced or after the drug withdrawal. Sometimes cardiovascular, hepatic complications are possible, that is why it is necessary to check these organs from time to time. In this aspect potential hepatotoxicity of flutamide requires a special attention, though it is seldom manifested (Wysovski,

Fourcroy, 1996). However, some authors report that pronounced hepatotoxicity of flutamide is observed in 9 % of patients (Cetin et al., 1999).

In 3% of patients nausea, vomiting, dyspepsia, dizziness, insomnia, fatigue are possible. Rare side effects include decreased libido and sexual activity, anorexia, burning pains in the epigastrium, heartburn, diarrhea, constipation, edema, and thirst. Under long-lasting therapy a number of spermatozoa in the ejaculate sometimes decrease. Though flutamide belongs to anilides it does not cause methemoglobinemia and cancer of the urinary bladder in men.

Flutamide is contraindicated to patients with hypersensitivity to this drug. Interaction with other drugs is not reported.

Bicalutamide (Casodex). It belongs to «pure» non-steroid antiandrogens, which do not possess hormonal activity. It is a selective blocker of androgen cellular receptors in men and animals. It is effective when administered orally. It is produced in the form of coated 50 mg tablets.

According to McKillop et al. (1993), pharmacokinetics of Casodex in healthy men under a single oral dose of 50 mg racemate is characterized by the following parameters. Blood plasma R-casodex [(-) enantiomer] concentration rises slowly and reaches a peak value of 559- 970 ng/ml at 15-48 h and then decreases with a half-life of about 4.2 days. S-Casodex [(+) enantiomer] concentration increases rapidly and within 2-4 h reaches 32-66 ng/ml and then it decreases with a halflife of 19 h. About 80% of the drug is excreted with the urine and feces as metabolites (bicalutamide glucuronides and hydroxylated derivative). Under standard PC monotherapy with Casodex its mean plasma concentration is 8.5 ± 2.9 ng/ml (Soloway et al., 1995b), half-life is 7-10 days.

Bicalutamide metabolism is accomplished in the liver and kidneys, prostate, seminal vesicles, adenohipophysis, spleen, central nervous system (hypothalamus), however the main metabolic process takes place in the liver. In contrast to flutamide, its active form being hydroxyflutamide, bicalutamide is an active form of the drug.

Treatment of PC patients with Casodex in a dose of 50 mg/day (1 tablet a day) is accompanied by a moderate increase of plasma testosterone level, however it does not cause hypertrophy or hyperplasia of Leydig cells (Jones et al., 1994). The clinical effect is observed in 56-79 % of patients with advanced PC. However, in a dose of 50 mg/day it is less effective than castration (Iversen, 1994). When administered for a long

time PSA level drops to postcastration values only when a daily dose is increased up to 150 mg. Since a decrease of PSA level is a prognostic criteria for the effectiveness of PC treatment, it is recommended to include Casodex (in a dose of 50 mg/day) in combined therapy, i.e. following castration or in combination with LHRH agonist, which increases the effectiveness of treatment considerably. The advisability of Casodex use for monotherapy of PC is now under study (Schröder, 1999). One of the benefits of Casodex is the possibility to take it once a day.

Casodex is well tolerated. The most common side effects of monotherapy, which are associated with antiandrogenic activity of the drug, include painfulness of the breast (26 % of patients), gynecomasty (23 %), hot flushes (9 %). Less than 5-8 % of patients demonstrate jaundice and increased activity of hepatic transaminases (these manifestations are transient), asthenia, constipation, vomiting, diarrhea (it is less often as compared to other non-steroid antiandrogens, 2.5 % of patients), peripheral edema, sweating. If there are pronounced hepatic disorders the drug should be prescribed very carefully taking into consideration its cumulative properties. In a double blind randomized study, diarrhea was observed significantly less often in patients who took Casodex (10 %) than in those who took flutamide (24 %), hepatic disorders were less often, and there were no cases of acute hepatic insufficiency (Schellhammer et al., 1995; Soloway, 1995). In case of renal dysfunction no dose adjustment is required.

Loss of libido is observed in less than 1% of patients. No cases of spontaneous impotence under monotherapy with Casodex were registered. That is why it is reasonable to prescribe Casodex to people who have big concerns about their sexual potency (Iversen, 1999).

Nilutamide (Anadron).

It belongs to non-steroid antiandrogens, does not manifest estrogenic, androgenic and progestational activities. Due to slow metabolism the drug can be taken once a day. It is produced in the form of 50 mg tablets.

Nilutamide is indicated for palliative treatment of metastatic PC as a supplement to surgical or drug (LHRH agonists) castration. It is prescribed in a dose of 300 mg/day (6 tablets) for a 4-week period. Then the maintenance dose of 150 mg/day (3 tablets) is taken.

Side effects include disorders of accommodation and color perception, «antabus-like» syndrome, interstitial pneumonia, a moderate

increase of hepatic transaminase activity, decreased libido, hot flushes, nausea, vomiting. Among rare complications bone marrow aplasia occurs. These manifestations are mostly moderately manifested and reversible following nilutamide withdrawal or dose reduction. Pronounced hepatic disorders are contraindications for nilutamide administration.

Nilutamide should be withdrawn if symptoms of interstitial pneumonia appear as well as abdominal pains of unknown origin, threefold increase of serum transaminase levels, decreased hemoglobin content.

It is not recommended to prescribe nilutamide to patients whose activities require concentrated attention, eye strain, immediate behavioral and motor reactions (drivers, for example). Nilutamide is incompatible with alcohol.

2.5. Steroid antiandrogens

Steroid blockers of male sex hormones receptors are synthetic derivatives of progesterone. Interest to progestins as potential antiandrogens arose when the ability of progesterone to suppress biological effects of androgens in target tissues was discovered.

As a result of pharmacological screening seven most active antiandrogens were selected among a great number of synthetic progestins. Well-known antiandrogens of the progestin family include megestrol acetate, chloromadinone acetate. But most well known and widely used for treating PC and other diseases is cyproterone acetate, which was synthesized and studied in the laboratories of «Schering AG» and «Bergkamen» (Germany) (Wiechert, Neumann, 1965; Neumann, Steinbeck, 1974; Neumann, 1994).

Cyproterone acetate (Androcur). Its chemical structure is as follows:

1 α ,2 α -methylene-6 α -chloro-4,5-pregnadiene-17 α -ol-3,20-dion-17 α -acetate (Fig. 2.13).

To treat PC Androcur-50 in tablets (1 tablet contains 50 mg cyproterone acetate) and Androcur-depot in ampoules (1 ampoule contains 300 mg cyproterone acetate in oil solution) are used.

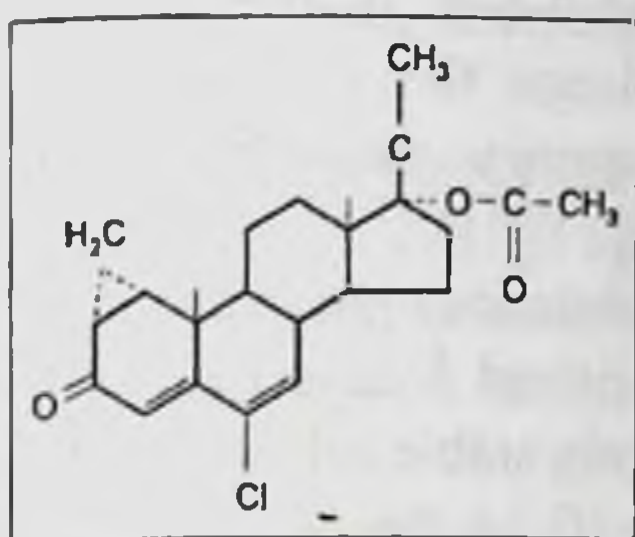


Fig. 2.13. Cyproterone acetate (Androcur)

The compound has antiandrogenic, progestational and antigonadotropic activities. The antiandrogenic effect is underlain by the ability of cyproterone acetate to bind competitively to cellular receptors of androgens in target organs and to block translocation of the DHT-receptor complex from the cytoplasm to the nucleus (Brinkman et al., 1983). Thus it prevents stimulatory effect of endogenous androgens on the tumor growth in PC patients.

In animals a marked atrophy of the prostate under the effect of cyproterone acetate was demonstrated. The antiandrogen administration in a dose of 10 mg/kg during 3 weeks resulted in a decrease of the weight of the accessory sexual glands to 10 % of the initial value. DNA, RNA, protein contents and activity of acid phosphatase, aminopeptidase and other functionally relevant enzymes decreased to postcastration level.

One of manifestations of antiandrogenic activity of cyproterone acetate is dose-dependent suppression of spermatogenesis. Decreased libido in men, dogs, rabbits, pigs and monkeys is associated with both antiandrogenic and progestational activity of the drug.

Like other active progestins, cyproterone acetate demonstrates a marked antigonadotropic effect, i.e. it inhibits secretion of gonadotropic hormones. As a result, testosterone secretion is decreased (Fig. 2.14). A combination of antiandrogenic and antigonadotropic properties allows considering cyproterone acetate as an androgen with dual action, and in this respect it is a unique remedy for PC patients.

Following oral administration of Androcur-50 tablets the drug is rapidly and completely absorbed from the gastrointestinal tract. Its concentration in blood reaches maximum 3-4 h later. The adipose tissue accumulates more than a half of the substance and its metabolites, wherefrom they are slowly released in blood. In the phase of distributing

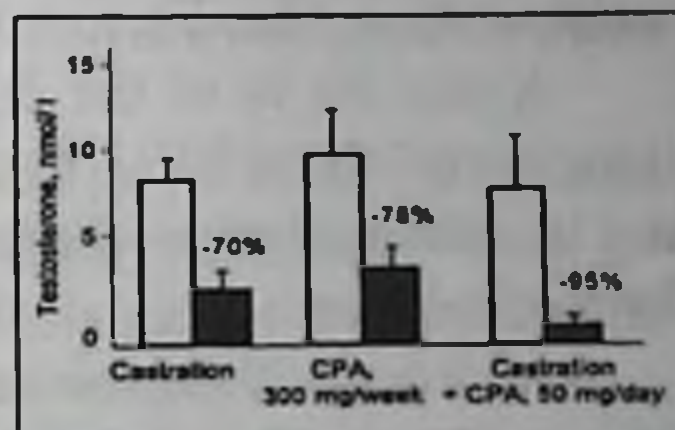


Fig. 2.14. Effect of cyproterone acetate (CPA) and castration on blood serum testosterone level in PC patients, respectively, before (open bars) and after 6-month treatment (black bars) (From Jacobi et al., 1982)

cyproterone acetate in tissues, its half-life makes 3-5 h. In the second phase, which reflects a kinetic equilibrium between the antiandrogen metabolism in the body and its elimination, the respective value is 1.6-2.0 days.

Following an intramuscular injection of Androcur-depot maximum blood concentration of cyproterone acetate is achieved 3 days later. An effective therapeutic concentration remains relatively stable following the 4th injection of the drug and is maintained within 10-14 days. Halflife in the first and second metabolic phases is 1.5-2.0 and 5.2 days, respectively.

The main metabolite of cyproterone acetate in the body is 15 β -hydroxycyproterone acetate, which has the same high antiandrogenic activity but 10-fold less progestational activity. About a half of administered antiandrogen is converted into this metabolite. Following oral Androcur administration in a dose of 100-200 mg/day concentration of both compounds in blood serum is approximately the same, 200-600 μ g/l.

About 30 % of the drug and its metabolites are excreted through kidneys and about 70% - through the liver. 80-90 % of cyproterone acetate and its metabolites is eliminated as part of glucuronides, 10 % - in the form of sulphates.

Androcur-50 (tablets) and Androcur-depot (solution for intramuscular injections) are prescribed for treating inoperable PC as a means of monotherapy, following castration or in combination with LHRH agonists (continuously or only at the initial stage of LHRH administration in order to prevent increased testosterone secretion).

Tablets are taken orally after meals. Non-orchietomized patients are prescribed 2 tablets of Androcur-50 2-3 times a day (200-300 mg). A daily dose of 300 mg facilitates a more pronounced decrease of LH and testosterone levels in blood plasma and is considered to be more effective. The treatment is long irrespective of whether improvement or remission is achieved.

Androcur-depot is administered intramuscularly in a dose of 1 ampoule (300 mg) once a week, it is possible to alternate injections and tablet administration. The usual treatment course is 6 months.

After orchietomy 2 tablets of Androcur-50 1-2 times a day (100-200 mg) or 1 ampoule (300 mg) of Androcur-depot once in 2 weeks is prescribed.

In combination with LHRH agonists, the treatment starts with administration of Androcur alone (2 tablets twice a day, i.e. 200 mg)

during 5-7 days, then combined with LHRH agonist for 3-4 weeks in the same dose. -

In order to weaken the effect of adrenocortical androgens during treatment with LHRH agonists Androcur-50 is taken in a dose of 2 tablets 1-2 times a day (100-200 mg).

Addition of Androcur to LHRH agonists and its administration following orchiectomy result in a significant decrease of the number of hot flushes evoked by surgical or pharmacological castration.

Side effects include those, which are directly associated with its pharmacological activity. Most often are transient (after drug withdrawal) suppression of spermatogenesis, impotence, enlargement and painfulness of breast, gynecomasty, galactorrhea, fatigue, depression, difficulties with concentrating the attention, headache. Changes of body weight, diarrhea, nausea, vomiting, constipation, edema, thrombophlebitis, hypochromic anemia, negative nitrogen balance, hypercalcemia are observed in some patients.

Cardiovascular complications are observed in 9.6 % of PC patients treated with Androcur (under treatment with diethylstilboestrol they appear in 34.3 %), gynecomasty in 6 % of patients (under treatment with diethylstilboestrol it makes 40 %).

Because of possible Androcur effects on the liver and the adrenal cortex a laboratory control of these organs (once in 6 months), peripheral blood count, blood glucose level measurement are recommended. Diabetic patients may need adjustment of insulin or other hypoglycemic drug dose. During treatment with Androcur one should avoid activities which require concentrated attention.

Contraindications for treatment with Androcur are: hepatic disorders including tumors (except PC metastases to the liver), Rotor and Dubin-Johnson syndromes (hereditary malignant hyperbilirubinemia), thromboembolism or its presence in the medical history, depressions, decompensated diabetes mellitus with angiopathy, sickle-cell anemia. In each separate case the advisability of treatment with Androcur should be considered individually taking into consideration all contraindications.

LOW DOSE ESTROGEN - ANTIANDROGEN THERAPY (LEAT) OF PROSTATE CANCER: LESSONS FROM ANIMAL RESEARCH

3.1. Theoretical background

Low dose estrogen-antiandrogen therapy (LEAT) was introduced by us as variant of PC combined therapy. Like surgical or pharmacological castration, which is used in combination with antiandrogens, LEAT is aimed at maximum androgen deprivation of the tumor and its metastases. The essence of the proposed method lies in combined use of estrogens in low doses, i.e. subtherapeutic ones as compared to conventional estrogen monotherapy, and of non-steroid antiandrogens. What makes LEAT different from combination of LHRH agonists with antiandrogens is more availability in terms of saving money and a better tolerance since it allows to avoid side effects that could be induced by LHRH agonists in the central nervous system functioning. Despite a considerable reduction of conventional estrogen dose, it successfully substitutes LHRH agonist as an antigonadotropic agent. The effect of residual testicular and adrenocortical androgens on PC cells is neutralized by an antiandrogen.

The risk of severe complications, cardiovascular first of all, decreases considerably. This is determined by an 8- 10-fold reduction of the estrogen dose as compared with generally accepted. The LEAT concept emerged about 10 years ago when we discovered that diethylstilboestrol is capable of potentiating antiandrogenic effects of flutamide in the rat prostate (Sinitsyn et al., 1988). Each of these drugs, which had been used separately

in «sub-threshold» doses, did not effect the weight of the ventral prostate. Surprisingly, when administered in combination the same doses induced a marked atrophy of the gland, particularly of its epithelium that was confirmed histologically. Then the mechanism underlying the pharmacological potentiation was elucidated, namely inhibition of LH and testosterone secretion by a synthetic estrogen, due to it less antiandrogen was required for effective blockade of cellular androgen receptors in the prostate.

The same year B.R. Rao et al. (1988) reported on inhibition of growth of inoculated prostate adenocarcinoma in rats by a combination of low doses of the non-steroid antiandrogen Anadron (nilutamide) and natural estrogen, estradiol-17 β . Though estradiol as a pharmacological preparation is not used in clinical practice for PC treatment, the results obtained corroborated a new approach to endocrine therapy.

Lately, Canadian scientists (Bruchovsky et al., 1990, 1993) obtained good clinical results in treating PC with a combination of diethylstilboestrol with the non-steroid antiandrogen Androcur (cyproterone acetate). However, it should be mentioned that Androcur, in addition to its antiandrogenic activity, demonstrates antigonadotropic effect as well, i.e. it «duplicates» estrogen effect on the neuroendocrine system.

In our opinion, a combined use of flutamide and low doses of a synthetic estrogen is an optimum combination in LEAT design. This is based on the results of animal research (Sinitsyn et al., 1988; Varga et al., 1995; Polyakova, 1997; Reznikov, Varga, 1994, 1995; Reznikov et al., 1996; Reznikov, Chaikovskaya, 1998) and of their protocols implementation, i.e. clinical trials, optimization of treatment, elucidation of underlying mechanisms of therapeutic effect in PC patients (Vozianov et al., 1995 a, b; 1996a,b; 1998 a,b; 1999; Vozianov, Reznikov, 2000).

This chapter gives the results of our animal research on assessing antiprostatic effect of flutamide (Nifolide) combinations with different estrogenic compounds in low doses and also elucidating hormonal and biochemical mechanisms of this action. The fact that PC cells respond to androgen deprivation in the same way as normal cells do (this is an essential basis of endocrine therapy of PC) allows using normal animals for such experiments, especially because known experimental models for PC are not identical to human prostatic adenocarcinoma. It is possible to

extrapolate data on pharmacodynamics, which were obtained in the normal rat prostate, on PC patients. The adequacy of the results of pre-clinical study of hormonal and antihormonal drugs as to their expected therapeutic activity in men was confirmed both by the world and our own previous experience in experimental and clinical pharmacology of drugs for PC treatment.

3.2. Flutamide and diethylstilboestrol

The effect of low doses of flutamide (Niftolide) and diethylstilboestrol and their combinations on the male accessory sex glands - ventral prostate, coagulating gland (the so-called anterior prostate) and seminal vesicles- were studied in adult Wistar rats. Flutamide doses ranged from 2.5 to 10 mg/kg b.w., diethylstilboestrol doses - from 10 to 50 $\mu\text{g}/\text{kg}$ b.w. The drugs were dissolved in oil and administered through a gastric tube daily during 30 days. Control animals were given a solvent.

In the previous studies flutamide applied in a dose of 10 mg/kg significantly decreased the ventral prostate weight after 10-day administration. However a month later this dose turned out to be insufficient to maintain the effect mentioned; this was associated with an ability of non-steroid androgen to increase blood testosterone level. The increased dose of 25 mg/kg resulted in atrophic changes in the rat prostate, which were found following 30-day flutamide administration as well.

As it was expected, flutamide in doses under 10 mg/kg given for 30 days did not change the weight of the ventral prostate though atrophy of the seminal vesicles was pronounced enough. Nor changed the prostate weight when diethylstilboestrol was administered in a dose of 10 $\mu\text{g}/\text{kg}$. At the same time a combined use of antiandrogen and synthetic estrogen resulted in a considerable reduction of the weight of the accessory glands, including that of the ventral prostate by 31 % (Table 3.1).

A maximum antiprostatic effect was found when flutamide was used in a dose of 10 mg/kg in combination with diethylstilboestrol in a dose of 10 $\mu\text{g}/\text{kg}$.

Table 3.1. Effect of flutamide and diethylstilboestrol on the weight of androgendependent rat organs following 30-day administration, mg/100 g b.w.

Treatment	Ventral prostate	Coagulating gland	Seminal vesicles
Control	100,6±4,3	49,2 ± 2,5	105,4 ±3,4
Flutamide, 5 mg/kg	91,6 ± 9,6	42,7 ± 2,5	72,7 ± 2,5*
Diethylstilboestrol, 10 mg/kg	98,9 ± 9,4	31,3 ± 3,4'	102,9 ±7,7
Flutamide, 5 mg/kg + + diethylstilboestrol, 10 mg/kg	79,0 ± 5,0*	35,3±4,1*	64,1 ±5,7*
Flutamide, 10 mg/kg	95,5 ± 7,7	45,9± 3,7	91,6 ±4,3*
Flutamide, 10 mg/kg + + diethylstilboestrol, 10 mg/kg	69,8 ± 5,5*	38,7 ± 2,5*	78,4 ± 8,7*

*p < 0.05 as compared to the control

It is known that fructose content in the accessory sex glands correlates with their functional activity and is under control of male sex hormones. In the experiments described flutamide (2.5 mg/kg) and diethylstilboestrol (50 µg/kg) applied separately did not effect fructose concentration. A combined use of these drugs decreased significantly its concentration in the ventral prostate (0.36 ± 0.02 µmol/g tissue), coagulating gland (3.17 ± 0.78) and seminal vesicles ($0.64 + 0.07$) with normal values of $0.45 + 0.02$; 6.54 ± 0.39 and 0.92 ± 0.5 µmol/g, respectively.

Thus diethylstilboestrol in minimal doses potentiates androgenic effects of flutamide in androgen-dependent organs. The central antigonadotropic effect of the estrogen plays the main role in the process. When assessing activity of steroid- Δ^{4-5} -3 β -oldehydrogenase, a key enzyme of androgen biosynthesis in the testes, we did not find an inhibiting effect of diethylstilboestrol on steroidogenesis in doses of 10-15 µg/kg.

Changes in blood plasma LH and testosterone concentrations showed that flutamide and diethylstilbestrol exert multi-directed effect on these hormone levels (Table 3.2). Under combined use the estrogen prevented completely flutamide-induced increase of pituitary-testicular hormone levels.

Changes in the antiandrogen and testosterone ratio towards the antiandrogen concentration prevalence brings to a situation in prostatic tissues when testosterone and DHT are more effectively displaced in the loci of specific binding.

Following the results of this study it seems reasonable to conduct clinical trials on the effectiveness of combined treatment of PC using subtherapeutic doses of flutamide and diethylstilboestrol.

Table 3.2. Blood plasma bioactive LH and testosterone contents in male rats under separate and combined flutamide and diethylstilboestrol administration for 30 days

Treatment	LH, IU/l	T, nmol/l
Control	33,75 ± 1,53	9,33 ± 0,21
Flutamide, 10 mg/kg	51,74 ± 1,28*	17,38 ± 3,47*
Diethylstilboestrol, 10 mg/kg	23,57 ± 1,08*	3,01 ± 0,17*
Flutamide, 10 mg/kg + diethylstilboestrol, 10 mg/kg	33,16 ± 1,53	11,10 ± 1,66

IU, units of activity of the international LH standard 69/104; *p < 0.05 as compared to the control.

3.3 Flutamide and hexestrol

Hexestrol (Synestrol) is a synthetic non-steroid compound, which has been used to treat metastatic PC, especially in the CIS countries. Taking into consideration the results of the previous studies with diethylstilboestrol it seemed reasonable to check if low doses of hexestrol potentiated flutamide antiandrogenic effects in the accessory sex glands.

Table 3.3. Effects of castration, flutamide and hexestrol on the weight of androgendependent organs in male rats, mg/100g b.w.

No of group	Treatment	Ventral prostate	Coagulating gland	Seminal vesicles	Testes
1.	Control	113,3 ± 8,6	50,3 ± 3,4	93,6 ± 5,4	1282 ± 71
2.	Castration p _{1,2}	20,3 ± 6,3 < 0,001	16,1 ± 1,5 < 0,001	46,2 ± 2,6 < 0,001	-
3.	Flutamide, 10 mg/kg p _{1,3}	78,5 ± 10,2 < 0,05	39,9 ± 2,0 < 0,05	84,8 ± 4,5 > 0,05	1165 ± 37 > 0,05
4.	Hexestrol, 40 mg/kg sc p _{1,4}	65,1 ± 11,6 < 0,05	26,2 ± 2,0 < 0,001	71,4 ± 5,0 < 0,05	979 ± 52 < 0,05
5.	Flutamide + hexestrol p _{1,5}	30,2 ± 7,5 < 0,001	19,3 ± 1,7 < 0,001	59,3 ± 4,2 < 0,001	966 ± 43 0,05
	p _{3,5}	< 0,01	< 0,001	< 0,01	< 0,05
	p _{4,5}	< 0,05	< 0,001	> 0,05	> 0,05

Means ± S.E. for 6-7 rats

The drugs were administered for 10 days in order to estimate their pharmacological activity. Flutamide was administered to rats orally being included in a carboxymethylcellulose gel. Hexestrol (oil solution) was applied subcutaneously in doses of 2, 10, 40, 200 or 1000 $\mu\text{g}/\text{kg}$ b.w.

Flutamide (10 mg/kg) decreased the weight of the ventral prostate and coagulating gland by 31 % and 21 %, respectively, without a considerable effect on the testicular size. In doses of 2-40 $\mu\text{g}/\text{kg}$ hexestrol decreased the organ weights to the same level as flutamide did or slightly more. Under the estrogen dose of 40 $\mu\text{g}/\text{kg}$ this decrease made 43 % and 48 %, respectively. With an increase of the estrogen dose up to 200 or 1000 $\mu\text{g}/\text{kg}$ the ventral prostate weight dropped to nearpostcastration values. A combined use of the antiandrogen and hexestrol in the lowest tested dose (2 $\mu\text{g}/\text{kg}$) decreased the prostate weight to 40-45 % of the respective value in intact rats, i.e. to the level, which was achieved only when a 100-fold dose of hexestrol alone was administered (200 $\mu\text{g}/\text{kg}$). In combination with flutamide, hexestrol administered in a dose of 40 $\mu\text{g}/\text{kg}$ facilitated a decrease of the weight of the ventral prostate and coagulating gland to 27 % and 38 % of the control values (Table 3.3). As to the coagulating gland and seminal vesicles, maximum effect identical to castration was found under even minimal estrogen dose (2 $\mu\text{g}/\text{kg}$) in combination with flutamide (Fig. 3.1).

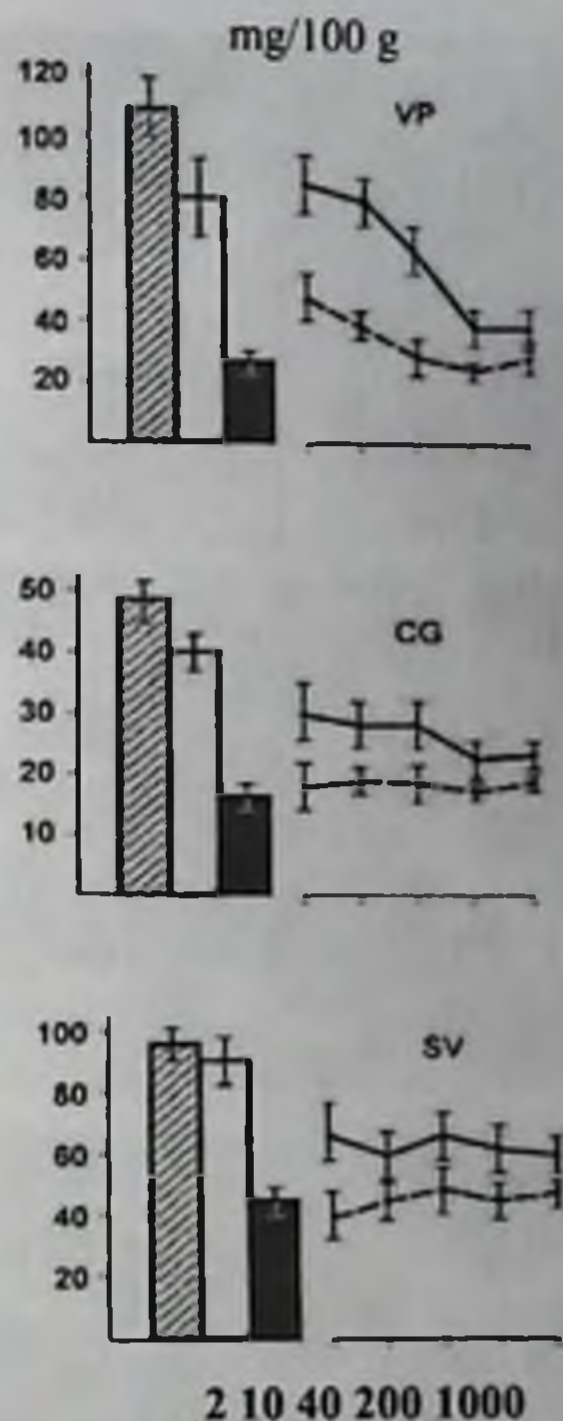


Fig. 3.1. Weight of the accessory sex glands of male rats that were given flutamide (10 mg/kg) and/or hexestrol (2-100 $\mu\text{g}/\text{kg}$ sc) for 10 days: VP, ventral prostate; CG, coagulating gland; SV, seminal vesicles.

Shaded bars refer to the control, open bars to flutamide-treated group, black bars - to castration (in 10 days)

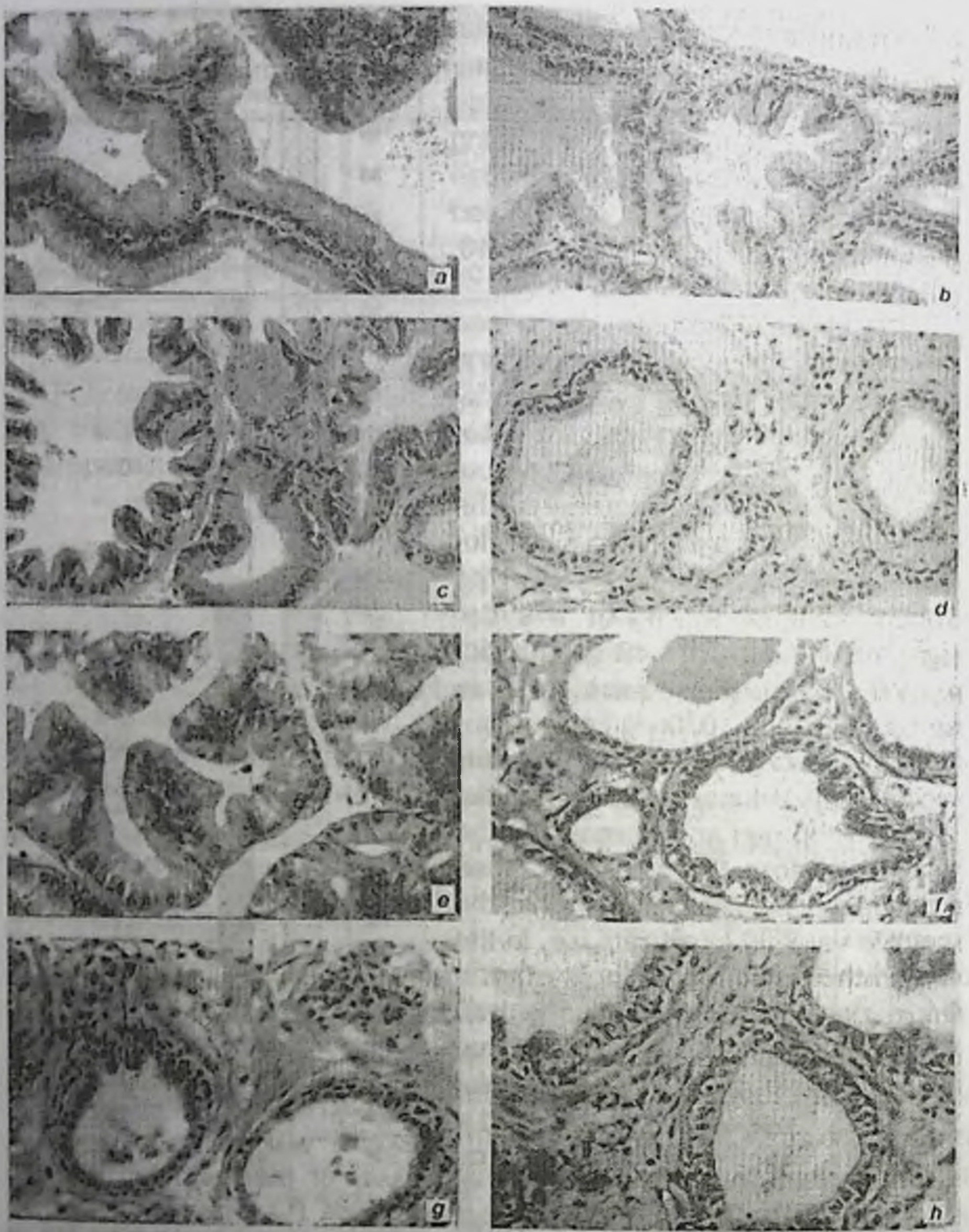


Fig. 3.2. Changes in the secretory epithelium of the rat ventral prostate 10 days after castration or administration of flutamide, hexestrol and chlorotrianisene. Staining with hematoxylin and eosin, x 200:

(a) control; (b) flutamide, 10 mg/kg; (c) chlorotrianisene, 0.2 mg/kg; (d) flutamide, 10 mg/kg + chlorotrianisene, 0.2 mg/kg; (e) hexestrol, 2 µg/kg; (f) hexestrol, 40 µg/kg; (g) flutamide, 10 mg/kg + hexestrol, 40 µg/kg; (h) castration

Table 3.4. Changes in DNA content and cell number in the rat ventral prostate following castration or 10-day flutamide and hexestrol administration

No of group	Treatment	DNA		Cell number, x 10 ⁷
		µg/kg tissue	µg/organ	
1.	Control	2,86 ± 0,37	809 ± 147	9,29 ± 1,68
2.	Castration	5,60 ± 0,63	299 ± 72	3,44 ± 0,82
	p _{1.2}	< 0,05	< 0,05	< 0,05
3.	Flutamide, 10 mg/kg	4,25 ± 0,54	849 ± 135	9,74 ± 1,55
	p _{1.3}	> 0,05	> 0,05	> 0,05
4.	Hexestrol, 40 µg/kg	4,43 ± 0,63	668 ± 150	7,68 ± 1,72
	p _{1.4}	> 0,05	> 0,05	> 0,05
5.	Flutamide + Hexestrol	6,93 ± 0,98	366 ± 28	4,14 ± 0,32
	p _{1.5}	< 0,05	< 0,05	< 0,05
	p _{3.5}	< 0,05	< 0,01	< 0,05
	p _{4.5}	> 0,05	> 0,05	> 0,05

Means + S.E. for each group of 5-7 rats

As table 3.4 shows, castration induced an abrupt decrease of total DNA content in the ventral prostate, which was accompanied by a twofold increase of its concentration in tissues; this is determined by a cytoplasm loss. A respective decrease of glandular cell number was observed which was calculated by DNA content. When flutamide (10 mg/kg) and hexestrol (40 µg/kg) were administered separately, only a tendency to an increase in DNA concentration without a significant decrease of its total amount and cell number was found. However, a combined use of the drugs resulted in pronounced changes of all parameters as surgical castration did.

The results of microscopic examination of the ventral prostate in rats that were given flutamide in a dose of 10 mg/kg demonstrate a mild decrease in the height of secretory epithelium and small areas with destructive changes. Such changes were found when hexestrol was applied (2 µg/kg). Hexestrol in a dose of 40 µg/kg caused manifested dystrophic and destructive damages. The lumina of secretory glands were narrowed. The lining epithelial layer lost its folds, epithelium desquamation

Table 3.5. Effect of flutamide and a microdose of hexestrol administered for 10 days on protein, nucleole acid contents and cell number in the ventral prostate

No of group	Treatment	n	DNA		RNA		RNA/DNA	Protein		Cell number, $\times 10^7$
			mg/mg tissue	mg/organ	mg/mg tissue	mg/organ		mg/mg tissue	mg/organ	
1	Control	20	3,1 \pm 0,1	888 \pm 45	2,1 \pm 0,2	606 \pm 48	0,7 \pm 0,004	49,4 \pm 2,2	14,7 \pm 1,2	10,2 \pm 0,5
2	Flutamide, 10 mg/kg p1,2	5	3,1 \pm 0,2 > 0,5	771 \pm 167 > 0,05	1,5 \pm 0,1 < 0,05	358 \pm 59 < 0,05	0,5 \pm 0,03 0,01	57,9 \pm 2,2 0,05	13,8 \pm 2,0 0,05	8,9 \pm 1,9 > 0,05
3	Hexestrol, 2 mg/kg sc p1,3	6	3,7 \pm 0,3 > 0,05	654 \pm 65 < 0,05	1,2 \pm 0,1 < 0,01	231 \pm 48 < 0,01	0,3 \pm 0,04 0,001	50,0 \pm 3,6 0,05	8,8 \pm 1,0 0,05	7,5 \pm 0,7 < 0,05
4	Flutamide + hexestrol p1,4 p2,4 p3,4	7	4,9 \pm 0,2 < 0,001 < 0,001 < 0,05	404 \pm 38 < 0,001 < 0,05 < 0,05	1,2 \pm 0,1 < 0,01 < 0,05 > 0,05	97 \pm 9 < 0,001 < 0,01 < 0,05	0,2 \pm 0,001 < 0,001 < 0,001 > 0,05	56,7 \pm 1,9 < 0,05 < 0,05 > 0,05	4,7 \pm 0,3 < 0,001 < 0,01 < 0,05	4,7 \pm 0,4 < 0,01 < 0,05 < 0,05

was found. Non-damaged epithelium consisted of cuboidal cells arranged in two layers, often with atrophic changes. In optically transparent cells of the inner layer, pyknotic nuclei were seen.

Under combined drug administration hyperplasia of the connective and muscular tissue was accompanied by spectacular dystrophic and destructive changes of the secretory epithelium. On the whole, the histologic image resembled that after castration (Fig. 3.2).

Convincing results were obtained while studying the effect of flutamide and hexestrol in a dose of 2 µg/kg. In these experiments potentiation of antiprostatic effect of flutamide by microdoses of hexestrol was found in all principal parameters, i.e. DNA and RNA contents and ratio, total protein concentration, cell number in the ventral prostate (Table 3.5). Thus biochemical studies confirm the atrophic changes in the prostate under combined administration of small doses of the antiandrogen and hexestrol.

Fructose measurements in the coagulating gland (anterior prostate), a sensitive indicator of secretory activity, support completely this conclusion (Table 3.6). When antiandrogen and estrogen were used in combination fructose content was similar to that observed 10 days after orchietomy.

Table 3.6. Fructose content in the rat coagulating gland following castration or today administration of Flutamide and Synestrol

No of group	Treatment	Fructose content	
		pmol/100 g tissue	pmol/organ
1.	Control	0,73 ± 0,03	0,91 ± 0,08
2.	Castration p _{1,2}	0,22 ± 0,02 < 0,001	0,09 ± 0,01 < 0,001
3.	Flutamide, 10 mg/kg p _{1,3}	0,97 ± 0,07 < 0,05	1,02 ± 0,10 > 0,05
4.	Hexestrol, 40 µg/kg p _{1,4}	0,51 ± 0,04 < 0,01	0,34 ± 0,05 < 0,001
5.	Flutamide + hexestrol p _{1,5} p _{3,5} p _{4,5}	0,28 ± 0,02 < 0,001 < 0,001 < 0,01	0,11 ± 0,01 < 0,001 < 0,001 < 0,01

Means ± S.E. for each group of 6-7 rats

Summing up the results of these studies it should be emphasized that they demonstrate the effect of potentiating antiandrogen action by low

estrogen doses. In a dose of 10 mg/kg flutamide produces a slight antiandrogenic effect on the prostate and other accessory sex glands. Hexestrol, when used in small doses, is able to potentiate this effect considerably like diethylstilboestrol does. The reaction observed is not just additive effects of these drugs. This is proved by a more pronounced decrease of the organ weights, a decrease of fructose level in the coagulating gland, DNA content and cell number in the ventral prostate as well as a considerable reduction of the latter under a combined use of the antiandrogen and estrogen.

Taking into account that changes of the hormonal profile are essential for manifesting antiprostatic effects of flutamide and estrogens we paid a particular attention to a functional state of the hypophysis, testes and testosterone metabolism in the prostatic tissues.

Flutamide when administered orally for 10 days in a daily dose of 5 or 10 mg/kg produced a 1.7-2.4-fold increase in the concentration of biologically active LH and a 2.1-2.5-fold increase of testosterone concentration in male rat blood plasma. This demonstrates an effective blockade of hypothalamic and pituitary androgen receptors (Table 3.7). Actually, 10 days after castration LH level increased to the same extent, i.e. 2.5 times. Hexestrol when administered to intact males inhibited LH secretion in a dose-dependent fashion (within the dose range of 10-40 $\mu\text{g}/\text{kg}$). The dose increase did not result in further decrease of blood testosterone level, which demonstrated postcastration values when a daily dose was 40 $\mu\text{g}/\text{kg}$. Hexestrol minimal dose, which effectively decreased blood testosterone concentration (3.5-fold), corresponded to 2 $\mu\text{g}/\text{kg}$.

Addition of hexestrol to flutamide not only prevented completely antiandrogen-induced increase of blood plasma LH level but also resulted in its further decrease as compared to intact animals. The same effect was observed regarding blood testosterone level. It is important that a daily hexestrol dose of 2 $\mu\text{g}/\text{kg}$, i.e. 400-500 times less than a standard dose used for estrogen therapy of human PC, was sufficient for a complete suppression of flutamide-induced stimulation of the pituitary hormonal function and that of male sex glands. It is obvious that this makes an ideal hormonal background for a maximum blockade of androgen receptors in the prostate since the ratio of testosterone and flutamide concentrations in tissues changes in favour of the antiandrogen.

One of the integral parameters of synthesis of male sex hormones in the testes is steroid Δ^5 -3 β -hydroxysteroid dehydrogenase (SDH) activity, an enzyme, which catalyzes pregnenolone conversion into progesterone,

and dehydroepiandrosterone conversion into androstenedione. In these experiments dehydroepiandrosterone was used as a substrate. Table 3.8 gives data that characterizes «the behaviour» of this enzyme under separate and combined administration of flutamide and hexestrol for a 10-day period. They convincingly demonstrate that hexestrol administration completely eliminates flutamide-induced activation of andro- genopoiesis in the testes evoked by an increase of LH secretion.

Table 3.7. Bioactive LH and testosterone contents in male rat blood plasma 10 days after castration or flutamide and hexestrol administration

Treatment	Dose, mg/kg	LH, IU/IT, nmol/l	T, nmol/l
Control	-	5,24 ± 0,40	7,80 ± 2,20
Castration	-	12,90 ± 1,00 ^a	0,67 ± 0,07 ^a
Flutamide	5,00	8,99 ± 1,49 ^a	16,10 ± 3,40 ^a
	10,00	12,60 ± 1,09 ^a	19,70 ± 4,50 ^a
Hexestrol	0,002	4,50 ± 0,50 ^a	2,20 ± 0,34 ^{a,b}
	0,01	2,33 ± 0,39 ^{a,b}	2,80 ± 0,83 ^{a,b}
	0,04	2,64 ± 0,26 ^{a,b}	0,58 ± 0,09 ^{a,b}
	0,20	2,98 ± 0,31 ^{a,b}	0,46 ± 0,08 ^{a,b}
	1,00	0,54 ± 0,09 ^{a,b}	3,02 ± 0,39 ^{a,b}
Flutamide + hexestrol	5,00 0,01	2,36 ± 0,60 ^{a,b}	1,40 ± 0,16 ^{a,b}
	5,00 0,04	3,01 ± 0,33 ^{a,b}	0,95 ± 0,22 ^{a,b}
	10,00 0,002	4,51 ± 0,74 ^b	2,40 ± 0,29 ^{a,b}
	10,00 0,01	2,04 ± 0,57 ^{a,b}	4,80 ± 1,03 ^b
	10,00 0,04	1,42 ± 0,43 ^{a,b,c}	0,70 ± 0,14 ^{a,b}
	10,00 0,20	1,94 ± 0,49 ^{a,b}	0,62 ± 0,11 ^{a,b}
	10,00 1,00	1,39 ± 0,25 ^{a,b,c}	0,74 ± 0,11 ^{a,b}

Means ± S.E. for each group of 5-13 rats

Note. Here and in the following tables LH content is assayed against the 1st international standard of human pituitary LH preparation 69/48. The difference is significant ($p < 0.05$ or less) as compared to control animals (^a) and those that were given flutamide (^b) or hexestrol (^c).

Table 3.8. SDH activity in the testes of rats that were given flutamide and hexestrol for 10 days

Treatment	SDH activity		
	per testis	per 1 g tissue	per 1 mg protein
Control	324 ± 33	238 ± 22	7,46 ± 0,82
Flutamide, 10mg/kg	566 ± 39*	417 ± 13*	13,31 ± 0,82*
Hexestrol, 40 µg/kg	320 ± 18	282 ± 18	9,02 ± 0,89
Hexestrol + flutamide	248 ± 12*	264 ± 12	9,15 ± 0,85

Means + S.E. for each group of 5 rats. * $p < 0.01$ as compared to the control

Inhibition of testosterone secretion and pharmacological blockade of androgen receptors in tissues are confirmed by histological data, which show suppression of spermatogenesis and changes in Leydig cells. The normal index of spermatogenesis is 3.56-3.59 and after hexestrol administration it decreased to 3.26 while after combined estrogen and flutamide administration to 3.15. In the latter case the lumina of some seminal vesicles demonstrated desquamated I order spermatocytes, a number of seminiferous tubules with the XII stage cycle of the spermatogenic epithelium increased. A number of spermatozoa in 2 ml epididymal spermatozoa suspension was as follows (mln/ml): normal - 64.7 ± 7.3 ; hexestrol - 28.84 ± 4.4 ; flutamide in combination with Synestrol - 3.9 ± 0.6 .

In the testes of rats that received hexestrol injections (40 µg/kg) Leydig cells were arranged in clusters of 5-7 medium-sized cells. They had oval, mildly hyperchromatic nuclei, nucleoli were hardly detectable. Under combined administration of the estrogen and antiandrogen a number of Leydig cells decreased, they were medium or small, with hyperchromatic nuclei. Thus, both hormonal and generating functions of the sex glands are most essentially inhibited under a combined use of flutamide and low dose of hexestrol.

A considerable contribution in the realization of antiprostatic action of the drugs studied is made by changes in testosterone metabolism, first of all those, which occur on the routes of its 5α -reduced metabolite formation. 5α -reductase activity was estimated in prostatic homogenates incubated with radioactive testosterone with subsequent chromatographic separation and quantitative assessment of DHT and 3α - androstandiol. Table 3.9 gives total data on the formation of both testosterone metabolites per 1g tissue or protein.

Table 3.9. Steroid 5 α -reductase activity in the rat ventral prostate 10 days after castration or flutamide and hexestrol administration

No of group	T treatment	5 α -reductase	
		nmol/h. g ⁻¹ tissue	nmol/h. g ⁻¹ protein
1.	Control	51,7 \pm 8,4	569 \pm 79
2.	Castration	2,3 \pm 0,9	52 \pm 21
	p _{1,2}	< 0,001	< 0,001
3.	Flutamide, 10 mg/kg	24,5 \pm 3,2	324 \pm 59
	p _{1,3}	< 0,05	< 0,05
4.	Hexestrol, 40 μ g/kg	6,5 \pm 3,2	117 \pm 56
	p _{1,4}	< 0,01	< 0,01
5.	Flutamide + hexestrol	11,6 \pm 1,4	283 \pm 36
	p _{1,5}	< 0,01	< 0,05
	p _{3,5}	< 0,05	> 0,05
	p _{4,5}	> 0,05	< 0,05

Means + S.E. for each group of 4-5 rats

In animals from all experimental groups, 5 α -reductase activity of prostatic tissues decreased significantly as compared to intact males but the rate of testosterone metabolism was different. Both separate and combined drug administration produced a considerable inhibition of DHT and 3 α -androstandio! formation. This might be associated with a weakened androgen induction of the enzyme synthesis.

Thus in the mechanism of atrophic changes of the prostate, which result from combined effect of low-dose hexestrol and flutamide, there are distinct multivector pharmacological effects. The atrophy of the organ is an integrated result of androgen receptor blockade, suppression of testicular testosterone synthesis and secretion and inhibition of DHT formation in the prostate.

Hexestrol is known to possess certain estrogenic activity when used orally as well, that is why it is used in tablets for maintenance

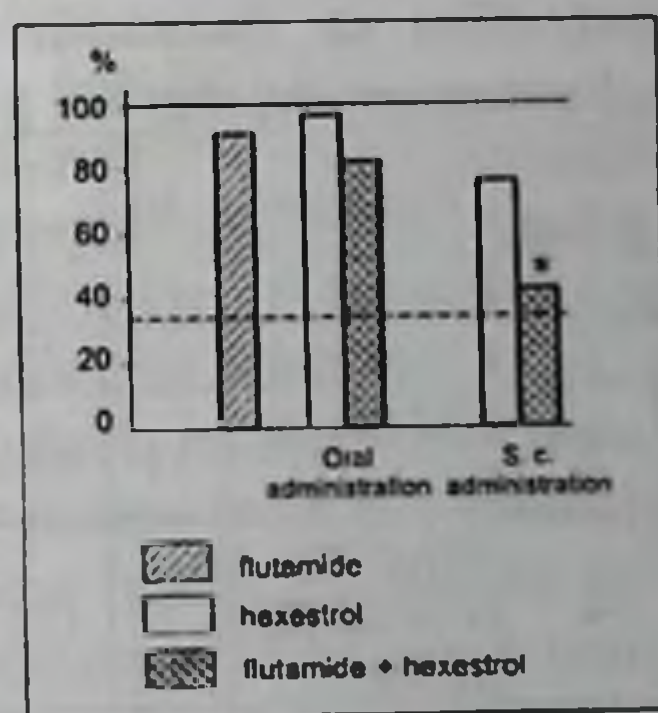


Fig.3.3. Changes in the weight of the rat ventral prostate under different ways of hexestrol (40 μ g/kg, open bars), flutamide (10mg/kg, shaded bars) administration or in combination of hexestrol with flutamide (cross-hatched bars) during 10 days

Solid line, control; dotted line, castration

*p < 0.05 as compared to the control

therapy of PC. The possibility to substitute estrogen injections with tablets within LEAT scheme seemed rather tempting. Proceeding from it a study was conducted in order to compare the effectiveness of flutamide (10 mg/kg, 10 days) in combination with hexestrol solution (40 µg/kg, s.c., 10 days) or tableted mass (40 µg/kg once a day, 10 days).

Unlike subcutaneous injections of hexestrol solution oral estrogen administration did not effect the weight of sex organs and did not potentiate flutamide antiandrogenic effect under combined administration (Table 3.10, Fig. 3.3). This conclusion is supported by DNA (Fig 3.4) and cell number measurements. Under oral hexestrol administration DNA concentration made 2.70 ± 0.13 µg/mg tissue (control - 2.70 ± 0.22 µg/mg), total content - 813 ± 43 µg (control - 836 ± 99 µg), number of cells in the ventral prostate - $(9.4 \pm 0.5) \times 10^7$ cells (control - $(9.1 \pm 1.1) \times 10^7$ cells). Under combined use of flutamide and hexestrol tablets these values were 3.60 ± 0.33 µg/g tissue, 721 ± 71 µg/organ, $(8.3 \pm 0.8) \times 10^7$ cells/organ, respectively (the difference, as compared to the control, is not statistically significant, except a slight increase of DNA concentration).

Table 3.10. Weight of androgen-dependent organs 10 days after castration or flutamide and hexestrol administration, orally or subcutaneously, mg/100 g b.w.

No of group	Treatment	n	Ventral prostate	Coagulating gland	Seminal vesicles	Testes	Epididymis
1.	Control	13	131 ± 9	57 ± 4	93 ± 5	1286 ± 51	347 ± 12
2.	Castration	6	20 ± 6	16 ± 2	46 ± 3	-	-
3.	Flutamide, 10 mg/kg	11	89 ± 13	40 ± 2	85 ± 6	1190 ± 40	279 ± 31
4.	Hexestrol, tablets, 40 µg/kg	7	131 ± 9	57 ± 5	89 ± 6	1334 ± 40	389 ± 12
5.	Flutamide + hexestrol, tablets	7	96 ± 15	36 ± 5	70 ± 6	1312 ± 51	291 ± 18
	<i>p_{1,5}</i>		>0,05	<0,05	< 0,05	> 0,05	> 0,05
6.	Hexestrol, 40 µg/kg	7	65 ± 12	26 ± 2	71 ± 5	979 ± 52	194 ± 33
7.	Flutamide + hexestrol, solution	6	30 ± 8	19 ± 2	59 ± 4	966 ± 43	140 ± 9
	<i>p_{1,7}</i>		< 0,001	< 0,001	< 0,001	< 0,001	< 0,001

	P _{5,7}		< 0,01	< 0,05	>0,05	< 0,05	< 0,01
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The histological structure of the ventral prostate following hexestrol tablets did not differ considerably from the control. Large secretory glands lined with high cylindrical epithelium were preserved. In the terminal departments of the secretory glands, the epithelium formed papillary prominences, however they were slightly shorter than in the control. In some epitheliocytes the nuclei shifted from the basal to the apical surface of the cell, which also resulted from the estrogen effect.

As a result of combined use of flutamide and hexestrol tablets in some secretory departments of the gland the height of the epithelium decreased as well as papillary prominences and their number.

Often the terminal departments looked widened. Scarce alveoli filled with excessively oxyphilic secretion showed epithelium desquamation. On the whole, the histological pattern was far from what is typical for castration or combined administration of flutamide and hexestrol solution.

Fructose content in the prostate, which reflects its functional state, correlated with the results of microscopic examination and DNA content. In contrast to hexestrol solution, which induced nearly a threefold decrease of total fructose content and 1.5-fold decrease of its tissue concentration (Table 3.6), estrogen tablets did not influence these parameters: the concentration was $0.89 \pm 0.07 \mu\text{mol}/100 \text{ mg tissue}$ (control - $0.83 \pm 0.04 \mu\text{mol}/100 \text{ mg tissue}$, $p > 0.05$), total content - $1.21 \pm 0.13 \mu\text{mol}$ (control - $1.13 \pm 0.11 \mu\text{mol}$, $p > 0.05$). Respective values under combined administration of flutamide and hexestrol tablets were $0.77 \pm 0.09 \mu\text{mol}/100 \text{ mg tissue}$ and $0.69 \pm 0.14 \mu\text{mol}$ ($p > 0.05$ as compared to control in both cases) while flutamide combination with hexestrol solution brought these values to postcastration level (Table 3.6).

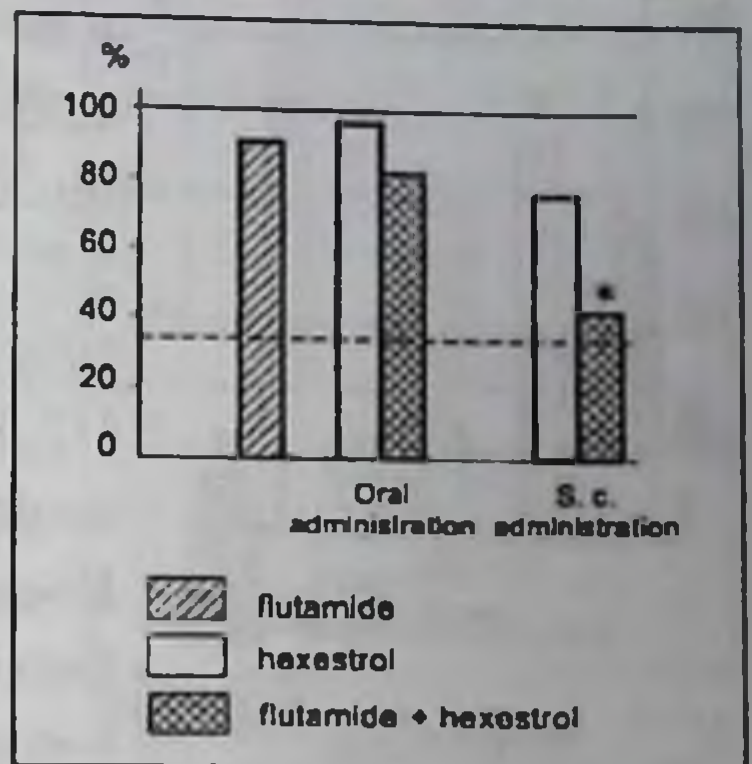


Fig. 3.4. Changes in total DNA content in the rat ventral prostate under different ways of hexestrol (40 $\mu\text{g}/\text{kg}$, open bars), flutamide (10 mg/kg , shaded bars) administration or in combination of hexestrol with flutamide (cross-hatched bars) during 10 days

Solid line, control; dotted line, castration

* See Fig. 3.3

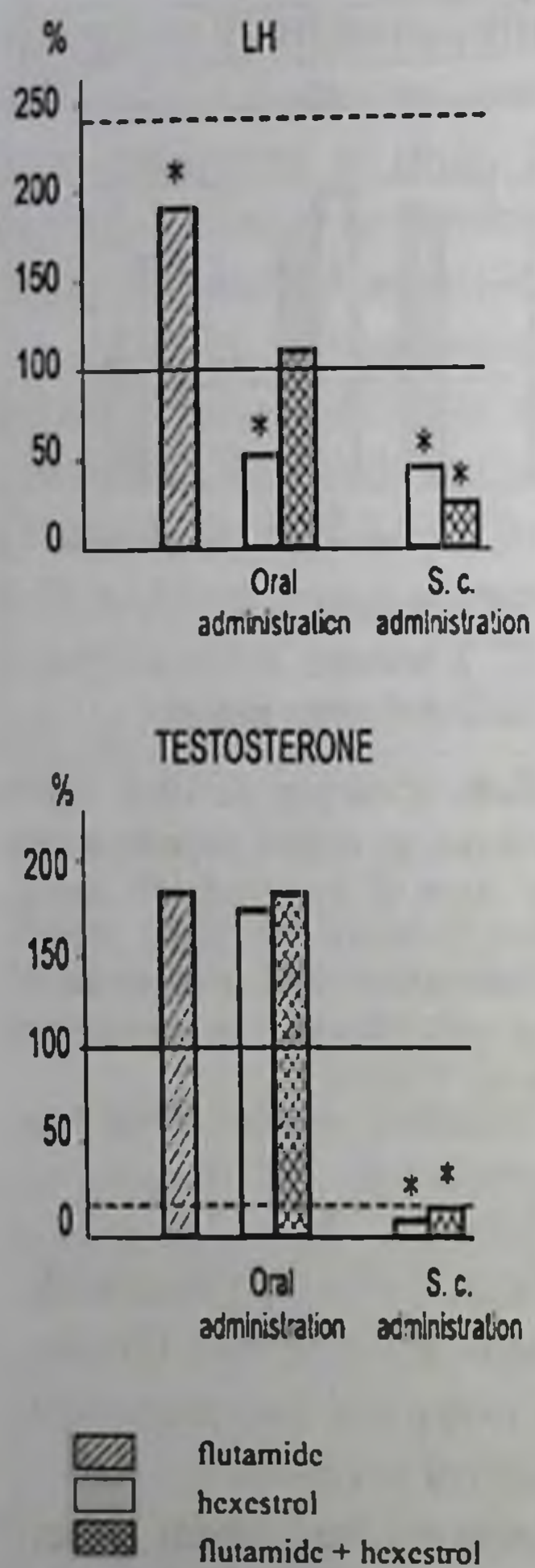


Fig. 3.5. Changes in LH and testosterone contents in blood plasma under different ways of hexestrol (40 µg/kg, open bars), flutamide (10 mg/kg, shaded bars) administration or in combination of hexestrol with flutamide (cross-hatched bars) during 10 days. Solid line, control; dotted line, castration
 * See Fig. 3.3

Ineffectiveness of oral use of hexestrol was shown when the hormonal status was studied (Fig. 3.5). Despite a mild decrease of blood LH concentration (from 5.50 ± 0.45 to 3.75 ± 0.26 IU/l, $p < 0.001$) testosterone concentration did not decrease significantly (13.5 ± 3.7 versus 7.9 ± 2.4 nmol/l in the control group, $p > 0.05$). Nor both hormone levels decreased under oral administration of flutamide and hexestrol (LH - 6.23 ± 0.36 IU/l, testosterone - 13.7 ± 2.0 IU/l, $p > 0.05$ as compared to the control).

Though oral hexestrol administration (separately and in combination with flutamide) prevented antiandrogen-induced activation of sex steroid synthesis, only a combination of flutamide with hexestrol solution resulted in a significant decrease in SDH activity in the rat testes (Fig. 3.6).

As it was to be expected from the results of the hormonal analysis, when hexestrol was administered as a part of tableted mass spermatogenesis was not disturbed. The seminiferous tubules demonstrated all stages of the cycle of the spermatogenic epithelium without any detectable changes of the histologic structure. The index of spermatogenesis did not differ from that in the control, spermatozoa content in 2 ml epididymal spermatozoa suspension was $66. \pm 3.3$ mln/ml (control - 64.7 ± 7.3 mln/ml, $p > 0.05$).

Proceeding from it changes in spermatogenesis, which were observed under combined administration of flutamide and hexestrol tablets,

should be explained by antiandrogenic effect of flutamide. The seminiferous tubules showed local damages of its integrity as a result of death of separate spermatocytes, however they were not numerous. Spermatozoa concentration in 2 ml epididymal spermatozoa suspension was 40.6 ± 6.8 mln/ml ($p > 0.05$ as compared to the control). Leydig cells in all phases of their life cycle, including B and C types, were preserved. They were medium and large with rounded or oval nuclei and distinct large nucleoli. Microscopic examination proved high functional activity of Leydig cells. This reaction, as mentioned in Chapter 2, reflects an enhancement of pituitary gonadotropic release as a result of pharmacological blockade of androgenic receptors in the hypothalamus and hypophysis.

A search for effective and convenient regimens of combined use of flutamide and hexestrol tablets was continued taking into consideration the fact that oral estrogen administration in a dose of $40 \mu\text{g}/\text{kg}$ once a day could turned out to be ineffective for maintaining its sufficient blood concentration for 10 days. That is why two versions of the study described above were designed. In the first one hexestrol was administered in a dose of $100 \mu\text{g}/\text{kg}$ b.w. once a day, in the second - $40 \mu\text{g}/\text{kg}$ twice a day with a 12 hour-interval.

When hexestrol tablets were given twice a day (in a daily dose of $80 \mu\text{g}/\text{kg}$) a slight 13-20 % decrease of the weight of the accessory sex glands was observed as compared to the normal values. But these changes were statistically significant only with respect to seminal vesicles. Under combined administration with flutamide, hexestrol did not potentiate flutamide effect on the ventral prostate, coagulating gland and seminal vesicles (Table 3.11).

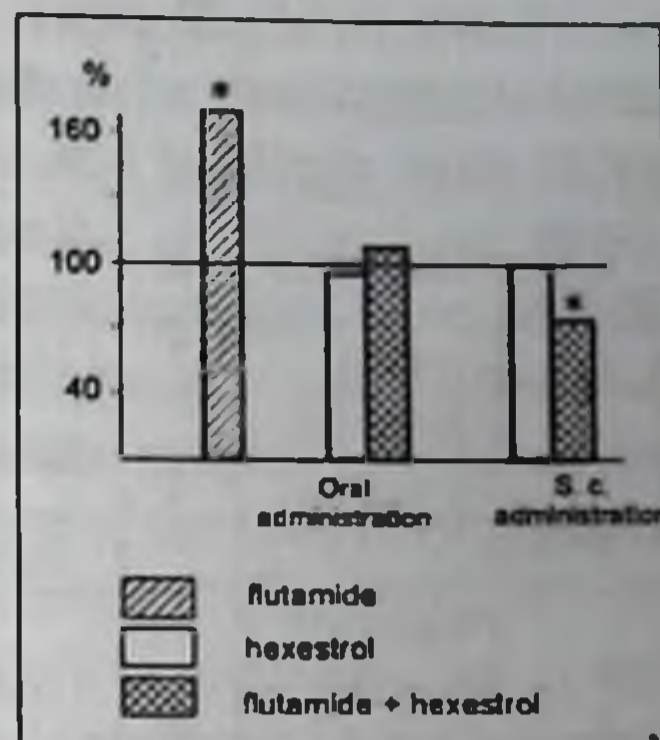


Fig. 3.6. Changes of AS-3p-hydroxysteroid dehydrogenase activity in the rat testes under different ways of hexestrol ($40 \mu\text{g}/\text{kg}$, open bars), flutamide ($10 \text{ mg}/\text{kg}$, shaded bars) administration or in combination of hexestrol with flutamide (cross-hatched bars) during 10 days. Solid line, control; dotted line, castration

* See Fig. 3.3

Table 3.11. Weight of the rat reproductive organs under different protocols of oral administration of flutamide and hexestrol for 10 days, mg/100g b.w.

No of group	Treatment	n	Ventral prostate	Coagulating gland	Seminal vesicles	Testes	Epididymis
1.	Control	7	139 ± 21	63 ± 5	113 ± 8	1044 ± 86	352 ± 7
2.	Flutamide, 10 mg/kg	5	100 ± 16	41 ± 2	85 ± 7	1215 ± 44	318 ± 12
	p _{1,2}		>0,05	< 0,001	< 0,05	>0,05	<0,05
3.	Hexestrol, 40 µg/kg, twice	6	120 ± 12	51 ± 4	90 ± 5	1274 ± 43	383 ± 9
	p _{1,3}		> 0,5	> 0,05	< 0,05	< 0,05	> 0,05
4.	Flutamide, 10 mg/kg + hexestrol, 40 µg/kg, twice	6	111 ± 11	51 ± 3	92 ± 4	1312 ± 46	343 ± 7
	p _{1,4}		>0,05	<0,05	<0,05	<0,05	> 0,5
	p _{2,4}		>0,5	<0,05	> 0,5	> 0,05	>0,5
	p _{3,4}		>0,5	>0,5	> 0,5	>0,5	<0,05
5.	Hexestrol, 100 µg/kg, once	7	96 ± 5	44 ± 3	87 ± 5	1288 ± 52	352 ± 20
	p _{1,5}		> 0,05	< 0,05	<0,05	<0,05	> 0,1
	p _{3,5}		> 0,05	> 0,05	> 0,5	>0,5	>0,05
6.	Flutamide, 10 mg/kg + hexestrol, 100 µg/kg, once	7	77 ± 16	33 ± 3	73 ± 6	1154 ± 47	254 ± 22
	p _{1,6}		<0,05	< 0,001	< 0,001	>0,05	< 0,001
	p _{2,6}		> 0,05	<0,05	> 0,05	> 0,5	< 0,05
	p _{4,6}		> 0,05	< 0,001	<0,05	<0,05	<0,01
	p _{5,6}		> 0,05	<0,05	>0,05	> 0,05	<0,01

Though under such pattern of hexestrol administration, there was a twofold decline of blood testosterone concentration, estrogen turned out to be unable to prevent flutamide-induced rise of testosterone level in male rats that were given a combination of hexestrol and flutamide (Table 3.12).

In case of a single oral use of hexestrol (100 $\mu\text{g}/\text{kg}$ a day) absolute values of weights of the ventral prostate and other accessory glands were slightly less than in double estrogen administration in a daily dose of 80 $\mu\text{g}/\text{kg}$, the difference between two groups was not significant. However the effect of combination of the estrogen and antiandrogen in respect to these organs was much more pronounced than under previous regimen of hexestrol administration. The weight of the ventral prostate decreased by 45 % as compared to the control group and those of the coagulating gland and seminal vesicles by 49% and 36 %, respectively (Table 3.11).

A more pronounced pharmacological effect in the latter case is associated with the absence of flutamide-induced increase of blood plasma testosterone level. And even more, it was 25 % lower than the normal value. Apparently, this is also the reason for greater effect of hexestrol (100 $\mu\text{g}/\text{kg}$ once a week) and flutamide combination on gonadal spermatogenesis. A decreased index of spermatogenesis and few local damages of the spermatogenic layer were observed in the testes. Spermatozoa content in 2 ml epididymal spermatozoa suspension was three times less as compared to the control and considerably exceeding in this respect the effect of flutamide combined with oral hexestrol in a dose of 40 $\mu\text{g}/\text{kg}$ twice a day (Table 3.12).

As shown by microscopic examination of the ventral prostate, morphological disorders corresponded to its changed weight. In both schemes of oral hexestrol administration (40 $\mu\text{g}/\text{kg}$ twice a day and 100 $\mu\text{g}/\text{kg}$ once a day) moderately manifested changes were found in the gland: a decreased size of the secretory glands, decreased height and number of papillary prominences of the epithelium. In the majority of the secretory glands, it remained high cylindrical but it was a bit lower than in the norm. Some glands were widened and filled with fine, weakly stained eosinophilic granules, lined with low cylindrical and cuboidal epithelium. In some cases the prostatic secretion was markedly oxyphilic, epithelium desquamation from considerable acinar area was seen. Under combined hexestrol and flutamide use, in addition to changes described translocation of nuclei from basal to apical part of the epithelial cells was found. On the whole, a combined flutamide and hexestrol administration in a dose of 100 $\mu\text{g}/\text{kg}$ once a day resulted in greater disturbances than under combined flutamide and hexestrol administration in a dose of 40 $\mu\text{g}/\text{kg}$ twice a day.

Basing on these results it was concluded that a dose of 100 µg/kg b.w. should be considered a minimal single dose, which induces anti-prostatic effect under oral use in combination with flutamide. Apparently, under oral dose of 40 µg/kg blood hexestrol concentration is insufficient to potentiate antiandrogenic effect of flutamide.

Table 3.12. Blood plasma testosterone level and spermatozoa content in 2 ml epididymal spermatozoa suspension under different schemes of oral flutamide and hexestrol administration for 10 days

No of group	Treatment	Testosterone, nmol/l	Spermatozoa, mln/ml
1.	Control	3,4 ± 0,8	58,8 ± 5,1
2.	Flutamide, 10 mg/kg	8,8 ± 3,1	46,0 ± 1,7
	p _{1,2}	> 0,05	< 0,05
3.	Hexestrol, 40 µg/kg, twice	1,5 ± 0,2	42,8 ± 2,0
	p _{1,3}	< 0,05	< 0,02
4.	Flutamide, 10 mg/kg + hexestrol, 40 µg/kg, twice	9,1 ± 2,5	42,2 ± 5,0
	p _{1,4}	< 0,05	< 0,02
	p _{2,4}	> 0,5	> 0,5
	p _{3,4}	< 0,01	> 0,5
5.	Hexestrol, 100 µg/kg, once	2,0 ± 1,1	31,3 ± 6,3
	p _{1,5}	> 0,05	< 0,01
	p _{3,5}	> 0,05	> 0,1
6.	Flutamide, 10 mg/kg + hexestrol, 100 µg/kg, once	2,6 ± 1,2	19,8 ± 2,4
	p _{1,6}	> 0,5	< 0,001
	p _{2,6}	> 0,05	< 0,001
	p _{4,6}	< 0,05	< 0,01
	p _{5,6}	> 0,5	> 0,2

Means + S.E. for each group of 5-7 rats

At the same time the unsuccessful attempts to optimize the regime and way of testosterone administration in combination with flutamide proved that it is not reasonable to use hexestrol tablets within LEAT schemes. According to all criteria pharmacological effects of parenteral estrogen administration were superior to that of tablets. However, it cannot be excluded that in some cases addition of a small dose of tableted hexestrol to flutamide might sustain the remission following the main course of LEAT.

3.4. Flutamide and fosfestrol

The phenomenon of accustoming of malignant prostatic tumor to endocrine therapy, i.e. developing a resistance, makes to search for other treatment modalities. It is known that there exists another factor, which is extremely important in selecting a treatment, namely, individual patient's reaction to a hormonal drug with respect to its effectiveness and tolerance. That is why development of LEAT method envisaged evaluation of antiprostatic activity of flutamide combination with different estrogenic drugs.

When studying a combined effect of flutamide and fosfestrol we proceeded from the fact that diethylstilboestrol potentiates flutamide effects on the prostate (diethylstilboestrol, being the active substance that is released in the body as a result of fosfestrol hydrolysis). Besides, we took into account that treatment with fosfestrol gives positive results almost in all morphological types of PC being superior to hexestrol in this respect.

A general design of animal research was similar to that of flutamide combination with hexestrol. Honvan (LEK, Yugoslavia) was administered subcutaneously taking into consideration good bioavailability in this type of administration, once a day in a dose of

2 mg/kg b.w., i.e. 8-10 times less than a conventional daily dose for PC treatment. A Honvan dose, very much approximated to a standard one, 10 mg/kg b.w., was used for comparison. In addition, effects of Honvan and Phosphoestrol used separately or in combination with flutamide were compared.

As we expected, minidoses of fosfestrol potentiated flutamide antiandrogenic effects (Reznikov et al., 1999 b). Pharmacological activity of fosfestrol, which was evaluated by its effect on the weight of the accessory sex glands in male rats, was manifested in a minimal dose of 2 mg/kg b.w. The ventral prostate weight decreased 1.5 times. Though in these experiments flutamide demonstrated only a tendency to a decrease of this parameter, its combination with a minidose of fosfestrol resulted in a considerable and significant reduction of the organ - 3-fold that of the control (Table 3.13). This striking effect is caused by potentiating of the antiandrogenic effect of flutamide as in above-mentioned experiments with combined administration of diethylstilboestrol and flutamide.

It is worth mentioning that an increase of fosfestrol dose to 10 mg/kg in combination with flutamide did not potentiate flutamide antiandrogenic

effects on the prostate, coagulating gland and seminal vesicles as compared to the effect produced by a minidose of the estrogen. In similar experiments Phosphoestrol manifested approximately the same antiprostatic activity as Honvan did, this regards both the effects of separate estrogen administration and its combination with flutamide.

Table 3.13. The rat sex system organs 10 days after administration of flutamide and fosfestrol, mg/100 g b.w.

No	Treatment	Ventral	Coagu-	Seminal	Testes	Epididymis
1.	Control	106 ± 11	49 ± 3	100 ± 2	1163 ±	335 ± 14
2.	Flutamide, 10 mg/kg	79 ± 10	40 ± 2	85 ± 4	54 1165 ±	240 ± 50
	p _{1,2}	> 0,05	<0,05	<0,05	37	> 0,5
3.	Fosfestrol,	65 ± 10	31 ± 4	75 ± 7	> 0,5	288 ± 23
	p _{1,3}	< 0,05	<0,01	<0,01	<0,05	> 0,05
4.	Flutamide + hexestrol, 2 mg/kg	36 ± 5	26 ± 2	64 ± 3	927 ± 26	169 ± 8
	p _{1,4}	< 0,001	< 0,001	< 0,001	<0,05	< 0,001
	p _{2,4}	<0,01	< 0,001	< 0,001	< 0,001	< 0,001
	p _{3,4}	<0,05	>0,05	>0,05	> 0,05	<0,01
5.	Fosfestrol, 10 mg/kg	42 ± 7	22 ± 2	66 ± 3	1056 ±	220 ± 9
	p _{1,5}	< 0,001	< 0,001	< 0,001	45	< 0,001
	p _{3,5}	>0,05	>0,05	>0,05	> 0,05	<0,05
6.	Flutamide + fosfestrol, 10 mg/kg	43 ± 8	23 ± 1	63 ± 2	> 0,05 844 ± 40	149 ± 12
	p _{1,6}	< 0,001	< 0,001	< 0,001	<0,01	< 0,001
	p _{2,6}	<0,05	< 0,001	< 0,001	<0,01	> 0,05
	p _{4,6}	> 0,05	>0,05	>0,5	>0,05	>0,05
	p _{5,6}	>0,5	>0,5	>0,05	<0,05	< 0,001

Means ± S.E. for each group of 6-7 animals

A microscopic examination showed that a decrease of the ventral prostate weight under separate fosfestrol administration and in combination with flutamide reflects histological changes in the tissues of the gland. In a dose of 2 mg/kg fosfestrol induced heterogenous changes within one group

of animals. About a half demonstrated negligible changes of the histological structure: the amount of the secretion in the lumina decreased as well as the height of the epitheliocytes in the terminal departments, slight spreading of the connective tissue and an increased number of sites with desquamated epithelium was found. In other animals, the response to fosfestrol administration (2 mg/kg) was much more pronounced. The secretory epithelium had cylindrical and cuboidal shape; spreading of the connective tissue was marked, the number and size of the terminal departments of the gland decreased. In the connective tissue segmentated leukocytes, large tissue basophils appeared, the number of fibroblasts increased.

When fosfestrol dose was increased to 10 mg/kg histological changes became stable and more profound. The lumina of the terminal departments became even narrower as well as the volume of epithelial cell cytoplasm, their shape changed to low cylindrical or cuboidal. Epithelial desquamation on numerous alveolar sites was found. Spreading of the connective tissue, which substituted reduced secretory departments of the gland, was seen. Cells of the basal layer of the glandular epithelium often had pyknotic nuclei and optically transparent cytoplasm. Hypertrophy and hyperplasia of myocytes was observed around the secretory glands.

A combined use of flutamide and fosfestrol resulted in enhanced degenerative and destructive processes in the prostatic tissue. Even in a dose of fosfestrol of 2 mg/kg the size of epitheliocytes was slightly less than in castrated animals. When a dose of estrogenic drug was increased to 10 mg/kg the atrophy was pronounced. Apparently, these observations support the possibility of a direct diethylstilboestrol effect on the prostate, this being an additional factor in the mechanism of fosfestrol therapeutic action in patients with PC.

Potentiating effect of fosfestrol on flutamide action was particularly convincing when prostatic DNA content was assessed. Neither flutamide nor fosfestrol in a dose of 2 mg/kg when applied separately caused significant changes in total DNA content. When used in combination there was a twofold decrease as compared to the norm. A respective two-fold decrease in the cell number was found (Table 3.14). There was a 7.8 - fold decrease in RNA content in the organ while biopolymer content increased 2.2. times. Under unchanged protein concentration in the prostatic tissues its total content decreased 2.9 times.

As shown in Table 3.14, a 2 mg/kg fosfestrol dose in no way yielded to fosfestrol in a dose of 10 mg/kg administered in combination with flutamide when used following the same protocol. Thus, a minidose of fosfestrol (2 mg/kg) is sufficient for potentiating flutamide effect.

Table 3.14. Effect of flutamide and fosfestrol administered for 10 days on protein, nucleic acid contents and cell number in the rat ventral prostate

No of group	Treatment	DNA		RNA/DNA		Protein		
		mg/mg tissue	mg/organ	mg/mg tissue	mg/organ	mg/mg tissue	mg/organ	
1.	Control	3,5±0,2	911±80	2,0±0,2	539±64	38,8±2,0	10,3±1,0	10,5±0,2
2.	Flutamide, 10 mg/kg p 1,2	4,2±0,5 > 0,05	849±135 > 0,5	---	---	---	---	9,7±1,60 > 0,5
3.	Fosfestrol, 2 mg/kg p 1,3	5,1±0,4 < 0,01	715±95 > 0,05	1,8±0,2 > 0,05	278±62 < 0,05	46,6±3,2 > 0,05	6,7±1,2 > 0,05	8,2±0,1 > 0,05
4.	Flutamide, 10 mg/kg + Fosfestrol, 2 mg/kg p 1,4 p 2,4 p 3,4		395±40 < 0,001 < 0,05 < 0,01	0,9±0,1 < 0,001 --- < 0,001	69±6 < 0,001 --- < 0,01	42,8±2,0 > 0,05 --- > 0,05	3,5±0,4 < 0,01 --- < 0,05	4,5±0,5 < 0,001 < 0,01 < 0,01
5.	Fosfestrol, 10 mg/kg p 1,5 p 3,5	5,6±0,4 < 0,001 > 0,05	534±86 < 0,01 > 0,05	1,0±0,1 < 0,001 < 0,01	96±15 < 0,001 < 0,05	43,6±2,5 > 0,05 > 0,05	4,1±0,5 < 0,001 > 0,05	6,1±0,1 < 0,01 > 0,05
6.	Flutamide, 10 mg/kg + Fosfestrol, 10 mg/kg p 1,6 p 2,6 p 4,6 p 5,6	4,6±0,4 < 0,05 < 0,05 > 0,05 > 0,05	415±52 < 0,001 < 0,05 > 0,05 > 0,05	0,9±0,1 < 0,001 --- > 0,5 > 0,05	79±10 < 0,001 --- > 0,05 > 0,05	41,7±3,7 > 0,05 --- > 0,5 > 0,05	3,7±0,4 < 0,001 --- > 0,5 0,05	4,8±0,6 < 0,001 < 0,01 > 0,5 > 0,05

Means ± S.E. for each group of 6-7 rats

Absence of significant difference in the effectiveness of these two schemes of combined effect on androgen-dependent organs is confirmed by the results of the study of fructose concentration and total content in the coagulating gland (Table 3.15). The data obtained show a dramatic decrease of the functional activity of the organ.

Table 3.15. Fructose content in the rat coagulating gland 10 days after flutamide and fosfestrol administration

No of group	Treatment	Fructose	
		μmol/100 g tissue	μmol/organ
1	Control	0,97 ± 0,19	0,77 ± 0,07
2	Fosfestrol, 2 mg/kg p _{1,2}	0,56 ± 0,18 > 0,05	0,42 ± 0,11 < 0,05
3	Flutamide, 10 mg/kg + fosfestrol, 2 mg/kg p _{1,3} p _{2,3}	0,53 ± 0,15 > 0,5 > 0,5	0,29 ± 0,06 < 0,001 > 0,05
4	Fosfestrol, 10 mg/kg p _{1,4} p _{2,4}	0,41 ± 0,06 < 0,05 > 0,05	0,20 ± 0,03 < 0,001 > 0,05
5	Flutamide + fosfestrol, 10 mg/kg p _{1,5} p _{3,5} p _{4,5}	0,40 ± 0,03 < 0,001 > 0,05 > 0,5	0,43 ± 0,23 > 0,05 > 0,05 > 0,05

Means + S.E. for each group of 6-7 rats

How does pituitary-testicular system respond to a separate and combined administration of flutamide and fosfestrol? The answer is given by measurements of blood plasma bioactive LH and testosterone (Table 3.16).

As well as in other similar experiments flutamide increased considerably blood testosterone level, this was induced by an elevation of LH secretion to postcastration values. Additional administration of fosfestrol in a dose of 2 or 10 mg/kg not only prevented completely flutamide-induced activation of the pituitary-testicular axis but also facilitated 7-10-fold decrease of blood plasma testosterone concentration, i.e. to postcastration level. It is worth mentioning that fosfestrol in a minimal dose of 2 mg/kg in no way yields to a high dose of 10 mg/kg, i.e. it

demonstrates high antigonadotropic activity. In combination with pharmacological blockade of androgen receptors by flutamide this effect produced by fosfestrol facilitates maximum androgen deprivation followed by atrophy of the prostate.

Table 3.16. Blood plasma bioactive LH and testosterone contents in male rats 10 days after castration or flutamide and fosfestrol administration

No of group	Treatment	LH, IU/l	T, nmol/l
1.	Control	4,30 ± 0,71	6,40 ± 1,20
2.	Castration	13,40 ± 2,20	0,67 ± 0,07
	p _{1,2}	< 0,01	< 0,001
3.	Flutamide, 10 mg/kg	12,60 ± 1,09	19,70 ± 4,50
	p _{1,3}	< 0,001	< 0,001
4.	Fosfestrol, 2 mg/kg	4,60 ± 1,09	1,38 ± 0,39
	p _{1,4}	> 0,5	< 0,01
	p _{2,4}	< 0,01	> 0,05
5.	Flutamide, 10 mg/kg + fosfestrol, 2 mg/kg	1,90 ± 0,93	0,66 ± 0,05
	p _{1,5}	> 0,05	< 0,001
	p _{3,5}	< 0,001	< 0,001
	p _{4,5}	> 0,05	> 0,05
6.	Fosfestrol, 10 mg/kg	1,56 ± 0,30	1,01 ± 0,13
	p _{1,6}	< 0,01	< 0,001
	p _{2,6}	< 0,001	< 0,05
	p _{4,6}	< 0,05	> 0,5
7.	Flutamide, 10 mg/kg + fosfestrol, 10 mg/kg	2,64 ± 0,93	0,95 ± 0,22
	p _{1,7}	> 0,05	< 0,001
	p _{3,7}	< 0,001	< 0,001
	p _{5,7}	> 0,5	> 0,05
	p _{6,7}	> 0,5	> 0,5

Means ± S.E. for each group of 6-7 rats

Judging by SDH activity in the testes (Table 3.17) it is inhibition of androgen biosynthesis that causes a dramatic decrease of blood testosterone level when fosfestrol is administered irrespective of the applied dose and the regime of use (either separately or in combination with flutamide). The extent to which the enzyme activity decreased as calculated per 1 mg protein did not increase with an elevation of fosfestrol dose from

2 to 10 mg/kg though under combined administration total SDH activity in the testes decreased more considerably under a 10 mg dose.

Table 3.17. Testicular SDH activity in rats that were given flutamide and fosfestrol for 10 days

No of group	T treatment	SDH activity		
		per the testis	per 1 g tissue	per 1 mg protein
1.	Control	359 ± 23	239 ± 11	18,3 ± 2,0
2.	Fosfestrol, 2 mg/kg	220 ± 19	191 ± 7	18,1 ± 1,6
	p _{1,2}	<0,01	<0,01	>0,05
3.	Flutamide, 10 mg/kg + fosfestrol, 2 mg/kg	195 ± 6	183 ± 3	12,1 ± 0,9
	p _{1,3}	< 0,001	<0,01	<0,02
	p _{2,3}	>0,05	>0,05	<0,02
4.	Fosfestrol, 10 mg/kg	200 ± 7	163 ± 8	15,8 ± 2,5
	p _{1,4}	< 0,001	< 0,001	>0,05
	p _{2,4}	>0,05	< 0,05	>0,05
5.	Niftolide, 10 mg/kg + fosfestrol, 10 mg/kg	137 ± 17	144 ± 13	11,6 ± 0,8
	p _{1,5}	< 0,001	< 0,001	<0,02
	p _{3,5}	<0,02	<0,02	>0,05
	p _{4,5}	<0,01	>0,05	> 0,05

Means + S.E. for each groups of 5 rats

Androgen deprivation is reflected by inhibition of spermatogenesis in the testes, one of its parameters being changes in the number of spermatozoa in the epididymis. While following dosed epididymal perfusion the number of gametes in control males was 79.6 ± 3.2 mln/ml, then after 10-day flutamide administration in a dose of 10 mg/kg it was 43.6 ± 5.6 mln/ml, and following fosfestrol administration in doses of 2 and 10 mg/kg - 32.0 ± 6.9 and 21.4 ± 5.4 mln/ml, respectively. Combined drug administration decreased the number of spermatozoa 16-20 times as compared to the control, to 4.9 ± 0.5 and 3.9 ± 0.6 mln/ml for respective fosfestrol doses of 2 and 10 mg/kg. Thus, in this study the effect of pharmacological potentiation was maximum.

As a result of combined use of flutamide and fosfestrol formation of 5 α -reduced testosterone metabolites in the prostate slowed down (Table 3.18). However, these changes were moderate in contrast to what we

observed under combination of flutamide and hexestrol. Taken together, the results of the study showed that a combination of flutamide with a minidose of fosfestrol was able to induce a considerable atrophy of the prostate, mainly of its epithelial elements.

Table 3.18. DHT and 3 α -androstanediol formation in the ventral prostate in rats 10 days after castration and following administration of flutamide and fosfestrol, pmol/h per 1 g tissue

No of group	Treatment	n	DHT	3 α -Androstanediol
1.	Control	9	310 \pm 24	236 \pm 14
2.	Castration	7	130 \pm 28	136 \pm 29
	p _{1,2}		< 0,001	<0,01
3.	Flutamide, 10 mg/kg	5	235 \pm 24	362 \pm 28
	p _{1,3}		< 0,05	<0,01
4.	Fosfestrol, 2 mg/kg	5	238 \pm 9	283 \pm 16
	p _{1,4}		< 0,05	> 0,5
	P _{3,4}		> 0,5	<0,05
5.	Flutamide, 10 mg/kg + fosfestrol, 2 mg/kg	5	247 \pm 15	190 \pm 6
	p _{1,5}		< 0,05	<0,05
	p _{3,5}		> 0,5	< 0,001
	p _{4,5}		> 0,5	< 0,001
6.	Fosfestrol, 10 mg/kg	4	259 \pm 11	219 \pm 15
	p _{1,6}		> 0,05	> 0,5
	p _{4,6}		> 0,5	< 0,05
7.	Flutamide, 10 mg/kg + fosfestrol, 10 mg/kg	5	233 \pm 19	253 \pm 22
	p _{1,7}		< 0,05	> 0,5
	p _{3,7}		> 0,5	< 0,05
	p _{5,7}		> 0,5	< 0,05
	p _{6,7}		> 0,5	> 0,5

As our study showed supplementation of this pharmacological combination with a microdose of hexestrol (2 mg/kg) did not potentiate antiprostatic effect considerably. Significant changes were found only in fructose content in the prostatic tissues. There was no additional decrease in the weight of the organ and DNA content. This is but natural since under such a combination (an androgen and two estrogens) no further decrease of testosterone level in blood plasma was observed. Consequently, a combination of flutamide with a small dose of hexestrol or fosfestrol is sufficient for effective androgen deprivation.

3.5. Flutamide and chlorotrianisene

Taking into consideration that injection forms of estrogenic drugs (Synestrol and Honvan) are inconvenient for prolonged use by PC patients further studies were aimed at elucidating antiprostatic effect of flutamide combination with chlorotrianisene (Reznikov et al., 1999a). Its convenience (tablets for oral administration), low toxicity and other advantages make chlorotrianisene a potential drug of choice for LEAT. As in experiments described above flutamide was administered in a dose of 10 mg/kg b.w. for 10 days. Chlorotrianisene was also administered through a gastric tube in the form of suspension in a dose of 0.2 mg/kg b.w. which is close to a minimal daily dose applied for human PC treatment.

A decrease of the ventral prostate size under the effect of flutamide or chlorotrianisene did not reach statistically significant values, the weight of the coagulating gland and seminal vesicles demonstrated a mild decrease. A considerable reduction of androgen-dependent organs was achieved by a combined administration of drugs: the ventral prostate weight decreased by 66 %, that of the coagulating gland by 59 %, seminal vesicles by 42 % (Table 3.19)

Table 3.19. Weight of the rat reproductive organs 10 days after administration of flutamide and chlorotrianisene, mg/100 g b.w.

No of group	Experimental conditions	Ventral prostate	Coagulating gland	Seminal vesicles	Testes	Epididymis
1.	Control	139 ± 21	63 ± 4	113 ± 8	1044 ± 86	352 ± 7
2.	Flutamide, 10 mg/kg	100 ± 16	41 ± 2	89 ± 7	1215 ± 44	318 ± 12
	p _{1,2}	>0,05	<0,01	<0,05	>0,05	<0,05
3.	Chlorotrianisene, 0,2 mg/kg	112 ± 10	50 ± 3	92 ± 3	1286 ± 29	372 ± 11
	p _{1,3}	>0,05	<0,05	<0,05	<0,05	>0,05
4.	Flutamide, 10 mg/kg + chlorotrianisene, 0,2 mg/kg	47 ± 5	26 ± 2	65 ± 2	1165 ± 61	240 ± 16
	p _{1,4}	<0,001	<0,001	<0,001	>0,05	<0,001
	p _{2,4}	<0,05	<0,001	<0,05	>0,5	<0,01
	p _{3,4}	<0,001	<0,001	<0,001	>0,05	<0,001

Means ± S.E. for each group of 5-7 rats.

Table 3.20. Effect of flutamide and chlorotrianisene administered for 10 days on protein, nucleic acid contents and cell number in the rat ventral prostate

No of group	Treatment	DNA		RNA		RNA/DNA	Protein		Cell number, $\times 10^7$
		mg/mg tissue	mg/organ	mg/mg tissue	mg/organ		mg/mg tissue	mg/organ	
1.	Control	2,6 \pm 0,1	839 \pm 74	1,6 \pm 0,03	521 \pm 70	0,61 \pm 0,04	54,5 \pm 2,6	18,1 \pm 2,2	9,6 \pm 0,8
2.	Flutamide, 10 mg/kg p _{1,2}	3,0 \pm 0,2 > 0,05	771 \pm 169 > 0,5	1,5 \pm 0,07 > 0,5	358 \pm 59 > 0,05	0,49 \pm 0,03 > 0,05	57,9 \pm 2,2 > 0,05	13,8 \pm 2,0 > 0,05	8,9 \pm 1,9 > 0,05
3.	Chlorotrianisene, 0,2 mg/kg p _{1,3}	3,0 \pm 0,2 > 0,05	795 \pm 74 > 0,5	1,2 \pm 0,08 < 0,01	322 \pm 34 < 0,01	0,40 \pm 0,02 < 0,01	53,8 \pm 1,9 > 0,05	14,3 \pm 1,3 > 0,05	9,1 \pm 0,9 > 0,5
4.	Flutamide, 10 mg/kg + chlorotrianisene, 0,2 mg/kg p _{1,4} p _{2,4} p _{3,4}	4,8 \pm 0,2 < 0,001 < 0,001 < 0,001	506 \pm 45 < 0,01 > 0,05 < 0,01	1,0 \pm 0,09 < 0,001 < 0,01 > 0,05	111 \pm 20 < 0,001 < 0,01 < 0,001	0,21 \pm 0,02 < 0,001 < 0,001 < 0,001	60,0 \pm 2,0 > 0,05 > 0,05 > 0,05	6,4 \pm 0,6 < 0,001 < 0,05 < 0,01	5,8 \pm 0,5 < 0,01 > 0,05 < 0,01

Means \pm S.E. for each group of 5-7 rats.

As to total protein, DNA and RNA contents and cell number in the ventral prostate the effect of potentiating of flutamide antiandrogenic action is as impressive (Table 3.20). A 1.8-fold increase of DNA content in the prostate (as compared to the control) is caused by a loss of liquid component of the cytoplasm in the epithelial cells, this is confirmed by histological studies.

In 60 % of animals that were given flutamide in combination with chlorotrianisene the size of the prostatic secretory glands decreased considerably. The height of the epithelial cells decreased, the cells were often arranged in two layers (Fig. 3.2). In other rats atrophic changes were less pronounced.

Fructose concentration in the coagulating gland tissues, which reflects its secretory activity, decreased 2.0 and 1.5 times as compared to the control when, respectively, flutamide and chlorotrianisene were used separately. Under combined drug administration the carbohydrate concentration decreased 7.0 times and its total content 2.6 times (Table 3.21).

Table 3.21. Fructose content in the rat coagulating gland 10 days after flutamide and chlorotrianisene administration

No of group	Treatment	Fructose	
		μmol/100 g tissue	μmol/organ
1.	Control	1,53 ± 0,11	0,98 ± 0,04
2.	Flutamide, 10 mg/kg p _{1,2}	0,75 ± 0,11 < 0,01	0,77 ± 0,11 > 0,05
3.	Chlorotrianisene, 10 mg/kg p _{1,3}	1,01 ± 0,10 < 0,05	0,84 ± 0,04 < 0,05
4.	Flutamide, 10 mg/kg + chlorotrianisene, 0.2 mg/kg p _{1,4} p _{2,4} p _{3,4}	0,22 ± 0,04 < 0,001 < 0,01 < 0,001	0,38 ± 0,06 < 0,001 < 0,01 < 0,001

Means ± S.E. for each group of 5-7 rats

Antigonadotropic effect of chlorotrianisene is less pronounced than that of diethylstilboestrol, hexestrol and fosfestrol. Under a combined administration in a dose studied it effectively prevented flutamide-induced rise of LH and testosterone levels in the rat blood plasma. It is in line with less pronounced than in other estrogen-antiandrogen combinations suppressive effect of chlorotrianisene on testicular

spermatogenic function - a decrease of the spermatozoa number in the epididymis by 46 % as compared to the control. Bearing it in mind pronounced atrophic changes in the prostate should be considered as a result of not only antigonadotropic activity of chlorotrianisene but also of its direct effect on the prostatic tissues.

Irrespective of mechanisms prevailing in chlorotrianisene potentiation of flutamide antiandrogenic effect on the prostate this effect is sufficient to regard clinical study of this combination in PC reasonable.

Table 3.22. Blood plasma bioactive LH and testosterone contents in male rats in the norm and 10 days after castration or Niftolide and chlorotrianisene administration

No of group	Treatment	LH, IU/l	T, nmol/l
1.	Control	6,10 ± 0,60	3,40 ± 0,77
2.	Flutamide, 10 mg/kg p _{1,2}	9,45 ± 0,77 < 0,01	8,8 ± 3,10 > 0,05
3.	Chlorotrianisene, 0,2 mg/kg p _{1,3}	3,42 ± 0,22 < 0,01	1,20 ± 0,07 < 0,05
4.	Flutamide, 10 mg/kg + chlorotrianisene, 0.2 mg/kg p _{1,4} p _{2,4} p _{3,4}	6,98 ± 0,74 > 0,5 < 0,05 < 0,01	6,90 ± 2,20 < 0,05 > 0,5 < 0,05

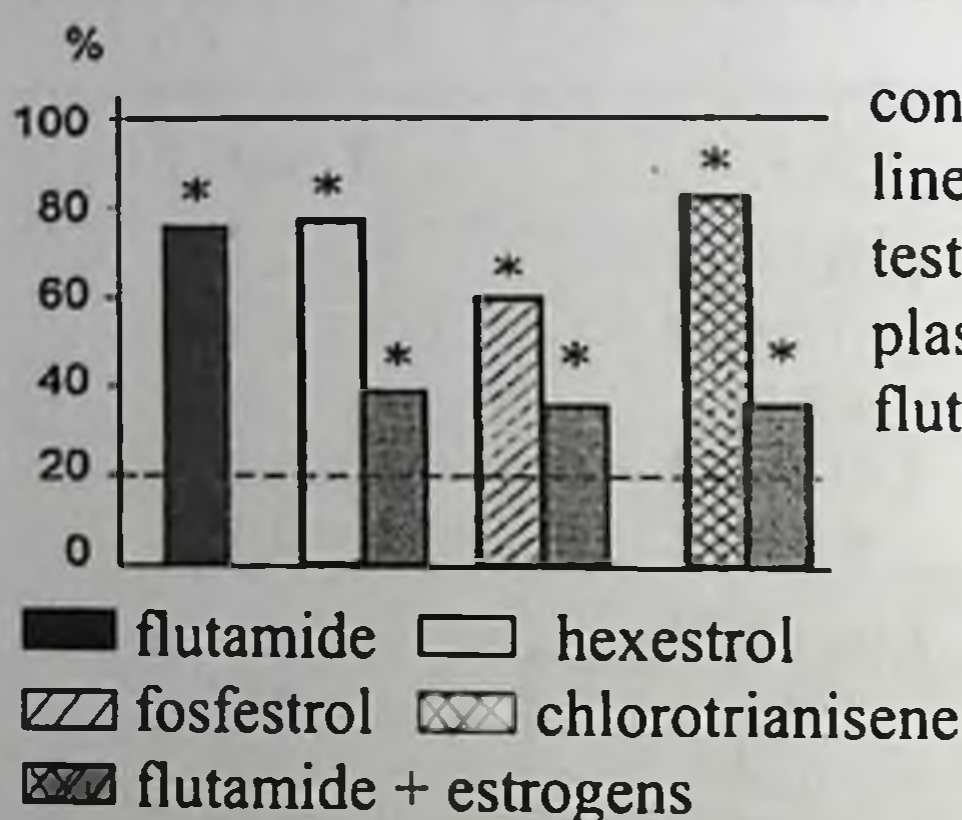
Means +S.E. for each group of 6-10 rats.

3.6. A comparative evaluation of antiprostatic flutamide activity in combination with estrogenic drugs

In order to compare antiprostatic activity of various combinations of flutamide with estrogenic drugs in minimal doses studied we have analyzed the percentage which characterizes changes in the main parameters as compared to the norm.

Despite the fact that hexestrol (2 µg/kg), fosfestrol (2 mg/kg) and chlorotrianisene (0.2 mg/kg) when used separately produced a moderate and different in its intensity effect on the prostatic weight of male rats (mean deviations from the normal values within 20-40 %), the results of their combined administration with flutamide were impressive and rather uniform, the prostate weight decreased, on average, by 62-67 % (Fig. 3.7).

As to such an important criterion of the ventral prostate atrophy as total DNA content, the effect of hexestrol, fosfestrol and their combinations with flutamide was uniform and combined drug administration brought DNA content to postcastration values (Fig. 3.8). A combination of flutamide with chlorotrianisene is effective enough (a more than 40 % decrease of DNA content) but still it yields to the former estrogens. Similarity of values, which characterize a decrease in prostate weight, is explained, apparently, by a more pronounced inhibition of its secretory activity resulted from direct effect of chlorotrianisene on tissues of the organ.



Various effects of drugs on DNA content in the ventral prostate are in line with their effects on LH and testosterone concentrations in blood plasma (Fig. 3.9). A combined use of flutamide with

Fig. 3.7. A comparative evaluation of the effect of minidoses of estrogenic drugs and their combinations with flutamide on the ventral prostate weight in rats.

Solid line, control; dotted line, castration.

* see Fig. 3.3

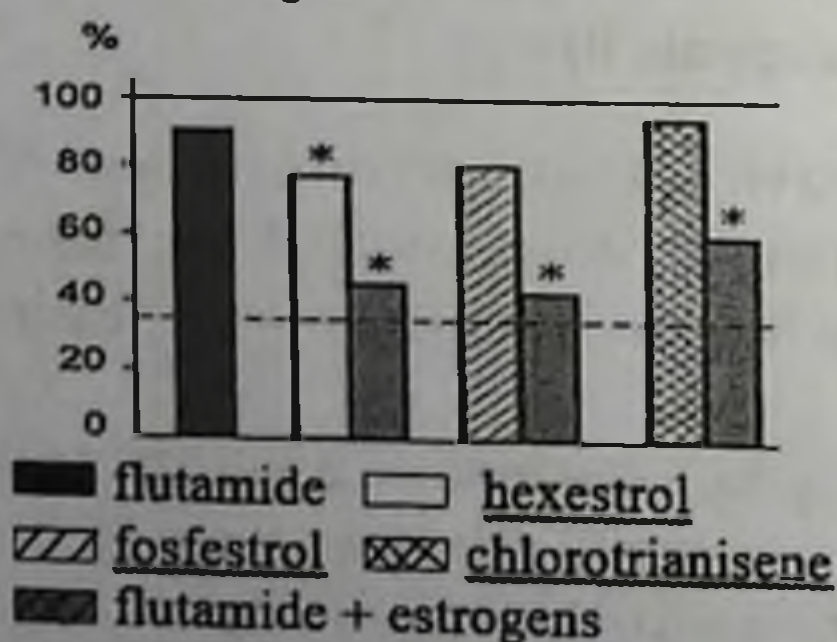


Fig. 3.8.

A comparative evaluation of the effect of minidoses of estrogenic drugs and their combinations with flutamide on DNA content in the rat ventral prostate: Solid line, control; dotted line, castration.

* see Fig. 3.3

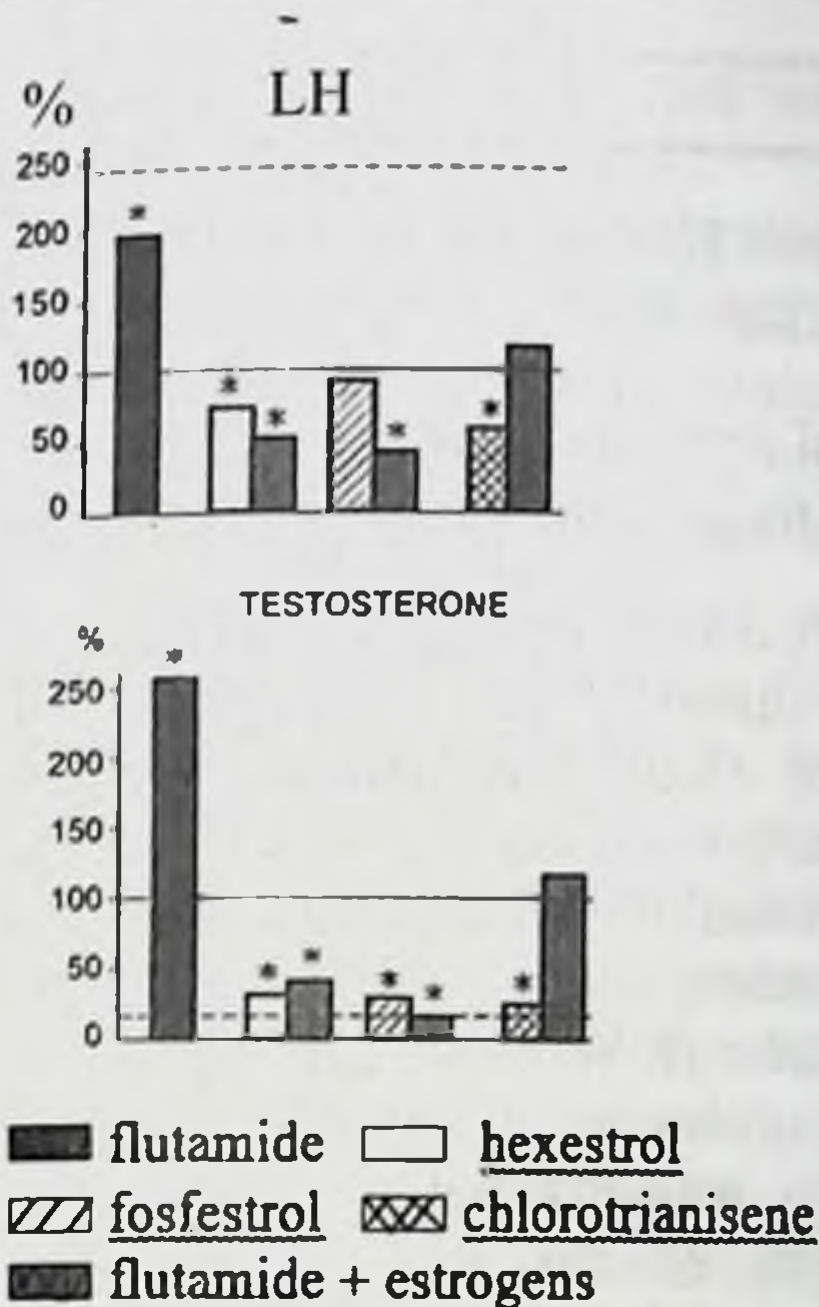


FIG. 3.9.

A comparative evaluation of the effect of minidoses of estrogenic drugs and their combinations with flutamide on LH and testosterone levels in the rat blood plasma: Solid line, control; dotted line, castration.

* see Fig. 3.3

low doses of hexestrol and fosfestrol not only prevented flutamide-induced rise of LH and testosterone levels in blood plasma in rats but also induced their dramatic decrease. When fosfestrol was administered in combination with antiandrogen, the effectiveness was higher especially regarding testosterone level. As to chlorotrianisene, in combination with flutamide it completely prevented flutamide-induced increase of blood LH and testosterone levels bringing them to normal values. However, this combination yielded to the previous ones in its effect on hormone concentrations. It is not surprising that its effect on DNA content in prostatic tissues was less pronounced. Nevertheless, inclusion of chlorotrianisene in the LEAT protocol may prove useful especially in case of resistance to other estrogenic preparations. Of course, only wide-scale clinical trials will make things clear.

ENDOCRINE MONOTHERAPY OF PROSTATE CANCER

4.1. Classification of prostate cancer and general principles of its palliative treatment

Prostate cancer is often found in aged and old men. Among oncologic diseases in human males it occupies the 2nd-3rd place demonstrating a stable tendency to incidence growth during the last decade. The disease is considered to be severe with a trend to early metastatic spreading and considerable changes in the upper urinary tract (S.Vozianov, 1994).

An interest to PC by urologists and oncologists grew after certain progress in hormonal therapy of this disease in the forties of the XX century. First publications on hormonal therapy of PC by Huggins, Hodges (1941), Huggins (1946) and others facilitated its deep study by urologists, roentgenologists, endocrinologists, pathological anatomists, biochemists.

PC became the first oncologic disease that was rather effectively treated conservatively. Since 1945 hormonal therapy of PC has been applied not only abroad but in the former Soviet countries as well (Topchan, Pomerantsev, 1947; 1949; Fronstein, Shapiro, 1952; Rozhdestvensky, 1954).

Many years of investigations showed that despite a considerable progress in developing new active estrogenic drugs and synthesis of new classes of drugs with essentially different mechanisms of antiprostatic antitumorous effect (LHRH analogues, steroid and non-steroid antiandrogens), development of new and improvement of the existing methods of hormonal therapy of PC, this method remains palliative with its disadvantages; for many patients it was found to be ineffective. Enthusiasm about

hormonal therapy alternated with great interest to radical surgery (Könyves, Andersson, 1984).

During last 10-15 years surgical treatment was widely used, after new modern diagnostic methods appeared and early diagnosis improved considerably. This was facilitated by new surgical instruments, latest achievements in anesthesiology and, which should be emphasized, use of hormonal drugs for neoadjuvant and adjuvant therapy.

However, the percentage of diagnosed PC at T1-2 stage, when radical therapy is possible, is within 5-15% (Portnoy, 1989; Bukharkin et al., 1994) that is why hormonal therapy remains the treatment of choice. At the same time it has been established that following the first course of successful endocrine therapy (castration, estrogen therapy) 12-18 months later the relapse occurs, and mean one-year survival makes 50%. Hence, patients need additional further treatment (second course), which includes other methods of hormonal, radiation, chemotherapy and their combinations (Fournier, 1996).

At present, one of tendencies in PC management consists in a follow-up after diagnosing local changes in the prostate when there are no clinical manifestations. According to some authors (Könyves, Andersson, 1984; Sogani, Fair, 1987; Johansson et al., 1992) the temporizing strategy with a follow-up is justified: the treatment (orchiectomy or estrogen therapy) begins only after pain symptoms appear. According to other authors, the treatment should start immediately after the disease has been diagnosed (Maier, Neuhold, 1988).

In this respect a retrospective study of PC patients with D1 stage of PC conducted by Kramolowsky (1988) is demonstrative. Following surgical (orchiectomy) or hormonal androgen blockade performed immediately after diagnosis, bone metastases appeared 100 months later, in non-treated patients or those treated with a delay - 43 months later ($p = 0.0087$). Life span between diagnosis and patients' death was 50 and 10 months ($p = 0.1110$), respectively.

An advantage of temporizing tactics is the possibility to avoid side effects and complications resulted from therapy, a disadvantage lies in the fact that the earlier treatment begins the higher survival is. So far this issue remains unclear. However, many experts keep to the opinion that delayed treatment is possible, but with caution and under strict control, in old patients with asymptomatic course, in case of coexistent diseases, in patients with initial stages of highly differentiated carcinoma (Kirk, 1995)

The following methods of hormonal therapy of inoperable PC may be distinguished:

- orchiectomy;
- estrogen therapy
- treatment with androgens (steroid and non-steroid);
- treatment with LHRH agonists;
- combined androgen blockade.

An overview of literature and our own experience show that among PC treatment methods which produce subjective, objective and social effects, individual combined stage-by-stage approach seems reasonable and effective. It gives adequate results and depends on the stage of tumor growth, patient's general state, histological type of the tumor and its response to different kinds of treatment (Sevastianov et al., 1996; Haapiainen et al., 1986; Merrill, 1988). It has been established that orchiectomy is indicated in differentiated adenocarcinoma and it should be preferred because of complications caused by hormonal therapy, however, this is not the case for patients with low-differentiated tumor and bone metastases because of worse prognosis. In such patients orchiectomy should be supplemented with other treatment modalities, the scheme and tactics of treatment should be revised.

Taking it into account, before reviewing different methods of PC treatment, which, as a rule, take into consideration type of the tumor, its spreading, malignancy rate etc. we believe it is reasonable to present an international TNM clinical classification of PC (1997).

TNM clinical classification

T - primary tumor

T_x - data is not sufficient for assessment of primary tumor.

T_o - primary tumor is not detected.

T_1 - clinically asymptomatic tumor, not palpable and not visualized instrumentally.

T_{1a} - incidental finding at histological study, the tumor makes up to 5 % of the resected tissue.

T_{1b} - incidental finding at histological study, the tumor makes up more than 5 % of the resected tissue.

T_{1c} - tumor found at puncture biopsy (e.g. because of increased PSA level).

T_2 - tumor is within the prostate.

T_{2a} - tumor extends to one lobe.

T_{2b} - tumor extends to both lobes.

T_3 - tumor extending beyond the capsule.

T_{3a} - extracapsular spreading (unilateral or bilateral).

T_{3b} - tumor involves seminal vesicles.

T_4 - fixed tumor or infiltrating neighbouring tissues but not seminal vesicles (neck of the urinary bladder, external sphincter, rectum, *m. levator ani* and/or pelvic wall).

Note.

1. Tumor detected in one or both lobes at puncture biopsy, but not palpable and not visualized, is classified as T_{1b} .

2. Invasion to the apex of the prostate or its capsule (but not beyond it) is classified as T_2 but not T_3 .

N - regional lymph nodes

N_x - data is not sufficient for assessing regional lymph nodes.

N_0 - no evidence of regional lymph node involvement.

N_1 - regional lymph node metastases.

M - distant metastases

M_x - data is not sufficient for detecting distant metastases.

M_0 - distant metastases are not detectable.

M_1 - distant metastases present.

M_{1a} - non-regional lymph node(s).

M_{1b} - bone(s).

M_{1c} - other structure(s).

pTNM - pathomorphologic classification

pT, pN and pM categories correspond to T, N and M categories.

G - histopathologic staging

G_x - differentiation cannot be assessed.

G_1 - highly differentiated tumor.

G_2 - moderate differentiation.

G - low differentiated/undifferentiated tumor.

Classification by Jewett (1975) is still widely used, especially in the USA.

A, B, C and D stages are distinguished.

Stage *A* - malignant tumor detected at histological study of tissue samples obtained at surgery for benign prostate hyperplasia or puncture biopsy.

$A_1 (T_{1a}N_0M_0)$ - tumor occupies less than 5 % of resected prostatic tissue or up to five microscopic tumor foci.

$A_2 (T_{1b}N_0M_0)$ - tumor occupies more than 5 % of resected prostatic tissue or more than five microscopic tumor foci.

Stage *B* - a nodule or induration detected palpably and limited by the capsule.

$B_1 (T_{2a}N_0M_0)$ - nodule of no more than 2 cm surrounded by unchanged tissue.

$B_2 (T_{2b}N_0M_0)$ - nodule within the capsule, more than 2 cm or two separate nodules even if their total size does not exceed 2 cm.

Stage *C* - carcinoma without evidence of metastases but spreading beyond the prostatic capsule.

$C_1 (T_3N_0M_0)$ - minimal spreading through the capsule felt by digital palpation.

$C_2 (T_4N_0M_0)$ - large tumor (more than 5 cm) spreading to adjacent organs.

Stage *D* - metastatic tumors irrespective of local spreading.

D_0 - metastases are detected by increased PSA and acid phosphatase in blood serum.

$D_1 (T_{0-4}N_{1-3}M_0)$ - tumor with pelvic lymph node metastases.

$D_2 (T_{0-4}N_{0-3}M_1)$ - tumor with metastases beyond pelvic lymph nodes.

Staging

Stage I	$T_{1a}N_0M_0G_1$	(A)
Stage II	$T_{1a}N_0M_0G_{2,3-4}, T_{1b}N_0M_0G_{x-4}, T_{1c}N_0M_0G_{x-4}, T_1N_0M_0G_{x-4}, T_2N_0M_0G_{x-4}$	(B)
Stage III	$T_3N_0M_0G_{x-4}$	(C)
Stage IV	$T_4N_0M_0G_{x-4}, T_{x-4}N_1M_0G_{x-4}, T_{x-4}N_1M_1G_{x-4}$	(D)

4.2. Castration

Bilateral orchiectomy is widely used all over the world as a simple and effective method of androgen ablation. Till now orchiectomy is considered as a «golden standard» of PC hormonal therapy (Cassileth et al., 1989; Fossa et al., 1994). A beneficial effect of castration is explained by direct elimination of a main source of androgens that produces more than a half of them. Early it was thought that the testes produce 95 % of total androgens (Nabors, Crawford, 1990), which was supported by a simple measurement of blood plasma testosterone level after castration. Recent studies showed that the testes and adrenals secrete 60 % and 40 % of total androgens in an adult male, respectively (F. Labrie, 1998). Orchiectomy gives an immediate therapeutic effect and alleviation of symptoms in 60-80 % patients with progressive PC (Iversen et al., 1989; Nabors, Crawford, 1990): the number of voidings reduces, urinary flow becomes improved, alleviation of pains induced by bone metastases, if there are any, is observed; within 4-6 weeks the size of the prostate diminishes. In experiments it was established that early castration slows down tumor growth and promotes survival (Grossman, 1986).

This approach seems effective in acute or chronic ischuria resulting from tumor compression of the prostatic part of the urethra. The experience shows that orchiectomy is the method of choice in dangerous compression of the spinal cord and bilateral hydronephrosis, grave and life-threatening complications (Korman, 1989). Orchiectomy is recommended to patients with cardiovascular diseases and also to persons who follow strictly the prescriptions on taking drugs.

Surgical castration is rather simple, reliable, as to therapeutic respect, procedure, which may be performed under local anesthesia with minimal surgical trauma even in the out-patient clinic. It is proved by many years of practice and a comparative analysis of results obtained with various methods of PC endocrine treatment. Despite the fact that nowadays there are new hormonal drugs, none of them gave a result that significantly surpassed the effect of bilateral castration. They differ only in side effects (Trachtenberg, 1987; Bollack, Rougeron, 1988).

The surgery consists in a complete removal of testes (together with *tunica albuginea testis*) and epididymis (bilateral orchiepididymectomy) or in the removal of testicular tissue without *tunica albuginea testis* and epididymis. Bilateral orchiepididymectomy is performed in the following

way: longitudinal incision is made at each side at the base of the scrotum, the skin and the testicular tunics are dissected. The testis with the epididymis and a part of the spermatic cord are isolated. The spermatic cord is clipped and crossed. The proximal part of the crossed spermatic cord is ligated. The testis and the seminal cord are dissected. A thorough hemostasis is carried out. A rubber strip is inserted into the wound for 1-2 days, if necessary. The testicular tunics and scrotal skin are sutured (Marinbach, 1980). However, often patients do not agree to undergo this procedure (Fossa et al., 1994). According to Merrill (1988), who prefers surgical castration, orchiectomy is indicated to 20-30 % of patients; but some of them refuse the surgery. The reason for it is stressful psychogenic effect of operation, irreversible loss of libido and erection, impotence, hot flushes. Sudden hot flushes following orchiectomy are observed in 70 % of patients, 30 % out of them associate these hot flushes with operation. These manifestations begin 1-12 months after orchiectomy and last for years, often till death (Charing, Rundle, 1989). It was shown that it is related to a decreased level of testicular androgens and even a slight increase of blood testosterone level prevents hot flushes.

In order to spare patient's psychics, A. Tsulukidze (1955) proposed to perform funiculotomy, crossing seminal cords on the level of the superficial inguinal ring, instead of orchiectomy. As I. Isashvili (1958) concluded, the effect of this procedure was similar to that of orchiectomy, it means that orchiectomy may be easily substituted with funiculotomy. We support E. Marinbach (1980) in his view that funiculotomy may be performed only in case of patient's flat refusal from orchiectomy.

More justified and less traumatic for patient's psychics is subcapsular orchiectomy (testicular enucleation or testicular pulpectomy). It differs from orchiepididymectomy in the following: after the testis is exposed *tunica albuginea testis* is dissected, testicular tissue (pulp) is removed, the grafts of *tunica albuginea testis* are clipped and under clips they are sewn with strong catgut ligatures. The grafts of *tunica albuginea testis* are dissected. The epididymis with the remnants of *tunica albuginea* is covered with testicular tunics that are sewn with purse-string suture.

In urological clinic of Samarkand State Medical University testicular enucleation is performed using incision of the scrotal skin along it's median line – Wesling's line (Fig. 4.1.). Suturing the skin of the scrotum after surgical access through scrotal median line leaves an almost

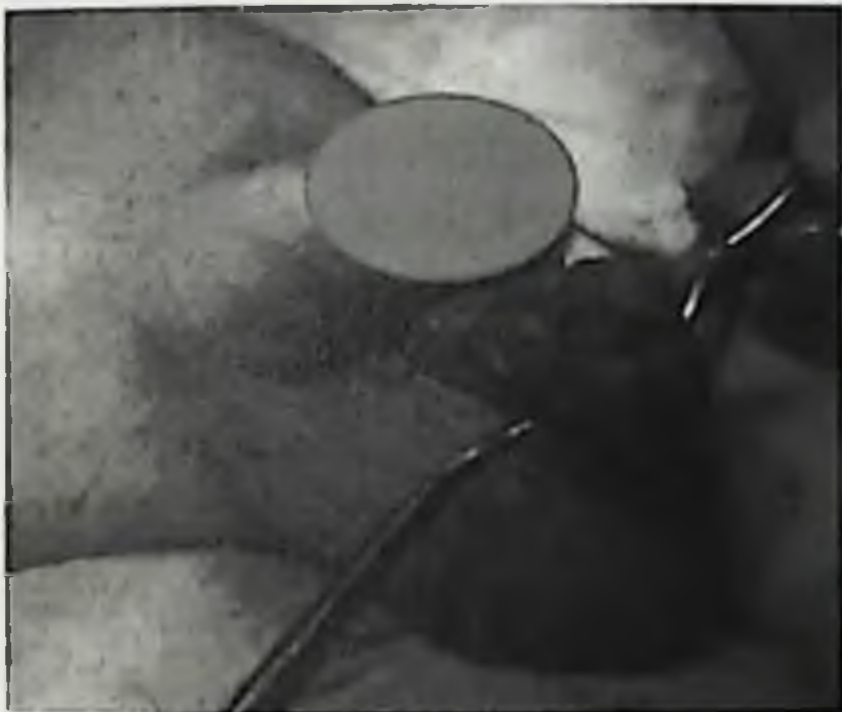
imperceptible postoperative scar resembling a Wesling's line (Allazov S.A. et al., 2018,2019).



1 – median line of the scrotum - Wesling's line



2 – incision of scrotal skin along the Wesling's line



3 – removing of testicular tissue on the left (testicular pulpectomy)



4 – stitches on the scrotal skin along the Wesling's line after bilateral pulpectomy

Fig. 4.1. Stages of testicular pulpectomy

In both cases we recommend that after sewing and ligation of the spermatic cord or remnants of *tunica albuginea* catgut ligature is used for consecutive sewing of testicular tunics and fixation of the cord or epididymal stump to the edges of the skin wound. It will make a psychological effect of the presence of diminished testis and shortens the wound size, this being important in case of infected wound and its secondary adhesion.

It should be mentioned that 45 % of urologists believe that this operation is less effective than orchiepididymectomy (Merrill, 1988). McDonald and Calams showed that after treatment with estrogens in the remaining tunica albuginea and in the epididymis extraparenchymal androgen-producing Leydig cells may be found (ref. Sorrentino, Romano, 1963). However, judging by a decrease in blood testosterone level, which is an important indicator of effective hormonal treatment, subcapsular orchiectomy is as effective as total orchiectomy. This operation may be supplemented with curettage of tunica albuginea, and a cosmetic defect may be improved by prosthetics.

Postcastration syndrome is the most severe side effect of orchiectomy in 70 % of patients (Klein, 1995). Postcastration changes cannot be identified with climacterium, when shifts in neurohumoral function develop gradually. A sudden elimination of gonadal hormones in castration effects the central and autonomous nervous systems, visceral organs, results in metabolic disorders and disturbances in hormone production and release. From the clinical point of view it is important that postcastration syndrome may be alleviated by preoperative administration of Androcur, steroid antiandrogen, or low doses of estrogens (Bruchovsky et al., 1993; Varenhorst, 1993).

Still the issue on advisability of the operation in general and on its necessity at early stages or in advanced (stages III - IV) PC cases is debatable. According to some authors, castration is justified at early stages of PC. Tkachuk et al. (1974) showed that in patients with early (I - II) stages in their native functioning testicular tissue androgen-producing Leydig cells prevail. In patients with advanced disease these cells are atrophic, they demonstrate inhibited androgen function, that is why the surgery seems meaningless. According to other authors (Atwein, Faul, 1990), endocrine therapy should always include orchiectomy in case of metastases. When choosing the optimal treatment for patients with advanced PC and pain syndrome, taking into account the results of hormonal therapy, mortality rate, complications and their severity after estrogen therapy as well as economic advantages, orchiectomy in combination with symptomatic treatment should be preferred as compared to orchiectomy in combination with estrogen therapy and symptomatic treatment (Zhukov, Buko, 1996). It is known that in Finland and Norway they prefer orchiectomy because of high rate of cardiovascular complications following estrogen therapy of PC (Könyves, Andersson, 1984).

Long-term follow-up of more than 1000 patients in the Department of Oncurology at the Institute of Urology and Nephrology, Academy of Medical Sciences of Ukraine, showed that during first days following early castration a subjective improvement is observed, disuric manifestations diminish, urination becomes easier, urinary flow better and micturate urges become less frequent. However, though palliative surgical treatment, bilateral orchiectomy, gives good clinical effect, elimination of testicular function because of orchiectomy does not result in a complete androgen blockade and is not sufficient for successful PC therapy. It is explained by the fact that after castration and elimination of testicular inhibitory effect, pituitary corticotropic function is intensified and there is an increase in the amount of adrenal-produced androgens. The results of long-term study of total androgen contents following castration showed that after the initial decrease there is a gradual, over 4-6 months, increase of it (Labrie, 1991). That is why following orchiectomy further treatment with hormonal, antihormonal, radiation and chemotherapeutic agents is required, this is confirmed by numerous clinical (Tkachuk et al., 1974; Micigan, Catalone, 1977; Marinbach, 1980; Khilinsky, Bodtilov, 1996; Sakalo, Klimenko et al., 1998) and morphological studies (Leiseru- kov, 1964).

To illustrate mentioned above let us consider the results of comparative study on therapeutic effects of orchiectomy and non-steroid antiandrogen, flutamide (Niftolide, locally produced flutamide tablets). Niftolide was applied in 84 patients with advanced PC at T₂₋₄N₀₋₁M₀₋₁ stage aged 73±6 years. All of them were newly treated patients with the diagnosis confirmed histologically. According to the WHO international scale the initial state scored 0 - 2. The patients were examined before and 3, 6, 12, 18 and 24 months after orchiectomy or beginning of antiandrogen administration. It included clinical examination, scoring of the general state, blood and urine laboratory tests, testosterone, LH, SHBG, alkaline phosphatase, PSA, X-ray examination of the lungs, ultrasonic examination of the kidneys, prostate and urinary bladder, uroflowmetry, bone X-ray examination or osteoscintigraphy. All patients were randomized into two groups: the first group comprised 40 orchiectomized patients, the second one included 44 patients who were given flutamide (250 mg 3 times a day). The results were evaluated by the progression-free time, PSA level and dynamics of metastatic spreading. An increase in PSA level or new metastases emerged was evaluated as progression of the

disease. In 75 % of orchiectomized patients and in 93 % of those treated with antiandrogen relapse was observed after 15 and 16 months, respectively. Mean progression-free time was the same in both groups, total survival made 65 months irrespective of the treatment. However after orchiectomy loss of libido, impotence, hot flushes were observed while after antiandrogen therapy the patients complained of gynecomasty (rarely) and increased tactile tenderness or painfulness of nipples (more frequently), in some patients gastric pains, diarrhea was observed, and that is why 4 patients (9 %) were excluded from the study.

Thus, neither orchiectomy nor monotherapy with antiandrogens results in complete recovery. In all patients the disease develops with the time. A combined method including orchiectomy and/or other therapeutic agents should be considered optimal (Sakalo et al., 1998).

At present, many authors who study the problem of PC therapy keep to the opinion that indications for castrations are: primary and secondary resistance to estrogens, low level of saturation with estrogens after a complete course of hormonal therapy, estrogen intolerance, low estrogen bioavailability in oral administration, pronounced functional deficiency of the liver, malfunctioning of the cardiovascular system (Matveyev, 1990).

We agree with the data cited but as to advisability and indications for orchiectomy, one more issue, which regards a deontological aspect of this operation, should be taken into consideration. It has been established that 18-20 % of PC patients are primarily tolerant to hormonal treatment, that is why orchiectomy may be prescribed only if hormone responsiveness of the tumor is proved. Otherwise, in every fifth patient this operation will be groundless (Zhavrid, Dosta, 1996). Besides, not only estrogen tolerance and co-existent diseases should be considered but also the possibility to take estrogens regularly as well as make laboratory tests on the adequacy of the hormonal therapy (Urbanovich et al., 1996).

4.3. Estrogens

Estrogen therapy of PC is hormonal therapy based on tight relationship between prostatic tumors and sex hormones. Estrogen therapy as well as orchiectomy has occupied leading positions in palliative treatment of PC for more than 50 years.

1. Antitumorous effect of estrogens in PC is based on:

2. Antigonadotropic effect, i.e. decreased production of pituitary gonadotropic hormones (Fergusson, 1976);

3. Antigonadal effect, i.e. direct inhibition of testosterone production in the testes (Hanch et al, 1978; Moger, 1980);

Possibly, antiprostatic effect, i.e. inhibition of testosterone conversion into a more active derivative, 5α -dihydrotestosterone (Dumitru et al., 1981), though most studies do not confirm this observation.

As shown above, orchiectomy, because of possible side effects (emotional stress psychogenic factor, loss of libido, impotence, hot flushes) and disagreement of many patients to undergo surgery, is often impossible. In such case estrogen therapy, the so-called hormonal castration, may be chosen. In monotherapy, hormonal castration, as well as surgical castration, is not effective enough for successful treatment of PC, since even long-term estrogen administration does not result in complete inhibition of testicular function and does not bring about a complete androgen blockade. And still for 35 % of patients hormonal therapy is more suitable than any other method for a number of reasons, and for 22 % of patients it is effective enough (Merrill, 1988). The advisability of hormonal castration is determined by the fact that administration of female sex hormones (estrogens) and their synthetic analogue, diethylstilboestrol, in a dose of 3 mg/day results in the same testosterone levels in blood plasma, which are observed following orchiectomy (Sogani, Fair, 1987).

Positive response to estrogen therapy is observed in 70-80 % of PC patients (Henriksson et al., 1990; Vacher, 1995; Schmid, 1995). However, even during first 20 years of estrogen use there appeared numerous observations which proved that unfortunately these drugs may induce adverse effects and complications of various gravity that were described in Chapter 2. They include not only increased breast tenderness, gynecomasty, loss of libido, impotence, gastrointestinal disorders but also severe complications such as myocardial infarction, disorders of cerebral circulation, thromboembolism of the pulmonary artery, and in 60-70 % of cases this may result in a fatal outcome (de Voogt et al., 1986; Henriksson et al, 1988; Debruyne, Dijkman, 1995). Lowering of doses does not produce positive effect, and even more, within a year after onset of therapy in 25 % of patients, who previously had no manifestations of atherosclerosis, cardiovascular complications are observed.

When comparing the frequency and type of side effects following DES (1 and 3 mg 3 times a day), Estracyte (560 mg orally for 8 weeks, then 280 mg), cyproterone acetate (250 mg a day, orally) and medroxyprogesterone acetate (500 mg i.m. 3 times a day for 8 weeks, then 200 mg/day orally), it was established that the most frequent complication was water retention, hypertension, ECG disorders, myocardial infarction, thromboembolism were less frequent, the highest risk is observed during first 6 months. As to the frequency of complications, DES occupies the first place followed by estramustin phosphate, medroxyprogesterone acetate and cyproterone acetate. Factors, which promote side effects, are old age, body weight over 75 kg, history of cardiac and vascular diseases (de Voogt et al., 1986; Smith et al., 1986).

Ischemic complications usually develop under oral estrogen administration, this is supposed to be associated with drug metabolism in the liver, where coagulogenic and fibrinolytic proteins are synthesized (Henriksson et al., 1988, 1990; Stege et al., 1989).

The study of fibrinolytic and coagulation systems in PC patients after estrogen therapy showed that following parenteral administration only a considerable diminution of antithrombin III is observed while under oral administration there is a considerable increase of factor VII. Oral use of estrogens is also associated with severe cardiovascular and hepatic side effects, which is not the case with parenteral administration. Oral estrogen diminishes the amount of adrenal dehydroepiandrosterone sulphate in the serum, while in parenteral administration it does not produce any effect on its content. At the same time under oral estrogen administration SHBG level increases, while orchiectomy does not effect its level (Carlström et al., 1989; Henriksson et al., 1990).

Various aspects of hormonal therapy which deal with therapeutic effectiveness of estrogenic drugs, their tolerance, frequency of side effects, survival, comparative evaluation of different treatment schemes etc. have been highlighted in many articles that differ by the results obtained and very often by the author's attitude towards this particular method.

In the Department of Oncourology at the Institute of Urology and Nephrology (Kiev, Ukraine) 50 year experience of treating PC patients with Synestrol (hexestrol) has been accumulated (Vozianov et al., 1990a; Vozianov et al., 1990b). Now we present the results of treating a group of patients (114 persons), who underwent a thorough clinical, laboratory,

histologic, X-ray, ultrasonic, UFM and hormonal examinations before, during and after therapy.

The age of patients ranged 42-79 years (mean age 60.5 years). As to staging, it was as follows: stage I (T₁N₀M₀) - 18 patients (15.8 %), stage II (T₂N₀M₀) - 36 patients (31.6 %), stage III (T₃N₀₋₁M₀) - 54 patients (52.6 %), stage IV (T₃₋₄N₀₋₁M₁) - 6 patients (5.3 %).

Histologic study of biopsies showed adenoma with malignancy in 35 cases (31.6 %), alveolar adenocarcinoma in 27 cases (23.7 %), small-cell adenocarcinoma in 30 cases (26.3 %), dark-cell adenocarcinoma in 9 cases (7.9 %), scirrhous carcinoma in 6 patients (5.3 %), cribriform clear cell carcinoma in 12 patients (10.52 %), undifferentiated carcinoma in 6 cases (5.3 %).

Treatment with Synestrol (3 ml of 2 % oil solution i.m.) lasted for 3 months. The results were assessed according to the WHO recommendations (Garin, Trapeznikov, 1975; Antitumorous chemotherapy, 1986):

complete remission - the tumor is not detected at digital rectal examination or ultrasonic examination, uroflowmetry and self-evaluation showed improved urination and less dysuria;

partial remission - the tumor reduction by 50 % and more;

stabilization - the tumor size fluctuates from - 25% to + 25 %;

progression - increase of tumor size by 25 % and more and new bone metastases.

In order to evaluate «the quality of life», patients' state was also scored according to the same WHO recommendations

0 - full activity, ability to do any work without any limitations;

1 - limited physical activity, ability to do easy work or sedentary work;

2 - out-patient is able to do everything required for himself but unable to do any other work;

3 - a patient needs nursing, in some cases hospitalization is required, able to do less than 50 % of work about the house;

4 - disability.

The results were summarized 1.5 and 3 months after beginning the therapy. General state, results of digital rectal examination, UFM, ultrasonic examination were taken into consideration, hormonal assays were run. In 93 patients (81.6 %) micturate urges become less frequent and urinary outflow becomes easier. In 6 patients (5.3 %) bone pains disappeared.

Following therapy the size of the prostate was reduced (Table 4.1, Fig. 4.2), uroflowmetric parameters improved, there was a two-fold increase in maximum urination rate (Table 4.2, Fig. 4.3), it confirms positive therapeutic effect of Synestrol.

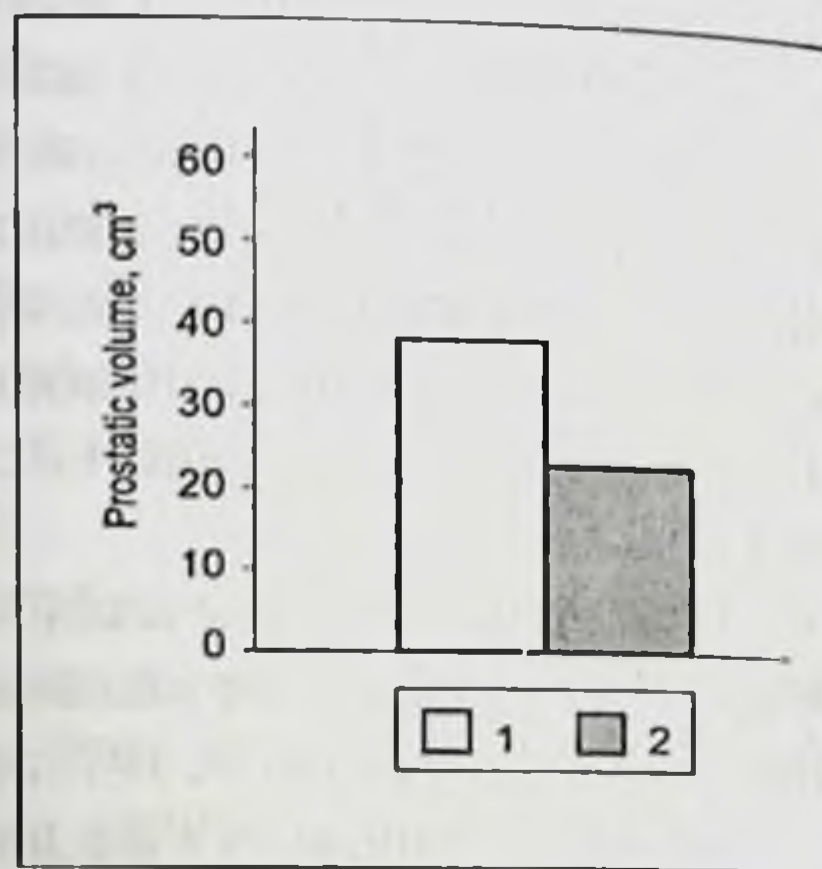


Fig. 4.2. Changes in the prostatic volume in PC patients before and after treatment with Synestrol 1, 2, before and after treatment, respectively

Table 4.1. Changes in the size of the prostate under 3-month treatment with Synestrol

Prostatic size	Before treatment	After treatment
Linear dimensions, cm		
frontal	4,52±0,2	3,93±0,2*
sagittal	3,97±0,2	3,07±0,2*
oblique	4,68±0,2	3,87±0,2*
Volume, cm ³	36,51±0,54	23,34±0,51*

* p < 0.05 as compared to pretreatment values

Table 4.2. Uroflowmetric parameters in PC patients treated with Synestrol

Parameter	Before treatment	After treatment
T_Q , S	46,82±3,49	37,58±6,63
$T_{Q\ max}$, S	6,15±0,88	9,83±1,10
$Q_{\ max}$, ml/s	5,71±0,55	11,13±1,16*
$Q_{\ aver}$, ml/s	4,68±0,57	5,50±0,59

Note. (T_Q) duration of urination; ($T_{Q\ max}$) duration of urination with maximum urination rate; ($Q_{\ max}$) maximum urination rate; ($Q_{\ aver}$) average urination rate.

* p < 0.05 before and after treatment

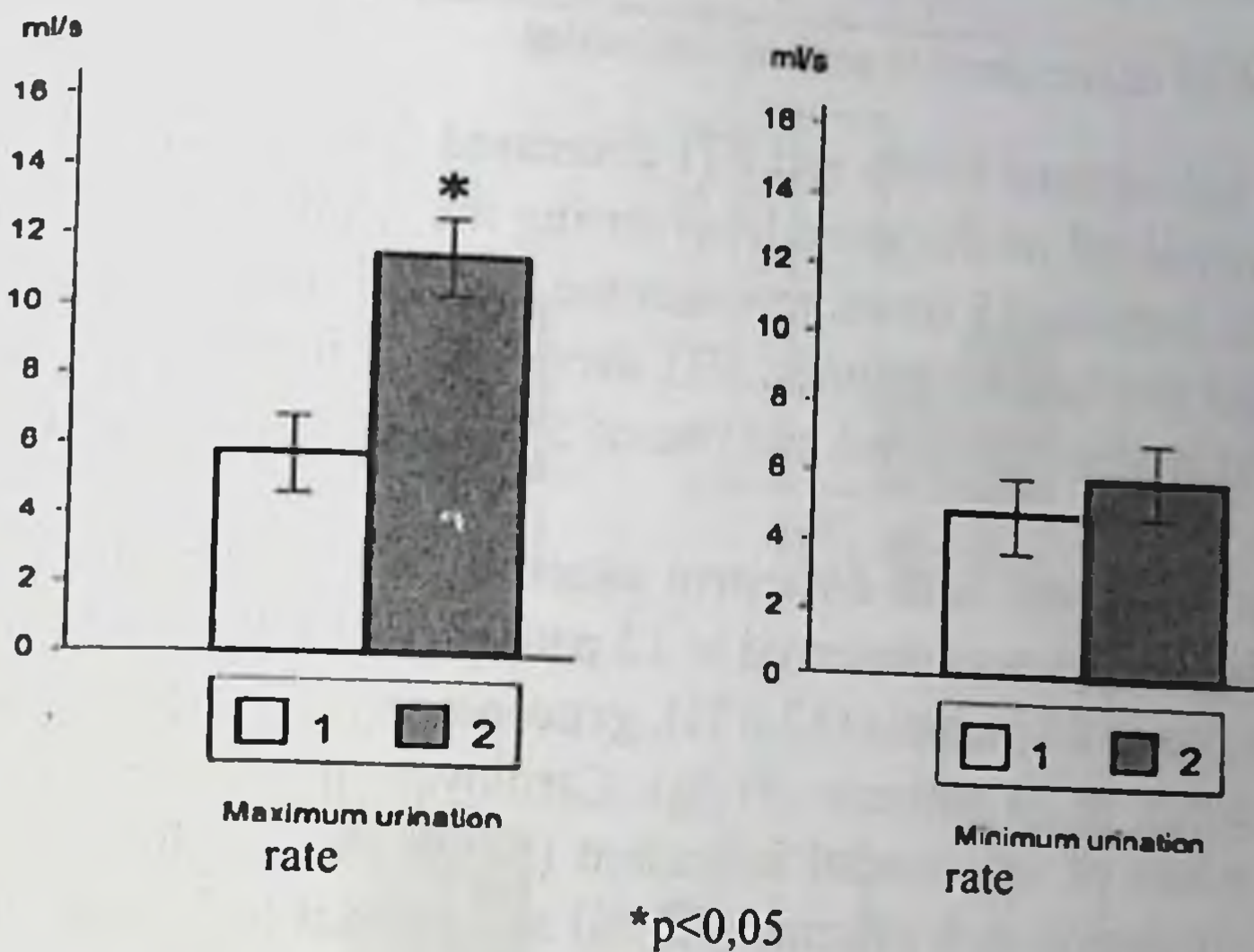


Fig. 4.3. Uroflowmetric parameters in PC patients under treatment with Synestrol 1, 2, before and after treatment, respectively

Level of sex hormones in blood plasma was considered to be a very important criterion. It allowed assessment of the treatment effectiveness and prognosis for a patient. Testosterone, LH, DHT, SHBG levels were measured and free testosterone index $FT = \frac{T, \text{ nmol/l} \times 100}{\text{SHBG, nmol}^3\text{H-DHT/l}}$

was calculated before, during and after treatment (Table 4.3).

Table 4.3. Parameters of hormonal status in PC patients under treatment with Synestrol

Parameter	Basal level	1.5 months later	3 months later
LH, IU/l	12,8±1,9	2,4±0,4*	6,3±2,0*
ΔLH, HJ/i	-	-8,9±2,0*	-6,5±2,4*
T, nmol/l	6,4±0,3	2,4±0,4*	2,9±0,6*
ΔT, nmol/l	-	-4,0±5,0*	-3,3±3,8*
SHBG, nmol ³ H-5a DHT/l	25,5±4,3	78,7±14,1*	72,9±9,8*
ΔSHBG, nmol ³ H-5a DHT/l	-	45,7±15,3*	47,4±9,0*
FTI	36,4±7,2	8,3±2,8*	7,6±4,5*

Δ FTI	-	$-28,5 \pm 8,5'$	$-28,8 \pm 5,6^*$
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*p < 0.05 as compared to pretreatment value

LH, testosterone levels and FTI decreased dramatically 1.5 months later and remained on the same level during the whole treatment period. LH content decreased 5 times, testosterone level 2.3 times, FTI 4,4 times. SHBG level increased 3.1 times. FTI decreases owing to a considerable decrease of testosterone level and rise of SHBG content in blood plasma (Fig. 4.4).

After treatment with Synestrol exacerbation of chronic thrombophlebitis in the legs was observed in 12 patients (10.5 %), cardiovascular complications in 60 patients (52.6 %), gynecomasty in 72 (63%), worsening of potency in 36 patients (31 %). Cardiovascular complications included 6 cases of myocardial infarction (5.3 %), acute disturbances of cerebral circulation in 6 patients (5.3 %) and arterial hypertension in 48 patients (42.1 %).

It should be mentioned that patients with a history of myocardial infarction and acute disturbances of cerebral circulation became invalid and their state scored 3-4, though no progress of PC was observed. Besides, these patients cannot be treated with estrogenic drugs because of danger of recurrent cardiovascular complications, this results in higher risk of PC progress. Here is an example.

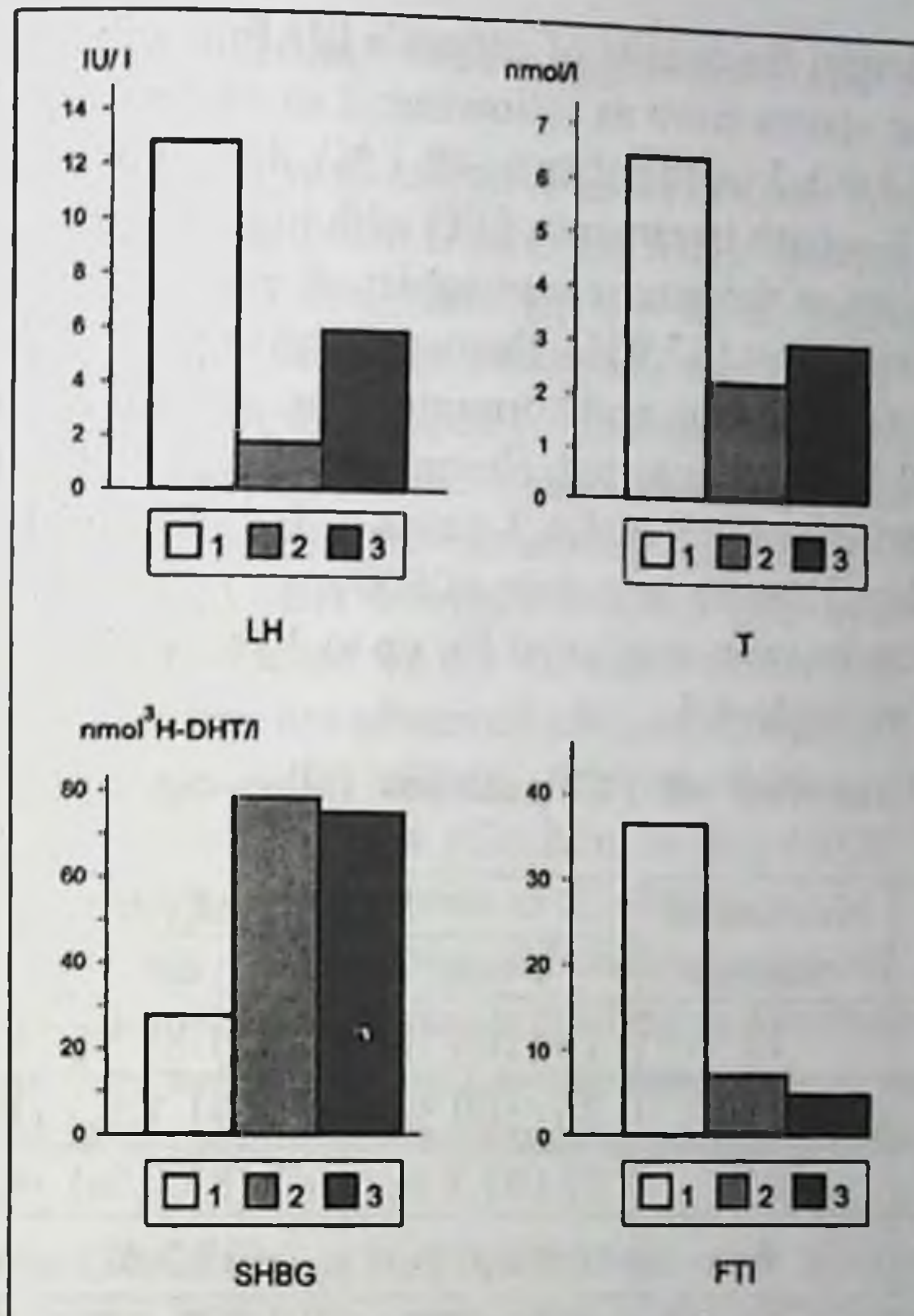


Fig. 4.4. Changes in blood plasma hormone levels in PC patients treated with Synestrol (1), basal level; (2), 3 months later; (3), 6 months later

Patient N. referred to the urologic outpatient clinic because of episodes of microhematuria and dysuria. At rectal and ultrasound examination a solid nodule 2 x 1.5 cm was found in the right lobe of the prostate. Puncture biopsy of the prostate was made with a pathology diagnosis of small-cell glandular cancer. The clinical diagnosis was PC, T₂N₀M₀. The patient was prescribed hormonal therapy, Synestrol 2% daily in a dose of 3.0 ml during 3 months. As a result, sharp pain at urination was over microhematuria disappeared, the size of the nodule reduced to 1.3 x 1.5 cm. The results were assessed as a partial remission. However, in the end of the third month of treatment an acute myocardial infarction developed which eventually resulted in disability to work. The patient faced the necessity to take cardiotropic drugs regularly and to give up special treatment for PC.

When evaluating the quality of patient's life following the treatment with Synestrol the scores were as following: 1 in 18 patients (15.8 %), 2 in 24 patients (21.1 %), 3 in 48 patients (42.1 %), 4 in 24 patients (21.1%).

Thus, after 3-month treatment of PC with high doses of Synestrol 2 % partial regression of the tumor was achieved in 48 patients (42.1 %), stabilization in 66 patients (57.9 %), there were no records of aggravation. All patients were followed-up and hormonal therapy continued in 30-day courses with a 1-1.5-month interval, alternating Synestrol 2% in a dose of 3 ml i.m, chlorotrianisene, 1 tablet 3 times a day, Microfollin Forte, 1 tablet 3 times a day, Honvan in a dose of 600 mg i.v. (or 1 tablet 3 times a day). Remote results were evaluated for up to 3 years. Data on patients' survival is given in Table 4.4.

Table 4.4. Survival of PC patients following treatment with Synestrol

Stage	Number of patients	Survival of patients		
		1 year	2 years	years
I (T ₁ N ₀ M ₀)	18	18 (100 %)	18 (100 %)	17 (94,4 %)
II (T ₁ N ₀ M ₀)	36	36 (100 %)	33 (91,7 %)	30 (83,3 %)
III (T ₃ N ₀₋₁ M ₀)	54	52 (93,3 %)	47 (87,0 %)	42 (77,8 %)
IV (T ₃₋₄ N ₀₋₁ M ₁)	6	4 (66,6 %)	2 (33,3 %)	1 (16,6 %)

In the group of patients with stage I one patient died of acute cardiovascular insufficiency 3 years later, in stage II group 3 patients died 2 years and 3 patients 3 years after beginning of the treatment. In 2 patients the cause of death was acute failure of cerebral circulation, in 3 patients there were cardiovascular complications and one patient died of metastatic spreading.

In stage III group 12 patients died during 3 years of follow-up (by the end of the first year 2 patients died of myocardial infarction), 2 years later 5 patients died (4 patients died of the disease progression and one patient died of acute failure of cerebral circulation), 3 years later 5 more patients died (3 patients died because of the disease progression, 2 patients died of myocardial infarction).

In stage IV group (with metastatic spreading, regional or distant metastases) during the first year of follow-up 2 patients died, during the second year another 2 patients died, and during the third year one patient died. The death was caused by the disease progression, cardiovascular

insufficiency, intoxication, and aggravation of chronic renal insufficiency.

Diethylstilboestrol is as effective as Synestrol. When patients with metastatic PC were treated with DES (3 mg a day) general state improved, dysuria and bone pains alleviated (in 69 % of patients). After DES treatment, as compared to other estrogens, the size of the prostate, as palpation shows, diminishes rapidly. Changes in metastases, life span before local and general disease progression and patient's death are similar to respective parameters following Estracyte. Testosterone and DHT levels decreased after 3 weeks of DES use, after 12 weeks acid phosphatase level decreased by 25 %, there was a 2-3-fold increase in prolactin content (it was not observed after orchiectomy). However, DES often causes marked side effects, this necessitates interrupting the treatment in 13 % of patients (Dachlin et al., 1986; Garnick, 1986; Hoogendijk, de Voogt, 1986; Smith et al., 1986).

While studying testosterone and androstenedione levels in blood plasma of PC patients after estrogen therapy and orchiectomy it was established that they both decreased to the same extent, and a conclusion was made that both methods of treatment are equally effective (Carlstrom et al., 1989).

Hormonal balance, acid phosphatase and alkaline phosphatase levels are very important for assessment of the effectiveness of estrogen therapy, they are also criteria for drug and dose selection in each particular case, besides, they are prognostic factors of patients' survival. These studies showed that optimal Estradurin dose is 320 mg every 4 weeks, this being slightly higher than standard doses mentioned above. It is not recommended to lower this dose because after lowering the dose all hormonal parameters come to the initial values, and this results in the disease progression (Stege et al., 1989).

Alkaline phosphatase concentration in PC patients with metastases is a prognostic criterion of survival, and serum alkaline phosphatase is more important than prostatic. When its level is within the normal range, 41.5 % of patients showed 38-month survival after hormonal therapy, when its level was high in 58.5 % of patients survival made 19 months (the difference is significant). Thus a conclusion is made that in PC patients with bone metastases monotherapy may be recommended and be more effective under normal levels of serum alkaline phosphatase (Rana et al., 1993).

Study of therapeutic effect of a combination of Microfollin (0.05 mg 3 times a day) and Estradurin (80 mg once a month) showed that in PC patients during the first 3 months after treatment 2α -glycoprotein, SHBG and prolactin levels increased considerably with a considerable decrease of FSH and LH concentrations while after castration 2α -glycoprotein, SHBG and prolactin levels remained the same, and FSH and LH contents increase (Dachlin et al., 1986).

After estrogen therapy of different stages of PC with a combination of Estradurin and Microfollin positive results are observed in 84 % of patients, disease progression within 2 years in 8 % as compared to 61 % and 23 %, respectively, after orchiectomy. After castration in 2/3 of patients the disease progression is observed during the first year. A retrospective analysis shows that in patients with poorly differentiated carcinoma and bone metastases after orchiectomy the prognosis is worse than after estrogen therapy, however after estrogen therapy cardiovascular complications are significantly more frequent, especially during the first 6 months of treatment (Haapiainen et al., 1986; Aro et al., 1989). Thus while treating patients with the I-II stages of PC, 6.5 % died, in 13.5 % the treatment was interrupted because of severe cardiovascular complications (21.2 % of them died), in 8.2 % because of gastrointestinal complications (Lundgren et al., 1986).

A special place among estrogenic drugs belongs to fosfestrol (Honvan, Phosphoestrol, Fostrolin, Difostiiben, Cytonal). This is explained by its effectiveness, bioavailability and mechanism of action described above, besides, it is well tolerated.

Following 3.5 h after infusion of 1.5 g Phosphoestrol, DES concentration in blood plasma reaches 5-7 $\mu\text{g/ml}$, this corresponds to $2 \cdot 10^{-5}$ mol/l. It is known that concentrations higher than $5 \cdot 10^{-6}$ mol/l exert cytotoxic effect on human breast cancer cells (Brandes, Hermonat, 1983; Oelschlagel et al., 1984). It is worth mentioning that after oral administration of 360 mg of the drug, its blood plasma concentration makes $(1-4) \cdot 10^{-6}$ mol/l 60-120 min later, i.e. it corresponds to the concentration recorded 45 min following Honvan infusion in a dose of 360 mg but it remains on a high level much longer, and this is very important for greater therapeutic effect (Fig. 4.5).

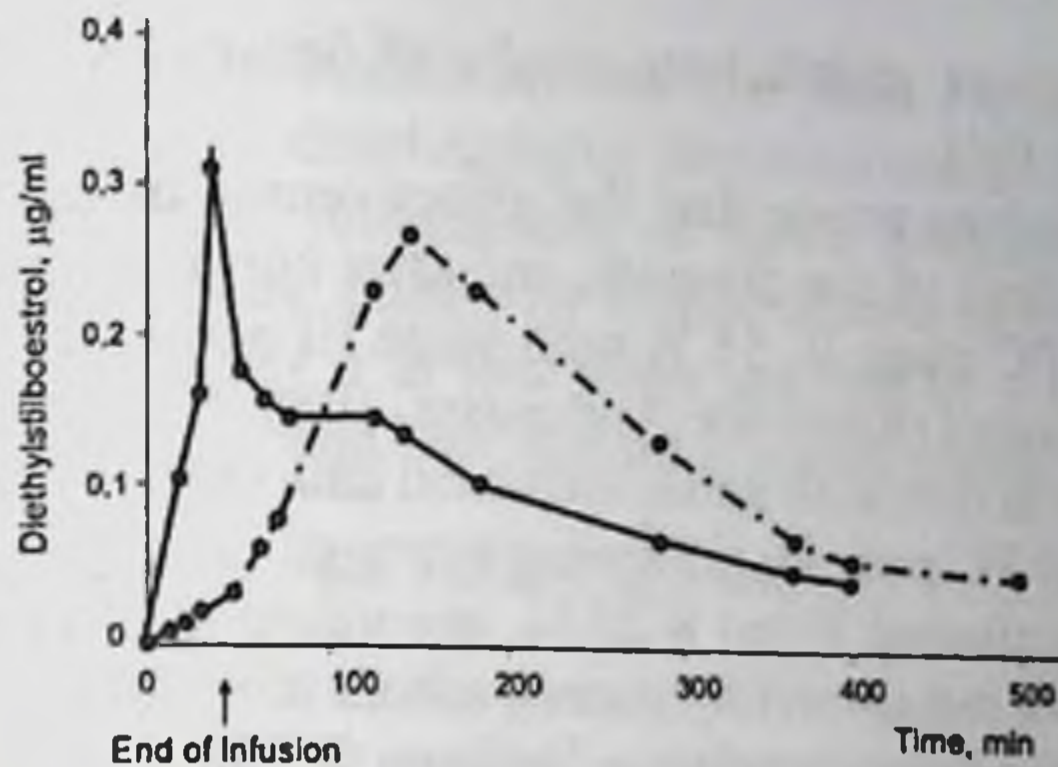


Fig. 4.5. Diethylstilboestrol concentration in blood plasma of PC patients after intravenous (solid line) and oral (dotted line) fosfestrol (Honvan) administration.

The study conducted at the clinical Department of Oncurology at the Institute of Urology and Nephrology (Kiev, Ukraine) showed that under treatment with fosfestrol side effects are more often observed during first 5-7 days and then disappear. More rarely they are observed when the drug is administered intravenously by drops in smaller doses. In hormone-dependent tumors positive effect is observed after 5-8 days of treatment, metastatic pain alleviates, general state and appetite improve, patient's activity increases. After treatment blood count improves, dysuria alleviates or disappears completely, the size of the prostate diminishes, positive changes in bone metastases are observed, in some cases they disappear, bone normal structure restores. Duration of treatment is an important factor effecting the result. The treatment should last till the patient responds to it, in other words, till there is progression under the treatment. We believe that fosfestrol is the estrogenic drug of choice for PC patients with bone metastases (Klimenko, 1996).

In the intervals between the treatment courses with Honvan maintenance therapy with other estrogenic drugs, e.g. Microfollin Forte, chlorotrianisene, Estradurin, should be given.

Special attention should be paid to Estracyte (estramustin phosphate), a drug that combines therapeutic features of hormonal and cytostatic chemical agent. That is why when estrogen therapy is ineffective, patients are given Estracyte or other methods of chemotherapy are applied

and often this gives satisfactory results (Könyves, Andersson, 1984; Servadio et al., 1984).

Many clinicians prove that the effectiveness of estrogen therapy depends on the stage of the diseases, and after hormonal treatment 68 % of patients with PC stage II, 55 % with stage III and 11 % with stage IV are alive up to 5 years (Könyves, Andersson, 1984; Servadio et al., 1984). These results are in line with some statistical data (Matveyev, 1998): total 5-year survival of PC patients following estrogen therapy is from 18 % to 62 %, with disseminated forms 8-22 %, according to some authors up to 43 %. But it is not confirmed by some authors (Gorilovsky et al., 1996). They have not found any correlation between the stage of the disease and tumor malignancy and the results of treatment with Honvan (Phosphoestrol) in PC patients.

To illustrate all mentioned above we present comparative results of the treatment of advanced PC with estrogens and other drugs as monotherapy and in combination with orchiectomy (Table 4.5) (Dawson, 1993; Klimenko, 1996).

Table 4.5. Comparative results of treatment of progressive PC (from Dawson, 1993)

Method of treatment, drug	Dose, mg	Number of patients	Result, %			
			SR	OR	R	S
Phosphoestrol (Honvan)	1000	151	61	31	-	-
Orchiectomy after estrogen therapy	-	132	39	12	-	-
Estrogen therapy after orchiectomy	-	39	17	-	-	-
Flutamide	750	230	-	-	15	20
Aminoglutetimide (Cytadren)	250	583	-	-	9	23
Ketoconazole	400	171	-	-	16	30
Megestrol acetate	100-160	118	-	-	5	36
	1000	21	81	-	-	-
Prednisolone	10	37	38	-	-	-
Hydrocortisone	50	10	60	80	-	-

Note. SR, subjective remission; R, remission; OR, objective remission; S, stabilization.

Thus estrogen therapy that for a long time was the leading method of palliative treatment of PC is as effective as other hormonal methods,

and surpasses them in its availability and low price. However, during recent years because of its disadvantages (frequent cardiovascular, gastrointestinal complications, disturbances of blood coagulability, immune status, high mortality rate caused by complications of estrogen therapy not by the main disease) it is less often applied as a first line of PC treatment though as a second line method it is still widely used.

4.4. LHRH agonists

Many years of clinical observation have shown that surgical and pharmacological castration applied as monotherapy do not result in complete androgen blockade and at the same time estrogen therapy causes numerous severe cardiovascular, thromboembolic, hepatotoxic complications, which often result in a fatal outcome. This prompted the search for novel drugs, more effective, without side effects. Among them LHRH agonists are of special importance, they facilitated a new level in PC management.

Multicentric randomized study conducted in France, Great Britain and Ireland proved that treatment with GnRH analogues was an alternative to surgical castration both in its effectiveness and side effects (Peeling, 1989, Schmid, 1995) (Fig. 4.6, 4.7). After treatment with these drugs androgen synthesis in the adrenals is not inhibited (Zhavrid, Dosta, 1996; Sivkov et al., 1996). When LHRH analogues were applied, in 10-14 % of patients LH and, respectively, testosterone secretion increased during first 10-14 days of treatment, which may result in short-term disease exacerbation in newly treated patients. These drugs differ from estrogens by the absence of complications. Rarely individual intolerance is observed. Heyman and Leiter (1989) described an unusual response of PC patient at the D₂ stage with lung metastases to LHRH agonist. After the treatment ulcer of the rectum developed, it was caused by the tumor necrosis. Morsi et al. (1996) reported a case of pituitary hemorrhage following Leuprolide administration. In their opinion, it was induced by a potent stimulating gonadotropic effect of the drug and possible gonadotrophoma.

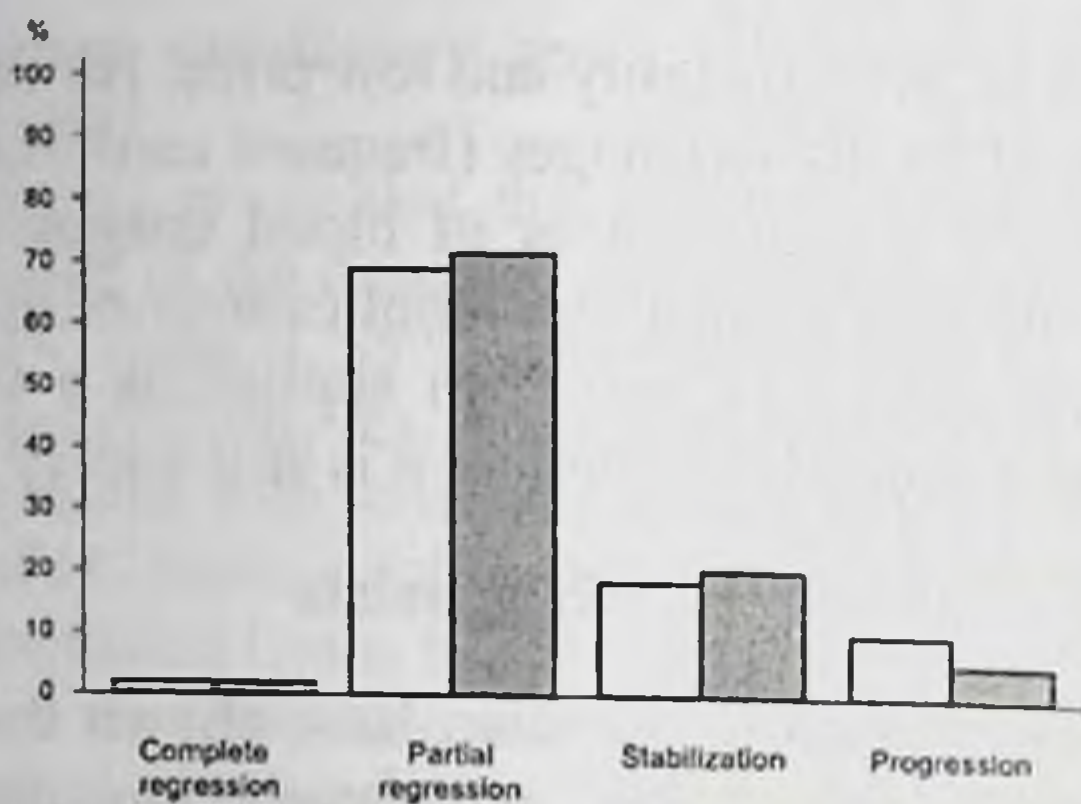


Fig. 4.6. Comparative evaluation of Zoladex (open bars) and orchiectomy (shaded bars) effectiveness in PC patients

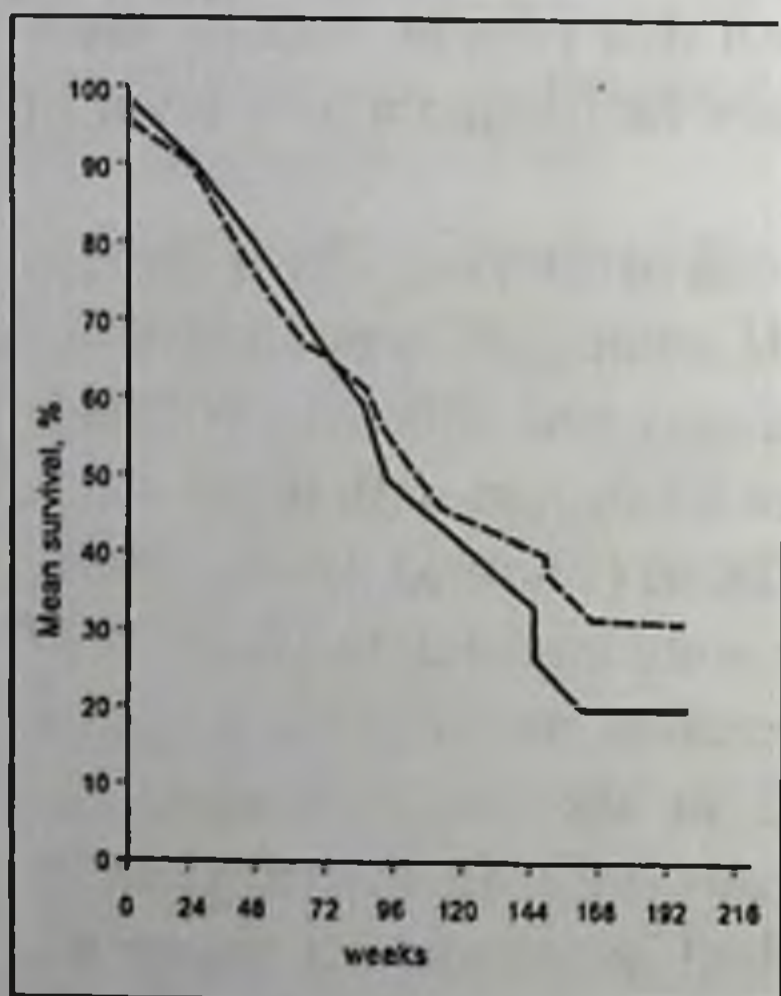


Fig. 4.7. Survival of PC patients following orchiectomy (solid line) and Zoladex (broken line)

LHRH agonists are not only highly effective for treatment of disseminated PC, giving positive curative results. They may also serve criteria of advisability and necessity of orchiectomy: if there are positive results of treatment with LHRH analogues within 3 months, orchiectomy is justified, in case of negative results surgical castration should be given up (Matveyev, Bukharkin, 1996).

Lately, special attention has been paid to selecting method of treatment by a patient as well as to patient's quality of life, that is why this alternative to surgical castration gains importance (Vacher, 1995).

The study showed that 70-80 % of patients preferred Zoladex or Decapeptil 20-22 % chose orchiectomy after being informed about details of surgical castration and drug therapy. After 3 months of treatment 93 % confirmed their choice (Cassileth et al., 1989; Sakalo et al., 1997). LHRH agonists are method of choice in patients who refuse from orchiectomy and those with a high risk of cardiovascular complications (Sogani, Fair, 1987).

Nowadays Zoladex (goserelin), Decapeptil (triptorelin), Leuprolide (leuprorelin) are most widely used for PC treatment. All these drugs are clinically acceptable analogues of native LHRH. First LHRH analogues (buserelin, naferelin) were taken daily as subcutaneous injections or nasal sprays.

Buserelin (Suprefact) is badly absorbed by the nasal mucous membrane (less than 5 %), that is why in order to achieve adequate testosterone inhibition it should be taken 6 times a day. Naferelin is also used as a nasal drug, the carrier solution of the active substance includes bile salt. It irritates mildly the nasal mucous membrane, that is why its absorption makes about 20 %, so 2 insufflations a day are sufficient (Chodac, 1989; Defosse, 1989; Varenhorst, 1993).

After buserelin parenteral administration (200 μg s.c., 2 times a day for 6 days, then 500-1000 μg 3 times a day sc for 14 days) and intranasal administration (300-400 μg 3 times a day) regression of the process is observed in 50.9 % of patients, aggravation in 20.3 %, stabilization in 28.8 %. In 78.6 % of patients alleviation of pain induced by bone metastases is recorded. During the first month of treatment rapid and during next 15 months a slow decrease of blood plasma LH content was observed. During the first week testosterone concentration increased from 3.9 to 4.5 ng/ml, later on it lowered reaching postcastration values and remained at this level for the whole treatment period. If treatment with buserelin is no success, castration or estrogen therapy never bring about an improvement. As to side effects, 80 % of patients complained of hot flushes during the treatment (Wenderoth, Jacobi, 1986).

The same results for all criteria given above were obtained following intranasal administration of buserelin as drops in a dose of 0.4 mg 3 times a day for 12 months (Schröder et al., 1987). When comparing blood hormonal parameters it was established that after intravenous buserelin administration there was no decrease in LH and FSH levels that was observed following intranasal buserelin administration. In the absence of correlation between blood plasma testosterone level and a clinical response to treatment there is a clear correlation between the successful treatment and lowering of cortisol concentration within 3-6 months. Three of 71 patients (4.2 %) died at the beginning of treatment. As to side effects, several cases of impotence were noted, they did not require the drug withdrawal.

However, methods of buserelin administration mentioned above are inconvenient, that is why further study was aimed at developing depot forms of LHRH analogues which would allow their administration once a month. Thus the first attempt of subcutaneous implantation of 3.3 mg buserelin monthly and 6.6 mg every two months was made. The study showed the convenience of this method, it gave more pronounced endocrine effect as compared to intranasal administration (Blom et al., 1989). Later on Zoladex, Decapeptil, leuprorelin acetate were developed.

Results of treatment with Zoladex presented by different authors and based on the same criteria (general state, frequency and character of remission, survival, side effects, hormonal changes in blood plasma, effectiveness as compared to other methods of androgen deprivation) differ slightly but in general they estimate highly this drug.

Table 4.6. gives summarized information on treatment of patients with advanced PC with LHRH agonists and estrogenic drugs (Klimenko, 1996; Klimenko, Aristova, 1997).

Table 4.6. Comparison of the results of PC treatment with LHRH agonists and fosfestrol (Honvan)

Result of treatment	LHRH agonist	Honvan	Reference
Remission Progression a year later	(n=12) 12 6	(n=11) 11 0	Winfield H., Trachtenberg J., 1984
Remission Side effects (hot flushes, gynecomasty)	(n=9) 7 9	(n=10) 9 3	Singer J.H. et al., 1984
Complete remission Partial remission Stabilization Progression Lack of data Side effects: hot flushes gynecomasty nausea, vomiting edema thromboembolism Average progression-free time One-year survival	(n=92) 1 34 44 10 3 51 3 5 2 1 60 weeks 87%	(n=94) 2 4 37 53 11 49 16 16 7 61 weeks 78%	Garnick M.B., 1984

Comparison of therapeutic effectiveness and frequency of side effects following Zoladex and surgical castration is given in Tables 4.7. and 4.8.

Table 4.7. Results of managing PC patients with Zoladex and orchiectomy (Peeling, 1989)

Assessment criteria	Zoladex (n=148)	Orchiectomy (n=144)
Objective effect, %		
complete remission + partial remission	71	72
no effect	18	22
progression	11	6
Subjective effect, %		
according to treatment protocol	66	75
clinically	94	95
Survival (30-month follow-up)		
alive	64 (43,3 %)	55 (38,2 %)
dead	84 (56,7 %)	89 (61,8 %)

Table 4.8. Frequency of side effects following treatment with Zoladex and orchiectomy, % (Peeling, 1989)

Side effects	Zoladex (n=148)	Orchiectomy (n=144)
Decrease of libido	73	79
Erectile disorders	84	85
Hot flushes	63	58
Breast swelling	5	4
Breast sensitivity	< 1	1
Transitory aggravation of bone pains	3	0
Scrotal complications (hematoma, infection), local reactions in the injection site	0	9

Zoladex toxicity with regard to cardiovascular system that is often observed after estrogenic drugs (DES) and results in their withdrawal in 12.7 % of patients was not noted in any single case.

In subcutaneous administration of Zoladex pill, which contained 3.6 mg substance, 125 µg of the drug is released and absorbed in the blood daily for 28 days, this dose is sufficient for therapeutic effect (Debruyne et al., 1988; Jaiguemin, 1990; Kaisary et al., 1991). After its administration to PC patient goserelin was reported to be found not only in the blood but also in tumor cells (Fretin, 1990).

Pharmacological castration depends on the dose of the drug: it occurs 22 days after administration of 500 µg Zoladex and 43 days after

administration of 250 μg Zoladex ($p=0.6$). After daily subcutaneous administration of the drug (in a dose of 250-500 μg) for 12 weeks, followed by its deposited form (3.6 mg once a month) for up to 98 weeks, blood plasma gonadotropin and testosterone concentrations increased dramatically during first 2 days, then they decreased gradually for the next 3 weeks. When depot forms are applied, no endocrine shifts are observed, blood plasma testosterone level is 5 % of the initial level. By the end of the third month after treatment Zoladex concentration in the serum persisted at the level of 0.47-0.53 ng/ml irrespective of the administered dose, and it did not correlate with hormone levels and tumor response to the treatment. Complications and side effects were similar to those described in Chapter 2 (Murphy et al., 1987).

According to Beacock et al. (1987), after treatment with Zoladex for 3-18 months in 69 % of newly treated patients with bone metastases and pain syndrome, alleviation of pain was noted, in 26.6 % the pain persisted. According to ultrasound examination, in 70.9 % of patients the size of the primary tumor decreased from 51.4 ± 4.1 to 20 ± 3 cm^3 (63 %). During 21-28 days LH level lowers to undetectable values, that of testosterone decreases to postcastration values and remains on this level in all patients for the whole treatment period. But in 26 % of patients bone pain persisted, the acid phosphatase level remained high or increased, osteoscans showed no improvement or even aggravation. In 35 % of patients after positive subjective changes exacerbation was observed 9 months later. No severe complications were noted.

Holdway et al. (1988) confirmed the results given above. In 88 % of patients with untreated metastatic PC subjective improvement occurred 6-24 months (on the average 12 months) later: alleviation of pain was reported, obstructive urologic symptoms improved. In 84 % objective signs of remission and stabilization were noted 3 months later, and in 72% of patients these were found after 6 months. In 92 % the size of the prostate decreased by 75 %, at the same time urinary flow increased, testosterone and DHT concentrations decreased considerably, androstenedione, dehydroepiandrosterone, acid phosphatase and alkaline phosphatase concentrations lowered. Plasma estradiol concentration decreased gradually from 89 ± 7 to 37 ± 15 nmol/l during 8 weeks and remained on this level till the end of treatment. In 60 % of patients rush of blood was noted, in 16 % there was disease relapse at the initial period of treatment.

Clinical observations show that in all patients with metastatic PC who were treated with Zoladex for 2.5 years, the effect persisted for 25 months on the average, 22-month survival was observed in 50%. After 3-month treatment partial remission was noted in 55.5%, regression of bone metastases in 15.8%, of lung metastases in 75%, of lymph node metastases in 75% of patients. Following 2 weeks after the onset of the treatment there was a significant decrease of hormone levels in the serum, with the exception of ACTH. All patients complained of the loss of libido and erection, in some patients there were hepatic disorders and rare cases of edema, hot flushes, however this did not require the drug withdrawal (Ahmed et al., 1986; Kanetake et al., 1989).

When another pattern was applied for this drug (drug depot formation through daily subcutaneous injections of 2-3 mg for a month), in 48.2% of newly treated patients partial remission lasting for 10 months was achieved. Subjective improvement was reported by 68% of patients. Testosterone level decreased to postcastration values during the course of treatment. No side effects were observed (Iversen et al., 1989).

Decapeptil, which is administered intramuscularly in the form of microcapsule, has similar characteristics and effectiveness (de Sy et al., 1986). When PC patients with local spreading or metastases are treated with Decapeptil («Beau- four Ipsen Int») in all cases testosterone level, following a shortterm increase, lowers to postcastration values. Improvement or stabilization is observed in 68% of patients, however this result is typical only for newly treated patients (Steg et al., 1985).

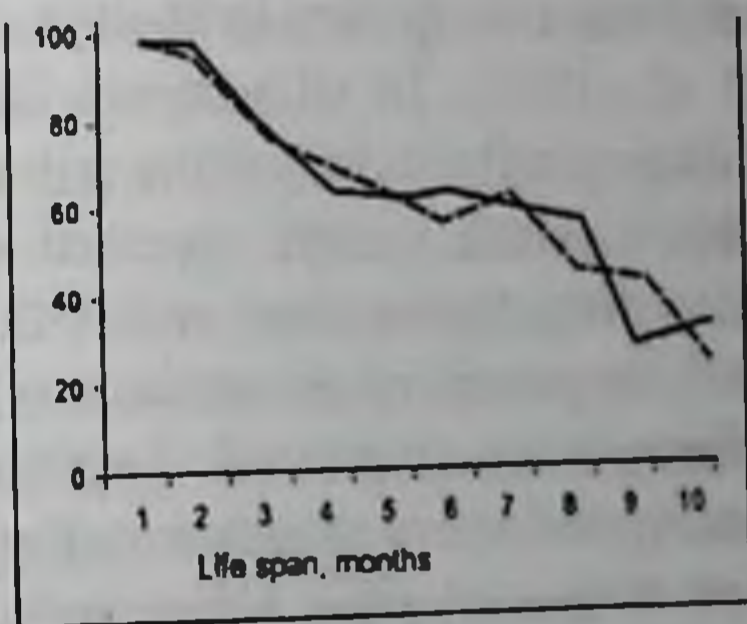


Fig. 4.8. Life span in PC patients depending on treatment
Orchiectomy, solid line; Decapeptil, broken line

The effectiveness of treatment with LHRH agonists, as compared to other methods, was studied in a number of randomized studies. It was demonstrated that Leuprolide, the first drug of this group, and later on buserelin and Decapeptil with prolonged action have the same effect on advanced PC as DES in conventional doses or as orchiectomy, and they can easily substitute them (Robinson et al., 1985, Roger et al., 1986; Botto et al., 1998) (Fig. 4.8).

When comparing the effect of Decapeptil and orchiectomy basing on the clinical course of the disease, changes in the prostate size, blood serum testosterone level, their effectiveness following 3-6 months seems to be the same, though after Decapeptil positive response is observed in more cases than after orchiectomy. All symptoms were irreversible. Testosterone level decreased to postcastration values and remained low during 9 months of treatment. No acute toxicity and severe side effects were found (de Sy et al., 1986). Similar comparative data on the effect on testosterone and DHT levels were obtained for Leuprolide (1 mg/day s.c.) and DES (3 mg/day orally). Acid phosphatase level decreased by 70 % and 84 %, respectively, bone pains alleviated in 73 % and 69 % of cases, the incidence of hot flushes following Leuprolide and other manifestations following DES decreased. After DES administration 13 % of patients had to discontinue the treatment and only 3 % after Leuprolide (Garnick, 1986).

At the Department of Oncourology at the Institute of Urology and Nephrology a randomized study with 33 patients with PC T₃₋₄N₁₋₃M₁ was carried out. Sixteen patients were treated with Decapeptil 3.75 mg, intramuscularly once in 28 days, and 17 patients were operated on (Sakalo et al., 1997). In all patients PC was newly diagnosed and confirmed histologically, none of the patients had received any special treatment before. Both groups matched each other in age, body mass, tumor spreading, testosterone and PSA levels in blood plasma. Pain syndrome and frequency of urination was scored 1-3. All drug-induced and side effects were registered. Testosterone and PSA levels were measured before and every month over the treatment period. The prostatic volume was measured using ultrasound (US) before treatment and then every 3 months. The size of bone metastases was assessed by X-ray examination and/or using osteoscintigraphy. The quality of life was evaluated according to Karnovsky every 3 months. Possible drug-induced toxic reactions were considered by blood count (total, coagulogram, biochemical parameters) and urinalysis. ECG and X-ray examination of the thoracic organs were performed.

The efficacy of treatment was assessed according to the WHO criteria. Diminishing the size of the tumor by 50 % and more, normalization of PSA level and reversible metastases development were assessed as partial regression. Discontinuance of tumor growth and no new metastases, lowering of PSA level and pain alleviation, normalization of body

weight and increased motor activity were considered as process stabilization.

Patients were followed-up for 3-16 months (on the average 9.6 months). In all patients the general state improved, motor activity resumed, there was an increase of body weight though the difference between two groups was not significant. Following Decapeptil injections more manifested improvement of dysuria was noted at the 1st, 3rd and 6th months of treatment. In two patients with acute ischuria after first Decapeptil injection urination was restored. In both groups pain alleviation was observed but the difference was not significant. Following 3 months of follow-up prostatic size decreased by 30-40 % but after treatment with Decapeptil those changes were more pronounced.

Lowering of blood plasma testosterone level to 0.5 µg/ml and less was achieved in both groups, however the pattern of this lowering was different. After castration it was rapid, and following treatment with Decapeptil postcastration levels were observed only 2 weeks later.

In 70 % of patients PSA levels were >10 ng/ml, in 62.2 % of them they were over 90 ng/ml. These values correlated with the treatment results: when PSA level was high the results of treatment worsened and life duration shortened irrespective of the method applied.

As to side effects, hot flushes were reported by 68 % of Decapeptil-treated patients and 66 % of orchiectomized men, libido decrease and erectile dysfunction were mentioned by 72 and 91 % of patients, respectively. Diminishing of testicular size and testicular hypotension were observed in all Decapeptil-treated patients. There were no cases of gynecomasty and cardiovascular complications. In two patients, following the first injection of Decapeptil, bone pains aggravated and persisted 7- 10 days.

After six-month treatment with Decapeptil partial remission was observed in 35 % of patients, stabilization in 48 %, progression in 17 %, following orchiectomy, in 34, 48 and 18 %, respectively. During 10 months there were 8 deaths among Decapeptil-treated patients and 9 deaths among orchiectomized men, in 2 of them the death was caused by thromboembolic complications.

Thus, the objective response to treatment, irrespective of the hormonal deprivation method (surgical or pharmacological), was observed in 70 % of patients but no statistically significant difference between the groups was found. At the same time following treatment with Decapeptil

in patients with advanced PC orchiectomy may be viewed as a second therapy line.

According to information provided by Dnipropetrovsk Regional Diagnostic Centre (Ukraine), Decapeptil 3.75 mg is effective at late stages of PC (Bibik, 1998).

It is of practical interest to consider data on pharmacodynamics, safety and bioequivalency of leuproreline depot, its various doses being applied in PC patients with the D stage. When the drug was used in a dose of 3.75 mg for an average period of 480 days (more than 60 % of patients were treated for over a year), partial regression of the tumor was observed in 64.3 %, when the dose made 7.5 mg regression was found in 71.4 %. Following a mean of 308 days in 52.5 % of patients progression of the disease was observed. It was manifested through bone metastases in 81 % and an increase in acid phosphatase level in 57 %. Survival was 2 years in 80.5 % of patients who received 3.75 mg and 81.3% in those given 7.5 mg, 3 years in 65.1 % and 66 %, respectively. Testosterone level was less than 1 ng/ml during the first 148 weeks, and LH and FSH levels were close to the normal upper limit. No serious complications were found. This data proves that a twofold dose is well tolerated but it does not result in improved therapy (Akaza et al., 1992). Later on similar study was conducted by Zerbib et al. (1997), but they used doses of 11.25 mg (once in 3 months) and 3.75 mg (once a month). Following 9-month treatment both doses of leuproreline showed comparable effectiveness and safety. During monthly measurement of testosterone level in blood plasma no considerable differences were revealed (0.27 ± 0.04 and 0.19 ± 0.03 ng/ml, respectively).

Villavicencio et al. (1994) mentioned that during similar study with Leuprolide complete remission within a year occurred in 3 %, partial remission in 3 %, progression of the disease in 21 %, in 10 out of 72 patients it was necessary to withdraw the drug (13.9 %) for various reasons. When prostatic acid phosphatase, PSA, T and LH levels were measured every 2-4 months the results and pattern of changes were similar to those given above. It is emphasized that the use of Leuprolide as well as treatment with other prolonged LHRH agonists might be an alternative to castration.

Many authors discuss the issue on eliminating most common side effects which occur when LHRH agonists, antiandrogens, ketoconazole, estrogens and progestins are used: loss of libido, impotence, hot flushes,

nausea, vomiting, hepatotoxicity, thromboembolic complications. Symptoms of the disease flare that occurs during treatment with LHRH analogues are stopped by antiandrogens or estrogens. Progestins may effect the intensity of hot flushes. Erectile dysfunction is the most difficult to eliminate (Kirschenbaum, 1994).

Antiandrogens a day before injecting LHRH agonists and then during 30 days after it successfully prevent an increased testosterone level and disease progression (Fig. 4.9). The same effect is produced by DES 7 days prior to Zoladex and 3 days after the onset of treatment (Takeuchi et al., 1995).

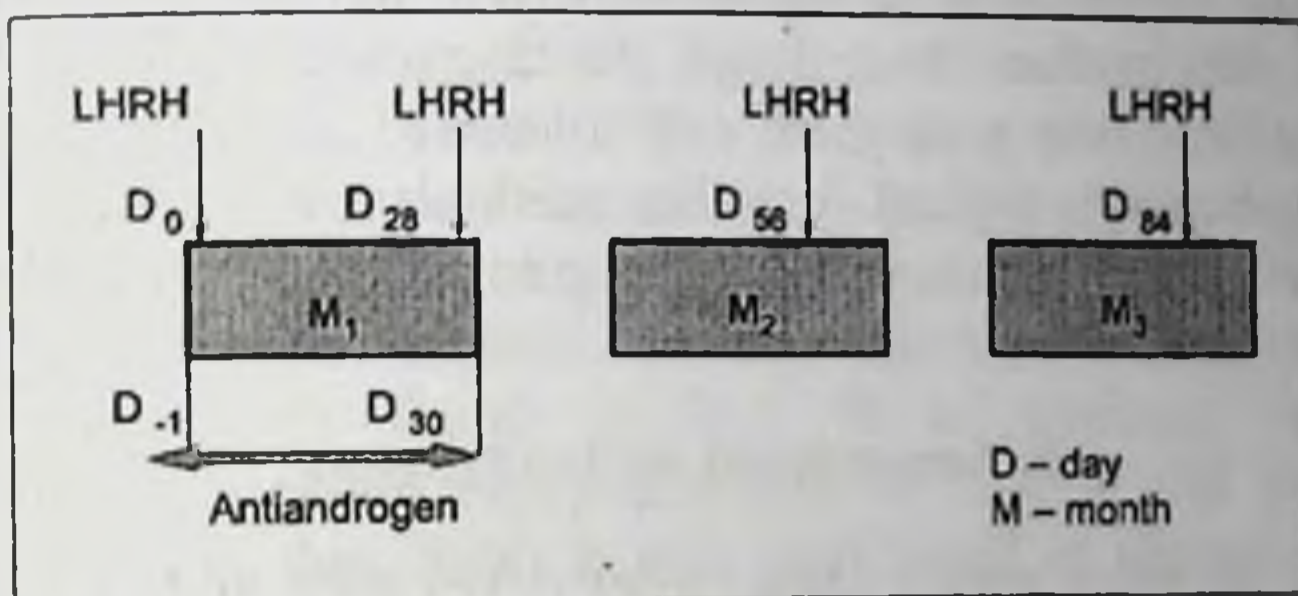


Fig. 4.9. Protocol of managing PC with LHRH agonists (Zoladex 3.6 mg, Decapeptil 3.75 mg). LHRH agonists are injected every 28 days, antiandrogens are taken during the first 30 days

In order to prevent gynecomasty irradiation of the breast before estrogen therapy is recommended. The most common scheme that is also used in Ukraine consists in a single irradiation of the breast following bilateral orchiectomy in a dose of 15 Gy, 2 weeks after it the treatment with DES begins (Servadio et al., 1984; Kirschenbaum, 1994).

In order to prevent thromboembolic complications acetylsalicylic acid in a dose of 0.3-0.5 g/day is prescribed together with estrogenic drugs (Smith, 1995). However this measure is still under discussion. Some authors (Aro et al., 1989) believe it is unnecessary to take acetylsalicylic acid together with hormonal therapy in order to prevent thromboembolic complications because not a single case of cardiovascular and thromboembolic complications was revealed after either simultaneous administration of Estradurin and acetylsalicylic acid (0.75 g per os daily). But there is also information that Estradurin per se does not possibly cause

such complications (Henriksson et al, 1990), that is why the previous opinion does not seem convincing enough.

We used acetylsalicylic acid in a dose of 0.5 g twice a day during the first month of treatment, then 0.5 g once a day up to three months in 30 patients together with hormonal therapy with Honvan and did not find a single case of thromboembolic complications. In our opinion, when aspirin is prescribed, coagulogram should be taken into consideration as well as the estrogenic drug taken by a patient. The matter is that estrogenic drugs differ in their therapeutic efficacy and also in frequency, type, severity of side effects and cardiovascular complications.

Thus the information on the use of LHRH agonists for treating advanced PC proves that these drugs are characterized by rather high therapeutic effectiveness, they are well tolerated, side effects as well as serious complications typical for other methods are not frequent. This allows considering them as an alternative to orchiectomy and estrogen therapy.

4.5. Non-steroid antiandrogens

During 30 years which passed after developing and implementing steroid and non-steroid antiandrogens in clinical practice, an enormous experience has been acquired as to application of both groups of drugs, dozens of publications based on open and randomized controlled studies with thousands of PC patients participating appeared.

The results reported by different authors differ slightly, sometimes they contradict each other but in general it might be concluded that antiandrogens are rather effective both in monotherapy and in combined treatment, they have certain advantages as compared to methods of hormonal therapy described above, it refers first of all to the relative frequency and severity of side effects and complications.

The first publications on clinical use of flutamide, a «pure» non-steroid antiandrogen, appeared in the beginning of the 70-s. Summarized data on the effectiveness of monotherapy with flutamide during a decade is given in Table 4.9 (Reznikov, Varga, 1988).

In the first studies that included a large number of PC patients who received flutamide in a dose of 750 mg/day, clinical improvement, diminishing of the primary tumor size and metastases to bones and soft tissues, regression of bone pain and hydronephrosis, improvement of general state and a considerable decrease of acid phosphatase level in blood plasma was shown in 88 % of cases. At the same time side effects were less

frequent and less severe though the drug was administered for a long period, up to 28 months. It is explained by the absence of side hormonal effect and by the highly selective blockade of androgen receptors. Flutamide does not affect libido and potency, this being very beneficial for patients. Actually, there are no side effects typical for estrogen therapy but even if there are such (diarrhea, nausea, epigastric pain, breast sensitivity, and skin eruption) usually there is no need to discontinue the treatment. In some cases the drug dosage should be reduced temporarily. Gastrointestinal disorders sometimes accompanied by diarrhea are observed, according to different authors, in 5-24 % of patients and result in the drug withdrawal in 6 %, breast tenderness in 34-100 % (Sogani et al., 1984; di Silverio et al., 1987; Brogden, Clissold, 1989; Crawford, 1989; Delaere, 1991; Tyrrell, 1991). But there are rare cases when flutamide may cause severe hepatotoxic complications. According to Wysovsky (1993, 1996), having analyzed treatment results for a 3-year period it was shown that hepatic disorders which sometimes resulted in a fatal outcome, were found in 26.9 % of patients. A case of Flucinominduced hepatic encephalopathy in 72-year old patient with metastatic PC was described. It was manifested in sleepiness, mental confusion, ictericity and increased hepatic enzymes contents in blood. After drug withdrawal the state of the patient returned to that before treatment within a week.

Table 4.9. The effectiveness of treating PC stages III and IV* with flutamide

Daily dose, mg	Number of treated patients	Number of patients with regression or stabilization	References
250-500	12	8	Irwin R., Prout G., 1973
750-1500	18	7	Stoliar B., Albert D., 1974
750-1500	13	11	Prout G. et al., 1975
750-1500	26	6	Sogani P. et al., 1975
750-1500	11	4	Hellman L. et al., 1977
750-1500	21	19	Sogani P., Whitmore W., 1979
Not mentioned	18	13	Narayana A. et al., 1981
750-1500	70	57	Neri R., Kassem N., 1982

* correspond to stages C and D

In similar studies of other clinicians who used the same protocol of flutamide monotherapy complete or partial tumor regression was observed in 11-71 % of patients, stabilization in 14-74 %, disease progression in 8-45 %, positive clinical effect and average 30-month survival in 50 % of patients (Matveyev, Bukharkin, 1991; Matveyev 1998; Danicello et al., 1987; Prout et al., 1989). Flucinom, both in monotherapy and in combination with chemical and surgical castration, slows down the progression of the disease considerably and extends progression-free period by 54 % (Fig. 4.10). Progression of the disease observed in 30-38 % of cases when antiandrogen is applied is explained by the polyclonal character of prostatic tumor and requires another treatment (Sagaster, Flamm, 1988). It should be mentioned that the effectiveness of flutamide in conventional doses for monotherapy of patients with advanced PC does not differ from the effectiveness of orchiectomy, LHRH analogues or DES, and in some patients who are resistant to castration it produces therapeutic effect comparable to that of Estracyte (600 mg/m² day) (Brogden, Clissold, 1989; Boccon-Gibod, 1992; 1993; Chang, 1992; Hilner, 1995). Only once it was shown that DES is superior to flutamide concerning patients' survival (Boccon-Gibod, 1993). However, more favourable results are observed following treatment with flutamide with prior bilateral orchiectomy. Labrie (1982), following this treatment design in 68 patients, found partial remission in 94 % of patients and stabilization in 6 %. No cases of disease progression were found. In a number of similar studies these figures were somewhat lower and differed considerably: partial remission was observed in 29-70 %, stabilization in 12- 50 % (Matveyev, Bukharkin, 1994). In the study that was carried out by these authors in the Cancer Research Centre (Moscow), these figures were 54 % and 43 %, respectively and progression was observed in 3 % of patients. According to 1998 data they were 48.7 %, 43.4 % and 7.9 %, respectively (Matveyev, 1998). The improvement of the quality of life, i.e. less intensive pain syndrome, alleviation of dysuria, and improvement of hematologic parameters, appetite, increased body weight etc. was found in 97 % of patients. As well as other authors, they mention that Flucinom, in contrast to estrogens, does not produce serious side effects on the cardiovascular system. While studying cardiac complications in selected PC patients with accompanying severe cardiovascular disorders, no aggravation of arterial pressure and ECG parameters was found during 4-

32-month treatment with flutamide, the state of the cardiovascular system remained stable (Aslamazov, 1994).

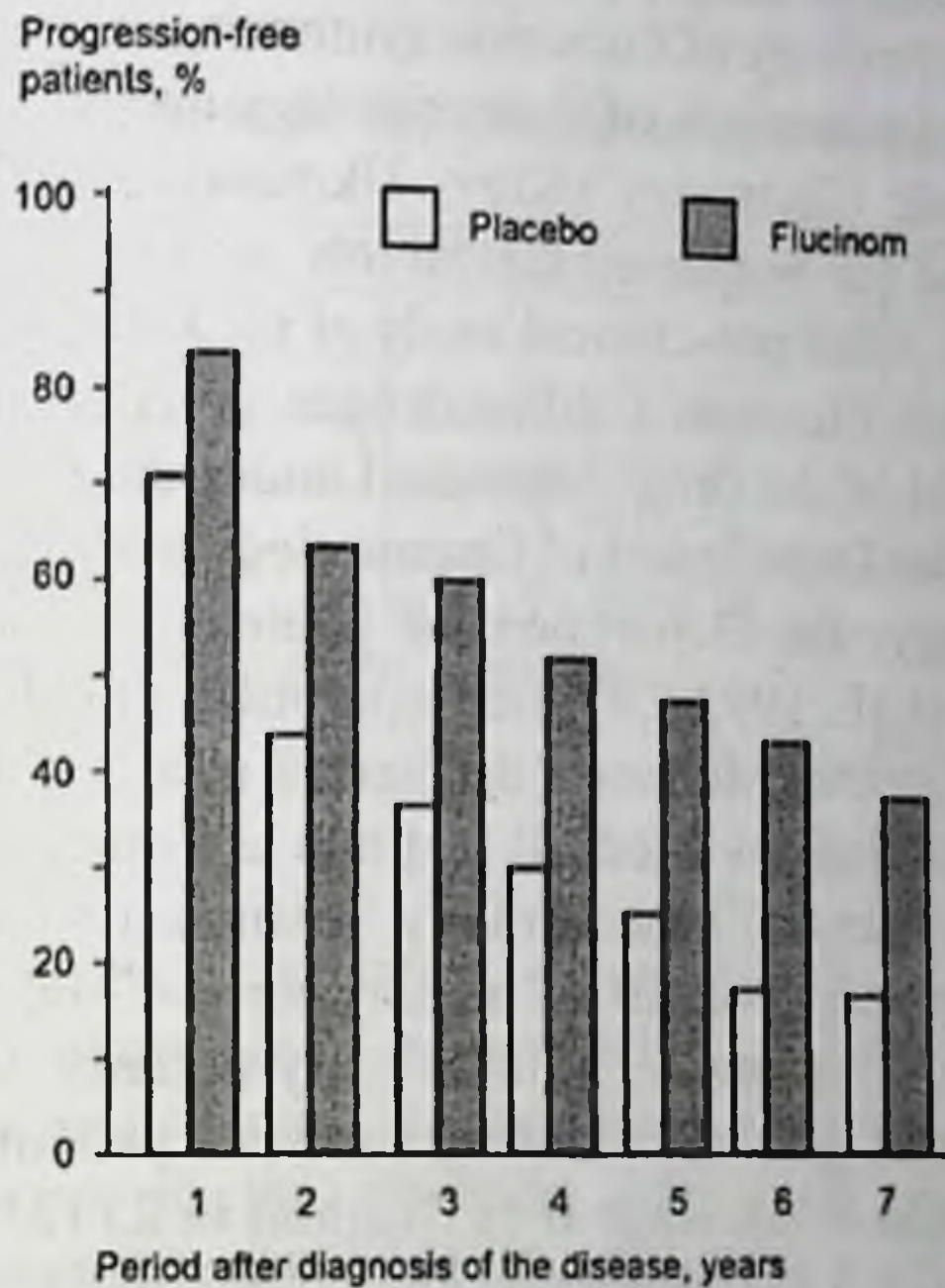


Fig. 4.10. Progression-free time in PC flutamide-treated patients

In order to determine optimal effective clinical doses of flutamide it was prescribed in doses of 90, 375, 750 and 1125 mg/day during 12 weeks and the results were compared. In doses of 375-1125 mg/day positive effect was observed in 48.8-46.7 % of primarily treated patients while in patients who were given flutamide in a dose of 375 or 750 mg/day and had received prior hormonal therapy positive effect was observed in 13.3 % and 8.3 %, respectively. The frequency of side effects, gynecomasty, nausea, vomiting, diarrhea, increased blood hepatic transaminase content correlated with the drug dose. This study showed that an optimal dose of flutamide in monotherapy of PC patients without hormone use is 375 mg/day (Aso et al., 1993a). When the efficacy of different doses of flutamide (750 and 1500 mg/day) and DES (1 mg/day) was compared in randomized double blind study carried out in 12 clinics, no difference in the patient response in all three groups was found but side effects were

more frequent in DES-treated patients (cardiovascular complications, gynecomasty) (Neri, Kassem, 1987)

Advanced technology of flutamide synthesis was developed in 1973 at V.P. Komissarenko Institute of Endocrinology and Metabolism and the Institute of Organic Chemistry (Kiev, Ukraine). Locally synthesized flutamide was used for preparing the tablets with the content of active ingredient 250 mg. After pre-clinical study of bioavailability, bioequivalence (in comparison with Flucinom), antiandrogen potency and safety, multicentre clinical trial of the drug (registered under the name of Niftolide) was carried out at the Department of Oncourology at the Institute of Urology and Nephrology, the Department of Urology at Kiev City Cancer Centre (Klimenko et al., 1993 a,b), the Department of Oncourology at the Cancer Research Centre (Moscow (Bukharkin et al., 1990), the Department of Urology at Kharkov Medical Institute and other clinics.

At the Department of Oncourology, Institute of Urology and Nephrology, Niftolide was given to 68 patients aged 40-80 years and older as monotherapy, 250 mg orally, 3 times a day (a daily dose of 750 mg) for 6 months. Stage I ($T_1N_0M_0$) was diagnosed in 2 patients (2.9 %), stage II ($T_2N_0M_0$) in 25 (36.8 %), stage II ($T_3N_{0-1}M_0$) in 23 (33.8 %), stage IV ($T_{1-4}N_{0-1}M_1$) in 18 (26.5 %) patients.

Histologically, alveolar adenocarcinoma was identified in 11 cases (16.2 %), small-cell adenocarcinoma in 15 (22.1 %), dark-cell adenocarcinoma in 3 (4.4 %), scirrhous carcinoma in 9 (13.2 %), undifferentiated carcinoma in 6 (8.8 %), adenoma with malignization in 4 (5.9 %), clear cell cribriform pattern in 6 (8.8 %), tubular-alveolar in 8 (11.8 %), solid-trabecular in 2 cases (5.9%)

The results of treatment were evaluated 3 and 6 months after the treatment began. To assess objective therapeutic effect general state of the patient, prostatic size (according to digital rectal examination) and ultrasound examination, uroflowmetry, metastatic changes as shown by X-ray examination and osteoscintigraphy were considered. Blood samples were taken for hormonal analysis.

During treatment with Niftolide no worsening of the general state was observed during the first 3 months. In 44 patients (64.7 %) urination improved, in 24 (35.3 %) the state remained without changes.

Side effects were observed in 5 patients (7.4 %): 3 patients (4.4%) complained of diarrhea, one patient (1.5 %) of the pain in the left iliac

region, one patient (1.5 %) complained of dramatic decrease of libido, 2 (2.9 %) complained of skin pruritus in the region of the hip.

Table 4.10. Changes in the prostatic size under treatment with Niftolide (Means +S.E.)

Prostatic size	Before treatment	After treatment
Linear measurements, cm		
frontal	4,41±0,22	4,11±0,21
sagittal	4,22±0,21	3,87±0,2
oblique	5,21±0,23	4,32±0,22*
Volume, cm ³	48,38±0,36	34,11±0,49*

* p < 0.05 as compared to pretreatment value

As digital rectal examination showed prostatic size was reduced in 28 patients (41.2 %), remained without changes in 40 patients (58.8 %). Changes in the prostatic size according to ultrasonography are given in Table 4.10. and Fig. 4.11.

The results of uroflowmetry are given in Table 4.10. A trend to an increase in the urination rate is obvious (Fig. 4.12).

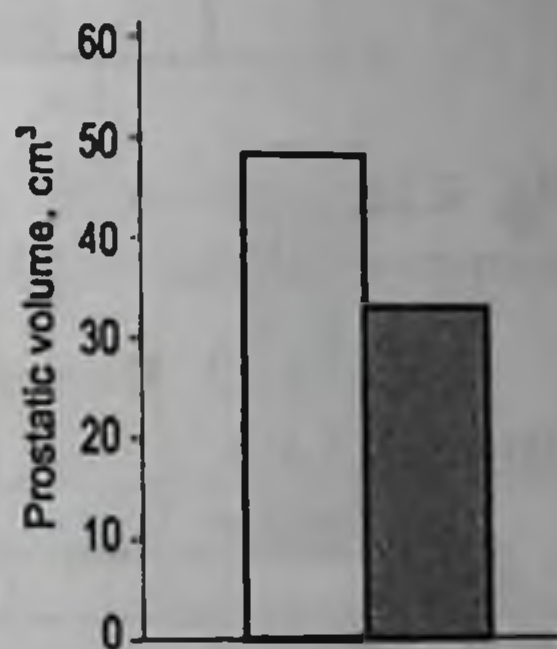


Fig. 4.11. The prostatic volume in PC patients before (open bar) and after treatment with Niftolide (shaded bar)

Table 4.11. The results of UFM in Niftolide-treated PC patients (Means ± S.E.)

Parameter	Before treatment	After treatment
T_0 , S	33,63±6,45	33,63±6,45
$T_{0\max}$, S	10,50±3,35	10,74±2,02
Q_{\max} , ml/s	8,35±2,44	10,70±1,66
Q_{aver} , ml/s	4,81±1,58	5,19±0,82

Hormonal and SHBG changes were studied 3 and 6 months later. The data is given in Fig. 4.13 and Table 4.12.

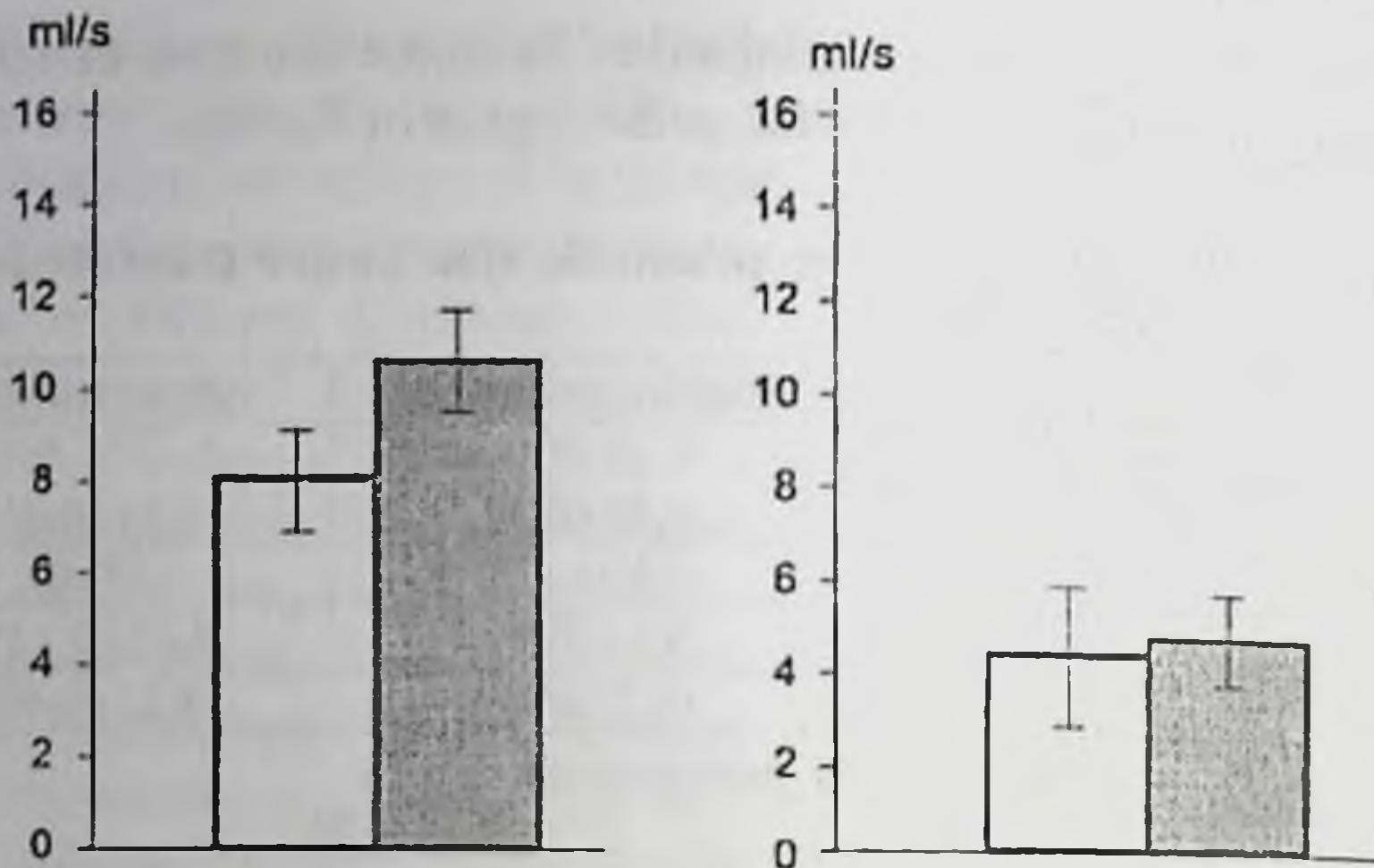


Fig. 4.12. Uroflowmetry results in PC patients before (open bars) and after treatment with Niftolide (shaded bars)

Table 4.12. Hormonal status in Niftolide-treated PC patients (Means \pm S.E.)

Parameter	Pretreatment level	3 months later	6 months later
LH, IU/l	6,4 \pm 1,0	12,0 \pm 1,2*	11,4 \pm 1,6*
ALH, IU/l		5,3 \pm 1,5*	4,8 \pm 1,7*
T, nmol/l	6,3 \pm 1,0	8,7 \pm 1,7	6,1 \pm 1,5
AT, nmol/l		2,2 \pm 1,3	0,7 \pm 1,1
SHBG, nmol ³ H-DHT/l	24,7 \pm 3,6	24,9 \pm 2,9	27,2 \pm 2,6
ASHBG, nmol ³ H-DHT/l		0,2 \pm 4,3	0,8 \pm 3,7
FTI	30,0 \pm 5,3	42,1 \pm 9,4	214 \pm 6,4
A FTI		10,8 \pm 7,1	-2,5 \pm 6,1*

* p < 0.05 as compared to pretreatment value

An increase in plasma LH level as compared to the pretreatment values was observed both 3 and 6 months later. Testosterone level increased slightly 3 months later and returned to basal values 6 months later. Besides, when studying individual response to 6-month treatment with Niftolide a decrease in FTI was found. It seems a positive factor since proves a decrease in tissue-available free testosterone fraction, this being important for evaluating the efficacy of treatment. Plasma SHBG content did not change over the whole follow-up period.

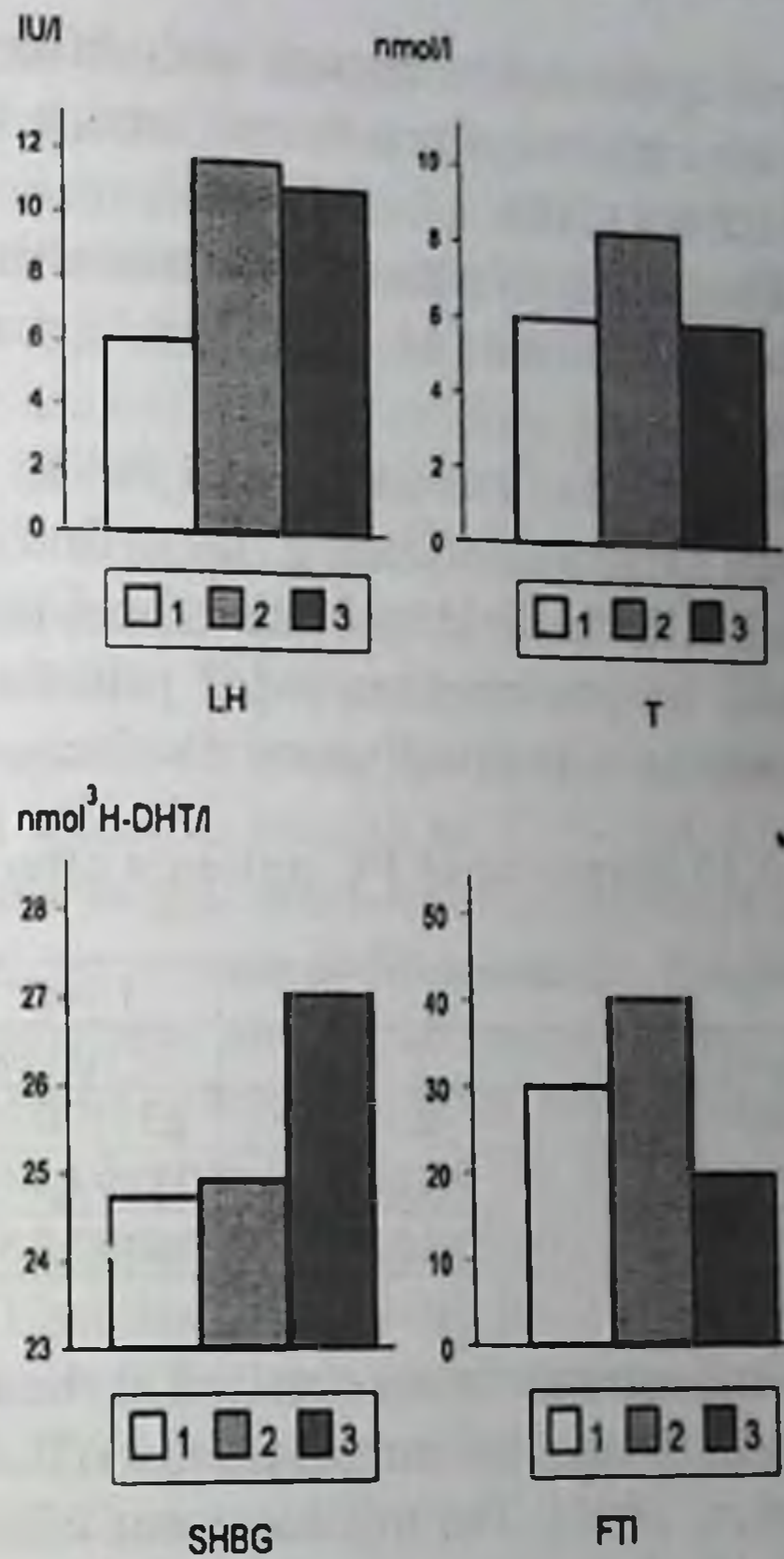


Fig. 4.13. Blood plasma hormone and SHBG levels in Nifolide-treated patients. 1, initial values; 2, 3 months later; 3, 6 months later

During the first 3 months of treatment partial remission was observed in 48 patients (70.6 %), 13 (19.1 %) of them had stage T₃₋₄N₀₋₁M₁, stabilization was reported in 20 (29.4 %) patients. The general state and urination improved, bone pain alleviated. But after 3-4 months of drug administration in 23 patients (33.8 %) there was an aggravation. Thus by the end of the treatment in 7 patients (10.3 %) the results were evaluated as partial remission, in 38 (55.9 %) stabilization, in 23 (33.8 %) as disease progression. Positive clinical effect that was observed during first 2-3 months is explained by the blockade of androgen receptors in target tissues but later on the disease may progress.

3-6 months after the treatment with Nifolide was over stabilization was observed in 22 patients (32.4 %), progression in 46 (67.6 %). In 4 patients there was acute ischuria, in another 4 patients signs of chronic pyelonephritis (with frequent recurrences in 2 and hydronephrosis in one patient). In one patient spinal metastases were found. Later on all patients

received maintenance therapy with different estrogenic drugs according to patterns given in the previous section where results of treatment with Synestrol are given.

The quality of patients' life scored as follows: 1 in 10 patients (29.4 %), 2 in 30 patients (44.1 %), 3 in 13 patients (19.1 %), 4 in 5 patients (7.4%).

Remote results of treatment for up to 3 years were studied in all patients (Table 4.12). During this period 20 persons died. Nine of them had stage IV, multiple metastases, in 6 patients with stages I-II generalization of the process occurred, 5 patients died of co-existent pathology (cardiovascular and respiratory insufficiency).

Table 4.13. Survival of PC patients after monotherapy with Niftolide

Stage	Number of patients	Survival of patients		
		1 year	2 years	3 years
I ($T_1N_0M_0$)	2	2 (100 %)	2 (100 %)	2 (100 %)
II ($T_1N_0M_0$)	25	25 (100 %)	23 (92 %)	20 (80 %)
III ($T_3N_{0-1}M_0$)	23	23 (93,3 %)	21 (91,3 %)	17 (73,9 %)
IV ($T_{3-4}N_{0-1}M_1$)	18	14 (77,7 %)	10 (55,5 %)	9 (50 %)

Similar results were obtained at the Department of Oncurology at the Cancer Research Centre (Moscow) (Bukharkin et al., 1994; Matveyev, Bukharkin, 1994). The treatment was effective in 75 % of cases (partial tumor and metastases regression in 30 %, stabilization in 45 %), in 25 % of patients the disease progressed. Low drug toxicity, absence of severe side effects were confirmed.

Another drug of non-steroid antiandrogen is Casodex (bicalutamide). Its affinity for androgen receptors is higher than in other antiandrogens (it is 4-fold that of flutamide). It rarely causes complications mentioned above, hence, it is rarely withdrawn (Eri, Tveter, 1993, 1994; Schellhammer et al., 1995; Soloway et al., 1995).

Prognostic factors for Casodex prescription as well as for other «pure» antiandrogens to patients with PC D₂ stage include functional state of a patient, PC stage, changes in bones as shown by scan data, hemoglobin content before treatment, acid and alkaline phosphatase levels, PSA content. Serum testosterone level is not considered an important

prognostic factor in antiandrogen therapy though its lowering to post-castration level following other modalities of androgen blockade was considered most important prognostic factor (Matzkin et al., 1993).

First randomized studies of bicalutamide effectiveness in monotherapy showed that progression-free time and mean survival rate following treatment with bicalutamide are comparable to those after castration (Decensi et al., 1991; Bales et al., 1995; Blackledge et al., 1995). Chodak et al. (1995) presented the results of open randomized study of 234 patients who were treated with bicalutamide (50 mg/day) and 243 orchiectomized or goserelin-treated patients. The treatment, on the average, lasted 39 weeks for the first group and 42 weeks for the second group of patients. The treatment was not effective enough in 53 % and 42 % of observations, disease progression was reported in 43 % and 33 % of cases. Bicalutamide was well tolerated. As compared to castration, hot flushes were less frequent, breast tenderness and gynecomasty were more common. It might be concluded that bicalutamide in the applied dose was less effective than orchiectomy but higher quality of life and absence of manifested side effects allow considering it an effective drug. When comparing the effectiveness of Casodex (50 mg/day for 24 weeks) with placebo in patients with progressive PC it was shown that prostatic size diminishes by 26.4 % versus 3.7 % after placebo, urination parameters and other symptoms improve (Eri, Tveter, 1993).

Schellhammer et al. (1995) who compared the effect of Casodex to that of Flucinom in patients with newly diagnosed advanced PC in randomized study did not find statistically significant difference in any criterion: «time before therapeutic failure», survival, time of primary response, PSA level, quality of life (Crawford et al., 1995).

When the effectiveness of different doses of Casodex was studied it was established that the objective improvement directly depended on the increased dose while the subjective improvement did not depend on it (in a dose of 50 mg/day subjective improvement is mentioned by 53 % of patients, in a dose of 200 mg/day, by 50 %) (Tucker, 1990; Thorti, 1996). The effectiveness of the drug is also judged by the PSA changes. After 3 months its level decreases in 99 % of patients, to normal values in 70 % (Tversen, 1994). After 10 months of Casodex use in monotherapy there is a significant 1.6-1.8-fold increase of blood testosterone and prolactin levels that persist till the end of treatment, it explains preserved potency

and libido in 75 % of patients (Kolvenbag, 1996). Nowadays it is preferred to use Casodex in combined androgen blockade.

The third widely used drug, which belongs to non-steroid antiandrogen family, is Anandron (nilutamide). Faure et al. (1983) were the first to report on 3 castrated patients with PC relapse who were treated with the drug. In 2 patients short-term (4 and 5 months) remission was observed, in one patient more prolonged stabilization of the tumor size was observed. According to summarized information, partial remission in patients with disseminated PC is observed in 46-58 % of cases, stabilization in 34-50 %, disease progression in 4-8 % of cases (Matveyev, Bukharkin, 1994). In our practice, following 12-month treatment partial remission was found in 50 % of patients, stabilization in 40 %, progression in 10 %. The improvement of the quality of life was similar to that observed in flutamide-treated patients.

When studying hormone levels in patients with clinical stage IV following orchiectomy and further 6-month treatment with Anandron, it was established that testosterone level decreased while gonadotropin level increased, prolactin and cortisol levels remained practically without changes (Sergeyeva et al., 1997). Retrospective analysis of the dynamics of these parameters depending on the clinical course of PC showed that in patients with prolonged remission testosterone level that decreased after the onset of treatment, remained low during the entire follow-up period while in patients with disease progression it showed a tendency to growth. Gonadotropic hormones contents were different only during the first month of treatment: under the favourable course of the disease it decreased and remained low, in progression it increased dramatically and then lowered. Prolactin level in both groups was the same. Cortisol concentration under favourable course first decreased keeping to this level and only a year later it showed a tendency to rise, under unfavourable course its concentration fluctuated within a wide range and only a year later it showed a distinct tendency to lowering.

According to authors who used Anandron in combined treatment of metastatic PC worsening of vision was noted in 30 % of patients, it was manifested in disorders of dark adaptation and color vision, nausea and vomiting nearly in 25 % of cases, alcohol intolerance in 20-30 %, pulmonary complications in 2 % (Beland, 1991; Decensi et al., 1991; Pfitzenmeyer et al., 1992). A case of fulminant hepatitis was also described. It occurred after 52-day treatment with a fatal outcome 6 days after icterus, though it might be caused by phenobarbital.

It should be emphasized that Anandron seems to be more effective in PC patients with recurrences in case of prior estrogen therapy. However higher doses of the drug should be taken than after orchiectomy because in estrogen-treated patients concentration of androgen receptors in the tumor tissue is higher than after castration.

When comparing the results of monotherapy with Anandron and castration in PC patients with bone metastases a favourable effect was observed in 92 % of patients after antiandrogen administration versus 72 % post-castration (Namer et al., 1988). After combined treatment orchiectomy + Anandron (300 mg/day) the effect was achieved in 84 % of patients versus 61 % after castration + placebo; median survival made 23 and 18 months, respectively (Belanger et al., 1988).

The advantage of Casodex and Anandron is their longer half-life (16 h and 56 h versus 5.2 h for flutamide), that is why they may be taken only once a day, which is especially important for old people (Cockshott et al., 1990; 1993; Denis, 1995; Furr, Tucker, 1995). Besides, single administration not only facilitates androgen blockade but also allows avoiding complications and side effects typical for drug fractional administration (McLeod et al., 1995).

However side effects, which occur after Anandron administration in 70 % of patients require discontinuation of the treatment. That is why since 1983 many specialists gave up Anandron having substituted it with flutamide (Labrie et al., 1985) though some authors still used it (Raynaud et al., 1986; Raynaud, Ojasoo, 1986).

A comparative study of results of monotherapy with prednisolone or flutamide in hormone-resistant metastatic PC is worth mentioning. The effectiveness of drugs was judged upon by the general state of patients, how the drugs were tolerated and the necessity to take analgetics. Equally favourable results were obtained in both groups though after prednisolone the patients more often mentioned alleviation of pain. Mean survival in both groups made 32.9 weeks, 35 % showed more than a year survival. A decrease in PSA following treatment with prednisolone was observed in 55 % of patients, after treatment with flutamide it made 50 % with its increased initial level in 54 % and 52 %, respectively (Datta et al., 1997).

This data confirms the results that had been published earlier. They deal with dexamethasone (0.75 mg twice a day) used in monotherapy in patients with advanced PC who had been orchiectomized: in the majority of patients PSA decreased and in overwhelming majority it decreased by more than 50 %. In every fourth patient with a 50% decrease of PSA,

regression of metastases was observed, in every fourth-fifth patient process stabilization was noted and only in every third patient disease progression was found (Storlie et al, 1995).

A combination of flutamide and ketoconazole was found to be effective in PC metastases to the meninges. After treatment symptoms disappeared, PSA decreased and was within normal range for more than 6 months, tumor cells were not found in the cerebrospinal fluid at repeated analysis (Mencel et al., 1994).

4.6. Steroid antiandrogens

Steroid antiandrogens were found among progestin derivatives, they exert dual effect: on the one hand they block active androgens of testicular and extratesticular origin, on the other hand they decrease secretion of testicular androgens by inhibiting LH production, it facilitates their use in monotherapy of progressive PC. Typical steroid antiandrogens are cyproterone acetate (CPA, Androcur) medroxyprogesterone acetate, megestrol acetate.

In 1966 Scott and Schrimmer for the first time used CPA for managing progressive PC. Later on the antiandrogen therapeutic effect in PC stages III-IV was confirmed by numerous observations. Data on the effectiveness of monotherapy with Androcur is summarized in Table 4.14 (Reznikov, Varga, 1988).

Table 4.14. The effectiveness of treating PC stages III-IV* with cyproterone acetate

Daily dose, mg	Number of treated patients	Number of patients with regression or stabilization	Reference
250	10	7	Scott W., Schrimmer H., (1966)
200-250	48	25	Wein A., Murphy J., (1973)
300	28	19	Smith R. et al., (1973)
300	21	16	Jacobi G. et al., (1982)

*correspond to stages C and D

Chapter 2 gives standard schemes of therapy with Androcur, however the optimal dose of CPA has not been established yet. The clinical experience shows that higher doses of Androcur (more than 250 mg/day) facilitate more pronounced androgen deprivation but at the same time they more often cause side effects (hepatotoxicity) (Sivkov et al., 1996). Most authors believe that the optimal dose for non-orchietomized patients is

300 mg/day. After Androcur administration to orchiectomized patients in a dose of 100 mg/day pain alleviation was observed in 92 % of cases, alleviation of edema of the legs in 33 % of cases, moderate positive changes in lung and bone metastases were found (Bracci, 1979).

Similar results were obtained when higher doses were applied (250 mg/day). After 3-month treatment testosterone levels in blood plasma decreased considerably (from 4.3 to 1.1 ng/ml) and remained at this level 6 months later (Sciarra et al., 1990). There was a clear difference in treating with Androcur newly treated patients and those who earlier underwent estrogen therapy: survival of treated patients with PC stages II-IV is significantly higher than in those treated with estrogenic drugs (Moise, 1985). Table 4.15 gives the results of clinical study (Wein, Murphy, 1973) with a thorough analysis of objective and subjective factors. It is obvious that in non-treated patients with C and D stages remission was achieved in 64 % of cases while in previously treated patients this figure is 45 %.

Table 4.15. Results of treatment of patients with all PC stages with cyproterone acetate

Stage	Number of patients	Mean age, years	Diminishing the size and tissue density of the prostate	Normalization of increased level of acid phosphatase	Pain alleviation	Improved urinary outflow
A, B	7	70	6/7	No increase	No pain	2/5
C	18	68	11/17	6/7	3/6	5/9
C*	7	74	3/7	2/2	2/3	1/3
D	8	63	5/8	3/5	4/5	1/3
D*	15	66	6/13	1/4	4/10	1/4
Total	55	68	31/52	12/18	13/24	10/21

CPA was administered in a dose of 200-250 mg/day. The numerator shows the number of patients with this symptom, the denominator gives the number of patients examined for this symptom. *Stage in patients who previously had received estrogens, castration or both.

Multicentre randomized study, which began in 1977 in 18 clinics in Europe, showed that CPA produces a manifested local effect: tumor regression in 66.7 % of patients and elimination of urination obstruction in 48 %.

When effectiveness of treatment with CPA, orchiectomy and their combination and with estrogens (DES, estradiol andecylate) was studied, no significant difference in general clinical response, time of objective

response, survival, time of disease progression and direct local effect on the prostate was found (Kravchuk et al., 1996; Beurton et al., 1987; Sciarra et al., 1990; Dracos, 1992).

Treatment with Androcur and flutamide in conventional standard doses (Androcur, 300 mg/day in tablets and one injection of Androcur depot 300 mg per week, flutamide, 750 mg/day in tablets) gives similar results. No significant difference in progression-free time and life span in both groups were found, however the incidence of complications was different. Painful gynecomasty was observed in 7.5 % of Androcur-treated patients and in 45.4 % after treatment with flutamide. Diarrhea was observed in 9.7 % and 23.1 %, nausea in 6 % and 19.2 %, hepatic dysfunction in 4.5 % and 10 %, thrombosis and embolism in 4.5 % and 0 %, respectively. It was necessary to discontinue the treatment because of side effects in 4.7 % from the first group and in 12.8 % in the second group, including those with hepatotoxicity 1.3 % and 5.4 %, gastrointestinal disorders in 0.7 % and 4.7 %, painful gynecomasty in 0 % and 1.35 %, vascular thrombosis in 0.7 % and 0 %, for other reasons in 2 % and 1.35 %, respectively. Less frequent complications, especially gastrointestinal, after CPA administration are explained by different pharmacological properties of CPA and flutamide and also by different routes of administration in case of using Androcur depot (Radelmayer, 1996).

A comparative evaluation of side effects caused by Androcur and flutamide showed that a decrease of potency is less typical for non-steroid androgens as compared to steroid ones (Lund, Rasmussen, 1988; Midliary, 1992). After treatment with flutamide potency and libido are preserved in 80 % of patients (Brogden, Clissold, 1989). But if nonsteroid antiandrogens were used in combination with castration, libido and potency preserved for similar periods.

Impotence and decrease of libido following Androcur treatment as a result of decreased plasma testosterone level and of progestin activity is obvious in 86 % of patients. Other side effects (hepatitis, hepatic tumors, hepatic dysfunction, gynecomasty and thromboembolism) are less frequent. Besides, because of progestin activity of Androcur hair shedding, increase of body weight, fatigability, gynecomasty, decreased adrenocortical function, changed carbohydrate metabolism are reported (Dracos, 1992; Barradel, Faulds, 1994; Rabe et al., 1994; Watanabe et al., 1994) but patients rarely experience hot flushes, that is why in order to prevent postcastration syndrome Androcur (150-300 mg/day) is prescribed to patients who are supposed to undergo surgical or pharmacological castration (de Voogt et al., 1990). In order to prevent hepatotoxicity

it is recommended that the drug is taken in short courses together with LHRH agonist and only to patients in whom no other drug is effective (WHO Drug Inf. 1995).

We also studied Androcur effectiveness in monotherapy of PC (Vozianov et al., 1996). The study included 57 patients aged 40 and older with PC stages I-IV (T₁₋₄N₀₋₁M₀₋₁).

Histologically, small-cell adenocarcinoma was diagnosed in 10 cases (17.3 %), cribriform clear cell carcinoma in 10 (17.5 %), dark-cell adenocarcinoma in 7 (12.3 %), highly differentiated in 12 (21.1 %), poorly differentiated in 6 (10.5 %), adenoma with malignization in 8 (14.0 %), scirrhous cancer in one patient (1,8 %), in situ cancer in 3 patients (5.3 %).

Androcur was prescribed in a dose of 100 mg (2 tablets) twice a day (a daily dose of 200 mg). Duration of treatment was 6 months.

The results were evaluated 3-6 months later after the onset of treatment. General state, data on digital rectal examination, ultrasound study of the prostate, uroflowmetry, sex steroid assays were taken into consideration.

During the first months of treatment the majority of patients in this group had improved general state, less frequent or even eliminated dysuria, nocturia decreased to 1-3 per night, uroflowmetry parameters improved. Only 12 patients (21.1 %) did not demonstrate significant changes of the general state over the treatment period.

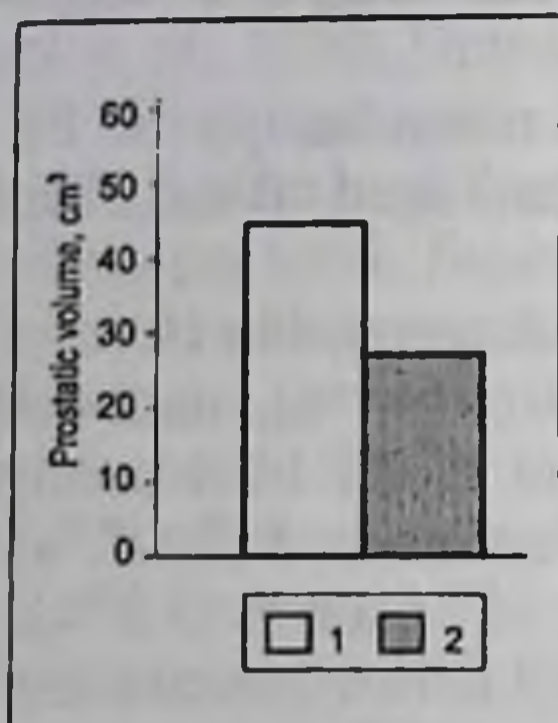
Side effects included depression in 3 patients (5.3 %), epigastric pain in one patient (1.7 %) in the first days of treatment. These manifestations eliminated after 3-5 days of drug withdrawal. In 10 patients moderate gynecomasty, in all patients breast tenderness, in 2 men (3.5 %) hematuria was observed. In 3 patients (5.3 %) cardiovascular complications and decreased potency in 3 patients (5.3 %) were reported.

The results of digital rectal and ultrasonic examination of the prostate usually were the same and confirmed diminishing of the prostatic size. Dynamics of changes in the prostatic size is given in Table 4.15 and Fig. 4.14.

Table 4.16. Changes in the prostatic size under treatment with Androcur (Means ± S.E.)

Prostatic size	Before treatment	After treatment
Linear measurements, cm		4,00±0,2*
frontal	4,80±0,2	3,51±0,2*
sagittal	4,37±0,2	3,82±0,2
oblique	4,12±0,2	26,60±0,46*
Volume, cm ³	43,29±0,41	

* $p < 0.05$ as compared to pretreatment values



The results of uroflowmetry before and after treatment with Androcur are given in Table 4.17. They show that average parameters of urination rate improved though did not reach the significance level (Fig. 4.15)

Fig. 4.14. The prostatic volume in PC patients before (1) and after treatment with Androcur (2).

Table 4.17. The results of UFM in Androcur-treated PC patients (Means \pm S.E.)

Parameter	Before treatment	After treatment
T_Q, s	$31,47 \pm 2,70$	$26,97 \pm 2,54$
T_{Qmax}, s	$8,76 \pm 0,85$	$8,33 \pm 0,88$
$Q_{max}, ml/s$	$11,82 \pm 1,20$	$14,78 \pm 1,68$
$Q_{aver}, ml/S$	$6,39 \pm 0,71$	$8,72 \pm 0,93$

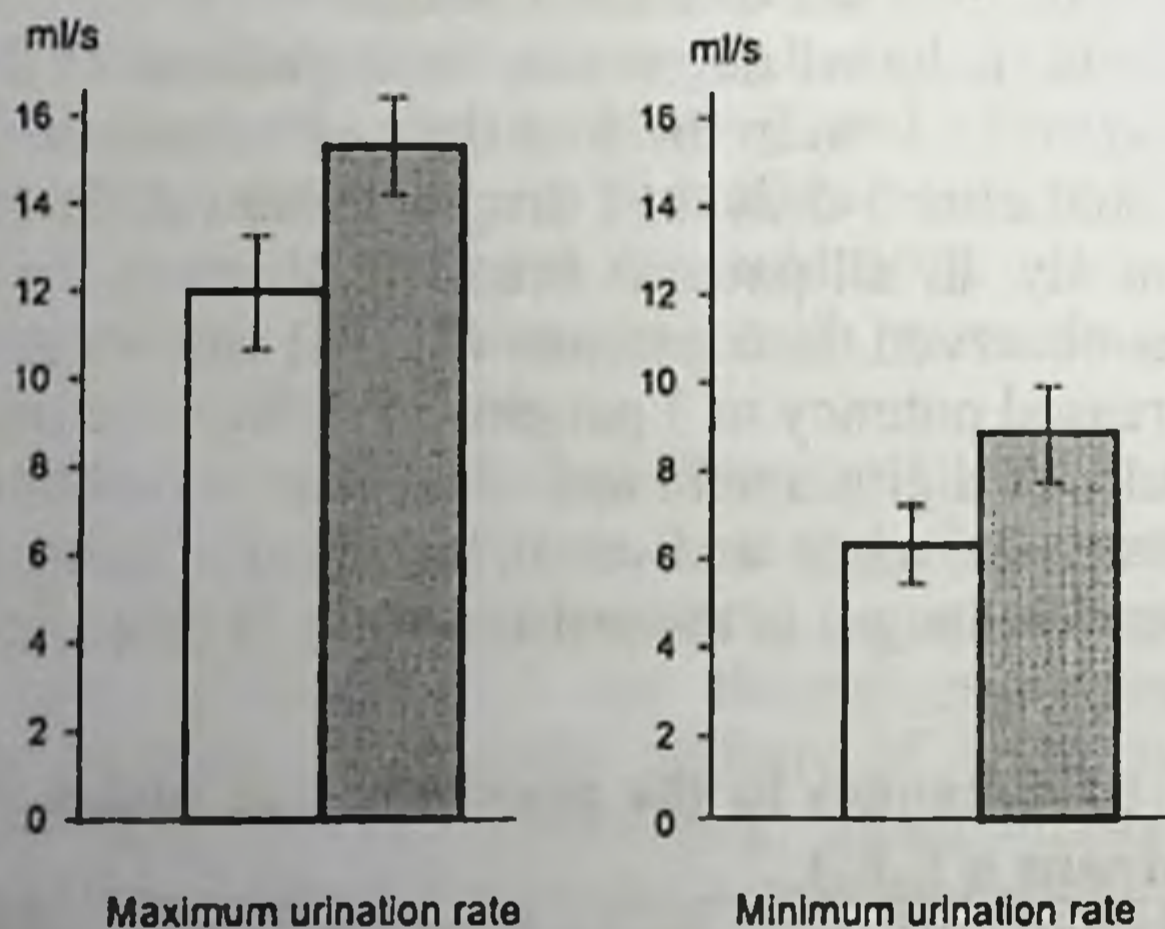


Fig. 4.15. Uroflowmetry data in PC patients before (open bars) and after treatment with Androcur (shaded bars)

Hormonal studies included assays of blood plasma LH, testosterone, DHT, SHBG and free testosterone index before, during and after treatment (Table 4.18).

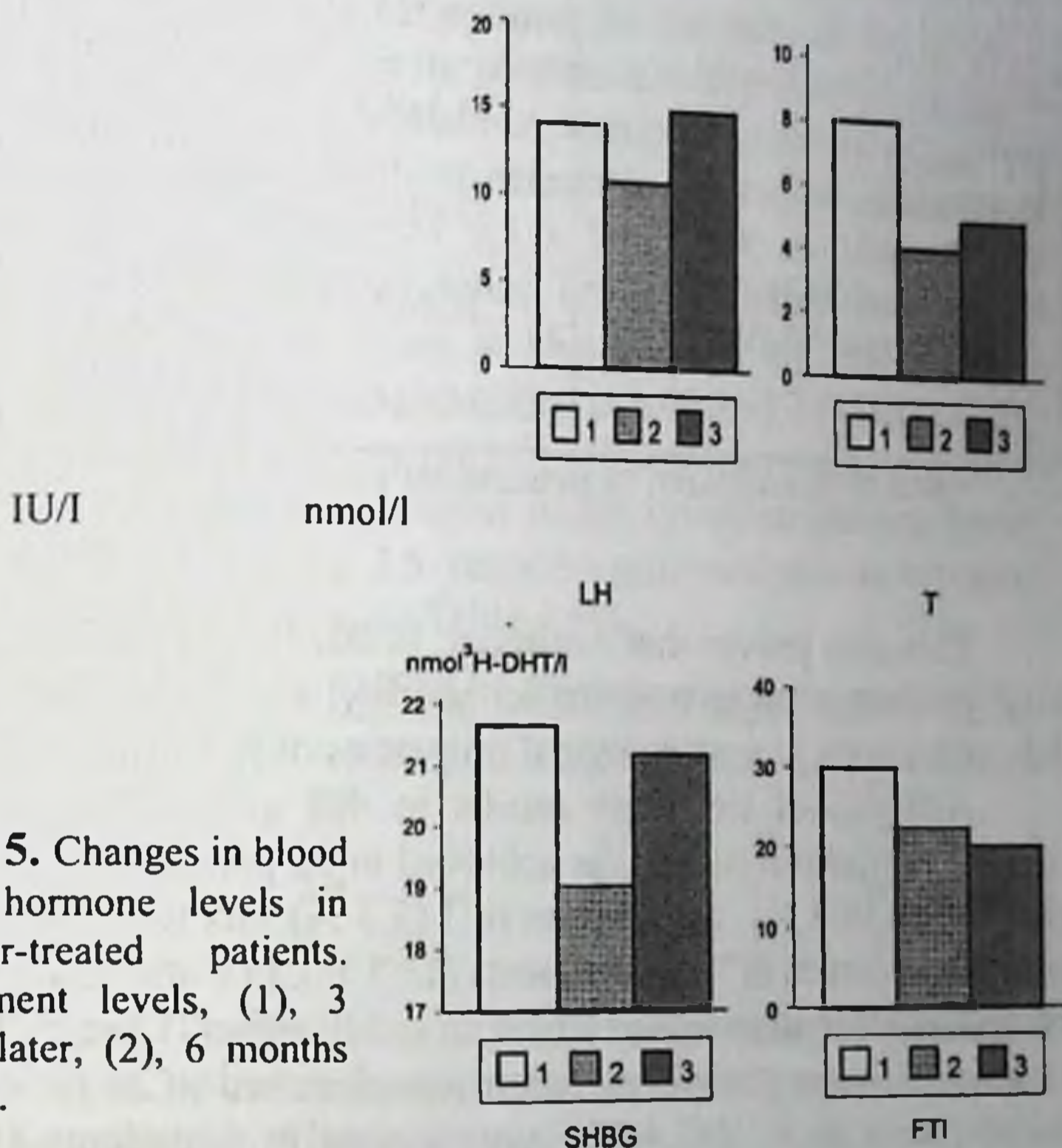


Fig. 4.15. Changes in blood plasma hormone levels in Androcur-treated patients. Pretreatment levels, (1), 3 months later, (2), 6 months later, (3).

The studies showed that testosterone and DHT levels decreased significantly during the whole follow-up period. There was a twofold decrease of testosterone level and 2.3-fold decrease of DHT content as compared to basal values (Fig. 4.15).

Average LH and FTI values demonstrated a trend to lowering. These changes reached the significance level when individual fluctuations of hormone contents were taken into consideration. LH level decreased following 3-month treatment and restored to initial values after 6 months of Androcur administration. FTI was decreased during the whole follow-up period. Androcur did not effect blood plasma SHBG level.

Table 4.18. Hormonal status in Androcur-treated PC patients (Means \pm S.E.)

Parameter	Pretreatment level	3 months later	6 months later
LH, IU/l		11,0 \pm 1,0	15,7 \pm 1,9
Δ LH, IU/l	14,2 \pm 1,3	-3,4 \pm 1,3*	0,3 \pm 2,2
T, nmol/l		4,2 \pm 0,4*	5,1 \pm 0,5*
Δ T, nmol/l	8,3 \pm 0,5	-4,1 \pm 0,6*	-3,0 \pm 0,6*
DHT, nmol/l		0,9 \pm 0,1*	1,0 \pm 0,1*
Δ DHT, nmol/l	2,0 \pm 0,2	1,1 \pm 0,2*	1,1 \pm 0,2*
SHBG, nmol 3 H-DHT/l		19,0 \pm 2,4	21,4 \pm 2,6
Δ SHBG, nmol 3 H-DHT/l	21,8 \pm 2,2	-3,4 \pm 2,1	-0,4 \pm 2,4
FTI		23,3 \pm 6,0	24,2 \pm 4,8
Δ FTI	36,6 \pm 4,4	-11,8 \pm 3,9*	-12,4 \pm 3,0*

*p < 0.05 as compared to pretreatment value

This data proves that Androcur, in addition to antiandrogenic effect, also possesses antigonadotropic activity, this being in line with the information on pharmacological properties of this drug.

Analysis of treatment results in this group showed that after 3 months partial remission was achieved in 33 persons (57.9 %), stabilization in 21 (36.8 %), progression in 3 (5.3 %). Six months later partial remission occurred in 7 more patients (12.3 %), in some patients with partial remission their state was assessed as stabilization. Thus by the end of the treatment course partial remission was observed in 24 patients (42.1 %), stabilization in 27 (47.4 %), progression in 6 patients (10.5%). In 3 patients (5.3 %) after a short-term improvement bone metastases were revealed. One patient died of process generalization 10 months later.

The difference in the indices of partial remission and stabilization 3 and 6 months later is explained by the fact that in some patients their state improved during the first 3 months, and later on it stabilized and remained without major changes, while in some patients whose state stabilized during the first 3 months a relapse of the disease occurred.

The quality of life scored 1 in 23 patients (40.4 %), 2 in 28 (49.1 %), 3 in 6 patients (10.5 %).

It should be mentioned that progression occurred mainly (4 cases out of 6) in patients with poorly differentiated PC. On the one hand, it confirms the statement that hormone sensitivity of the tumor depends on

the degree of its differentiation, on the other hand, it proves rather high clinical effectiveness of Androcur. To illustrate this here are the extracts from case reports.

Patient K., 68 years old, complained of thin flow frequent urination, nocturia - 6-8 times per night. In his opinion, he has been ill for about 3 months. At digital rectal examination the prostate is enlarged, solid, contours are not clearly cut. The right lobe is tuberos, interlobar groove is smoothed out. The neighbouring tissue is without detectable infiltration. Ultrasound examination shows prostatic size of 5.5 x 5.0 x 4.8 cm, hyper- and hypoechoic areas are detected in both lobes. Transrectal puncture biopsy is performed. Alveolar adenocarcinoma is identified by pathologist. The diagnosis: PC T₃N_xM₀. Androcur is prescribed in a dose of 2 tablets twice a day for 6 months. During the first month of treatment nocturia improved to 2-3 times, then the urinary stream became wider, urination became easier. Patient's state stabilized. During 2.5 years no progression was revealed. UFM shows improved urodynamics (Table 4.19).

Table 4.19. The results of UFM in Androcur-treated patient K.

Parameter	Before treatment	3 months later	6 months later
T_0, S	28,0	26,0	35,0
T_{Qmax}, S	7,0	9,0	7,0
$Q_{max}, ml/S$	7,4	7,4	10,9
$Q_{aver}, ml/s$	4,1	4,5	8,1

Patient R., aged 70, visited the urologist complaining of weakened urinary flow, nocturia 3-5 times per night, the feeling of incomplete emptying of the urinary bladder. After examination the clinical diagnosis was: benign hyperplasia of the prostate, stage II. Prostatectomy was performed, pathohistological diagnosis was poorly differentiated adenocarcinoma. The final diagnosis was PC T₂N_xM₀. The patient was prescribed Androcur for 6 months. During the first 3 months the state improved, prostatic size diminished from 4.0x4.0x3.8 to 2.6x2.2x3.0 cm after treatment. Before treatment solid areas were detectable in the prostate, after 3 months the prostate had homogenous structure. Nocturia decreased to 2 times, urination improved. UFM data is given in Table 4.20. Improvement of urination parameters is obvious: maximum urination rate increased from 4.2 to 14.4 ml/s, an average rate from 2.7 to 8.5 ml/s. During the next 3 months the patient's state stabilized.

Table 4.20. The results of UFM in Androcur-treated patient R.

Parameter	Before treatment	3 months later	6 months later
T_0, S	27,0	41,0	35,0
$T_{Q_{max}}, S$	21,0	19,0	15,0
$Q_{max}, ml/s$	4,2	14,4	9,1
$Q_{aver}, ml/s$	2,7	8,5	6,1

When the treatment was over the patients were followed up at the out-patient clinic of the Kiev City Oncologic Centre. The further treatment of these patients depended on their state.

In 17 out of 24 patients (70.8 %) in whom after 6 months of treatment the result was evaluated as partial remission, 12 months later their state was assessed as stabilization, in 6 patients (25.0 %) their state worsened, one patient died. In all 6 patients with aggravation local enlargement of the tumor occurred, it was detectable at rectal and ultrasonic examination, in 3 cases it was accompanied by aggravated dysuria, in 2 cases by acute urine retention, in one case by general weakness, nausea, pain in the hepatic area. In 3 of these patients dysuria manifested 2.5 months after Androcur withdrawal, that is why they were prescribed Synestroi and prednisolone according to the conventional protocol, after it their state stabilized. In 3 patients following stabilization during treatment with Androcur acute retention of urination came back, they were prescribed Synestroi and then cryodestruction of the tumor was performed (pathohistological diagnosis was poorly differentiated adenocarcinoma). After that urination restored and the state stabilized.

In 18 out of 27 patients (66.7 %) in whom stabilization of their state was established, 6 months later stabilization of the process was obvious. In 9 patients their state aggravated, it was manifested in the enlarged prostate and increased dysuria (4 patients), weakness and signs of intoxication (3 patients), hydronephrotic transformation of the kidneys (caused by tumor infiltration in the vesical triangle, Lieutaud's trigone) and aggravated signs of chronic renal insufficiency (2 patients).

Results of 6-month follow-up after treatment with Androcur showed stabilization in 35 patients (61.4 %), aggravation in 21 patients (36.8 %). One patient (1.8 %) died 10 months after the onset of treatment because of process generalization.

Long-term results were studied for 3 years. The survival rate is given in Table 4.21.

Table 4.21. The survival rate in PC patients after treatment with Androcur

Stage	Number of patients	Survival of patients		
		1 year	2 years	3 years
I (T ₁ N ₀ M ₀)	9	9(100%)	9 (100%)	9 (100%)
II (T ₁ N ₀ M ₀)	28	28 (100%)	28 (97,5 %)	25 (89,3 %)
III (T ₃ N ₀₋₁ M ₀)	16	16(100%)	14 (87,5%)	12 (75,0%)
IV (T ₃₋₄ N ₀₋₁ M _i)	4	4 (100%)	-	-

Thus, during 3 years 11 patients died. Out of 3 patients with stage II who died 3 years later, 2 patients died because of process progression and one patient died of carcinoma of the stomach. All patients with metastases (stage IV) died within a year of disease progression and generalization, aggravated renal insufficiency and intoxication.

Another steroid antiandrogen similar in its structure to CPA is chloromadinone acetate. This drug inhibits pituitary gonadotropic function, decreases blood plasma testosterone level and intervenes in realization of biological effect of male sex hormone on the cellular level by competing with androgen receptors and lessening 5 α -DHT formation. It is used both in monotherapy and in combination with chemical agents. Comparison of the results of monotherapy with chloromadinone acetate and flutamide in PC patients shows equal lowering of PSA level and comparable objective response. Both compounds were well tolerated but in some patients the treatment was accompanied by diarrhea, hepatotoxicity and affected libido and potency. When chloromadinone acetate is used, side effects that are typical for cyproterone acetate and steroid antiandrogens are observed, that is why in some cases dose reduction is required (Akaza et al., 1993; McRawa et al., 1994). As compared to estrogens, chloromadinone acetate causes gynecomasty less often, cardiovascular complications and hepatotoxicity occur as often as in estrogen therapy.

Similar results on therapeutic effectiveness, incidence, type of complications and side effects are observed after treating PC patients with multiple metastases with megestrol acetate.

In 1985 Heller was the first to substantiate the use of megestrol acetate for treating PC. Megestrol acetate inhibits androgen production both in the testes and in the adrenals and blocks their receptors. The drug was prescribed for oral administration in a dose of 160 mg/day to patients

in whom orchiectomy or DES proved ineffective. Following 6-week treatment in 3.6 % of patients partial remission was observed, in 25 % stabilization occurred. Toxicity was insignificant and in 17.8 % of patients it was manifested in transient increase of hepatic enzyme contents in blood, in 10.7 % in hot flushes. The effectiveness of megestrol acetate was lower in patients who underwent prior treatment with hormonal drugs (Crombie et al., 1987).

Study by Daniel et al. (1990) showed that though after treatment with megestrol no objective improvement occurred, subjective state of patients improved, in some patients tumor progression delayed by 6-12 months, prostatic acid phosphatase level decreased by 40-50 %. So this drug might be considered a reserve drug (second line therapy).

Basing on given clinical data it has been concluded that steroid antiandrogens in their effectiveness in PC do not yield to non-steroid antiandrogens and estrogens and may be regarded an alternative treatment (Smith, 1995).

An undoubted advantage of antiandrogens is low frequency of side effects and severe complications, cardiovascular first of all. It is essential because in the view of many oncologists about a half of patients die during estrogen therapy not of primary disease but of cardiovascular insufficiency (Smith, 1995). And still there is certain caution as to side effects under treatment with steroid and non-steroid antiandrogens. Even weak androgenic activity that remains in treatment with CPA limits its therapeutical possibilities since for stimulation of prostatic tumor growth even minimal androgen effect is sufficient (Neumann, 1987).

4.7. Other drugs

More than 10 years ago an attempt was made to treat metastatic PC with tamoxifen, non-steroid synthetic antiestrogenic drug, and aminoglutetimide (Orimeten, Cytadren), a drug that blocks steroid biosynthesis in the adrenal glands at the stage of cholesterol conversion into pregnenolone. The premise for tamoxifen treatment was clinical experience of effective therapy of advanced breast cancer and also the fact that PC is also a hormone-dependent disease. But a comprehensive analysis showed that in none case the tumor size decreased, on the contrary, it developed in some patients, and it was concluded that tamoxifen did not exert therapeutic activity in PC (Horton et al., 1988).

Orimeten was prescribed following orchiectomy as well. 12 weeks after the onset of treatment in 25 % of patients alleviation of pain occurred and for a prolonged period general state improved, in 21.4 % process stabilization was noted. No correlation between therapeutic effect and testosterone, DES, estradiol and prolactin levels was found. Unfortunately, in 96.4 % of cases side effects occurred (depression, nausea, insomnia, and in 21 % of patients treatment with Orimeten was stopped. And still, despite its toxicity the drug might be beneficial in treating hormone-resistant advanced PC (Harnett et al, 1987).

One of the drugs for treating PC is ketoconazole, a well-known antimycotic drug. In 1984, quite by chance it was discovered that ketoconazole oral administration blocked synthesis of adrenal and testicular androgens, in animal research it was shown that after drug administration blood plasma free testosterone level decreases by 18 %, that of 17β - estradiol by 60 %. This is achieved by direct effect on cytochrome P450 and 17α - and 20α -dihydroxyprogesterone conversion though it was not established exactly how ketoconazole itself effects tumor cells (Flamm et al., 1988, Witjes et al., 1989).

The results of ketoconazole treatment are controversial. Usually large doses of the drug are prescribed (600-1200 mg/day) to patients with advanced metastatic disease not responsive to hormonal treatment when no other more effective therapy is available.

In some patients ketoconazole causes subjective improvement though it does not bring about objective remission. The effectiveness of ketoconazole treatment is higher in newly treated patients who have not received any treatment before, and an average survival in these patients makes up to 73.3 weeks (de Coster et al., 1986; Vanuytsel et al., 1987; Johnson et al., 1988; Moffat et al., 1988; Eichenberger, Trachtenberg, 1989).

Ketoconazole is indicated to patients with metastatic PC with disseminated intravascular syndrome, acute paraparesis or paraplegia, life-threatening complications, in cases of surgical castration or when the diagnosis needs histological confirmation, in patients in whom biopsy or orchiectomy cannot be performed because of hemorrhage. The advisability of such treatment is also determined by the fact that testosterone level decreases 48 h after ketoconazole administration while after estrogen administration it happens only 10-14 days later, and spontaneous

hemorrhage in dissemination syndrome in PC patients of ketoconazole administration can be stopped within 48 h (Lowe, Somers, 1987).

At the same time treatment with ketoconazole was ineffective in 57 % of patients, in 66.7 % side effects were observed, in many patients it was impossible to keep blood plasma testosterone level at low level that is why this drug is not widely applied in clinical practice.

COMBINED ENDOCRINE THERAPY OF PROSTATE CANCER

Various modalities of hormonal monotherapy of PC, their advantages and disadvantages have been reviewed in the previous chapter. None of the mentioned methods gives a total androgen blockade that determines the effectiveness of palliative therapy in PC patients.

This is the reason why in the last decades most clinicians prefer combined treatment methods that include orchiectomy in combination with estrogens, antiandrogens, corticosteroids or LHRH analogues, with antiandrogens. Combined treatment facilitates complete androgen blockade, and this gives positive results in more than 75-80 % of patients, improvement of the quality of life, less incidence of complications though survival and progression-free time following combined treatment are almost the same as after monotherapy as shown by many authors (Gonzalez et al., 1997).

5.1. Castration and estrogens

Until recently orchiectomy in combination with estrogens has been widely used for of PC treatment. This method is more effective than orchiectomy or estrogen therapy alone (Servadio et al., 1987). Testosterone level in patients with PC stages III-IV following orchiectomy and maximum doses of Synestrol, 1, 6 and 12 months after the onset of treatment decreased to 2.0 nmol/l (with the maintenance estrogen therapy) with the pretreatment level of 19.0 ± 2.0 nmol/l. Only in some patients it increased up to 5 nmol/l and this required a higher estrogen dose. The tumor size decreased more than by 50 %, the general state normalized. After treatment

with Synestrol alone in the same period testosterone concentration decreased to 3-4 nmol/l, 6 months later it reached 4-8 nmol/l and a year later was 4-8 nmol/l and dose adjustment was required (Urbanovich et al., 1996).

In patients with $T_2N_xM_0$ PC stage best results were observed after orchiectomy + estrogen therapy, and this is proved by a 5-year survival rate of 83.7 ± 10.5 % (Nechiporenko et al., 1996).

Study of results of orchiectomy in combination with Estrasine, a novel locally developed Ukrainian drug with prolonged antitumorous and estrogenic effect and treatment with Estrasine alone showed higher effectiveness of combined therapy: after one month partial regression was observed in 16.7 % of patients, stabilization in 83.3 %. Following monotherapy with Estrasine stabilization was noted in 75 %, disease progression in 25 % of patients. After 3 months the respective values were 50 % and 30 % in the first group, in the second group they were much worse. The difference is obvious, however to make a final conclusion on the effectiveness of this method further clinical study is needed (Pereverzev et al., 1997).

Similar results were obtained in patients with disseminated carcinoma ($T_{3-4}N_xM_{0-1}$) who were treated with orchiectomy in combination with estramustin phosphate. Complete and partial remission was observed in 29 % of patients, disease progression in 33 %, side effects in 22 % of patients, 7 % died during the first year. After orchiectomy + flutamide these values were 28 %, 18 % and 18 %, respectively, i.e. there is no significant difference between two protocols (Flamm, Fischer, 1988).

Many authors emphasize better therapeutic effect of combined treatment of PC patients with orchiectomy and estrogens as compared to monotherapy but at the same time having analyzed 5-year survival, incidence of complications and side effects they mention the shortcomings of this method: even in older patients orchiectomy is a serious psychologic stress and estrogen therapy results in cardiovascular complications in 24-29.5 % of patients (Drawz et al., 1987; Nesterova et al., 1997). During 5 years after orchiectomy and treatment with Synestrol 44 % of patients died, after orchiectomy alone 28.4 % died. Use of estrogens was accompanied by painful gynecomasty, hyperpigmentation, aggravation of liver tests, angina pectoris, and sudden death (9.3 %) caused by cardiovascular complications. Orchiectomy and symptomatic treatment are supposed to be justified in patients with disseminated PC and pain

syndrome especially when mortality and complication rates as well as especially when mortality and complication rates as well as economic factors are taken into consideration (Zhukov, Buko, 1996).

An important argument that supports advisability of a combination orchietomy + estrogens is the fact that orchietomy does not lower the level of adrenal androgens which promote tumor growth. Oral estrogen administered simultaneously decreases blood serum content of dehydroepiandrosterone sulphate, an adrenal steroid (parenteral administration of an estrogen does not effect this hormone), and increases SHBG level that is not effected by orchietomy (Carlstrom et al., 1989).

When studying testosterone, hydroxyprogesterone, androsterone, its sulphate and cortisol levels in blood plasma of PC patients following orchietomy and therapy with different estrogenic drugs it was established that hormonal therapy resulted in a decrease of all androgen levels and in an increased cortisol concentration, under any treatment protocol. Estramustine phosphate is the only exception. After its use cortisol concentration increases with preserved testosterone level. It is associated not with intensified adrenal function but with hepatic dysfunction (Pousette et al., 1989).

It is of interest to compare combined treatment consisting in orchietomy + estrogens to orchietomy in combination with other methods effecting the tumor, i.e. radiation therapy and chemotherapy. Five-year survival rate after orchietomy combined with intravenous administration of fosfestrol-(Honvan) (500 mg for 20 days, then 100-300 mg per os) was observed in 47 % of patients, 10-year survival rate in none. After orchietomy + radiation therapy (2 weeks after surgery 45-59 Gy administered to the pelvic region, then 15-20 Gy to the prostate) these values were much higher making 75 % and 46 %, respectively. But after radiation therapy a number of disorders in the intestine and the urinary bladder were reported (Moriyama et al., 1988). A similar study by A. Ponukalin and Yu. Mitryayev (1997) showed that after orchietomy and estrogen therapy 3- and 5-year survival is 21 %, after radiation and estrogen therapy it is 54.5 %, following orchietomy + radiation therapy + chemotherapy + estrogen therapy it reaches 76.9 %.

A thorough medical and statistical analysis of the data obtained showed that 5-year observed and adjusted survival rate of patients with local PC is 7.7 % and 19.8 % following orchietomy + hormonal therapy and median survival rate before disease progression is 19.6 ± 0.06 months.

Under combined hormonal, chemical and radiation therapy these values are 47.7, 68.5 % and 0 months, respectively. Five-year survival rate before disease progression or recurrence in mentioned groups of patients was 0 and 50.1 % ($p < 0.05$) (Sviridova et al., 1997).

5.2. Castration and antiandrogens

Study of antiandrogen efficiency in monotherapy showed that antiandrogens alone did not allow maximum androgen blockade. Later on androgen resistance may develop thus making antiandrogen therapy ineffective. That is why a combined treatment was proposed. It included surgical (orchiectomy) or pharmacological castration and antiandrogens, «pure» (non-steroid) or steroid. The advisability and the effectiveness of such combination is confirmed by many authors who reported positive results and only some cases of disease progression (Gaillard-Moguilewsky, 1991; Khilinsky, Bodrilov, 1996; Mokhort, 1996; Labrie et al., 1998). At present, this combined method is considered to be the main one in managing metastatic PC since it allows longer life span and improved quality of life as compared to patients who underwent only orchiectomy (Loran et al, 1997).

The results of PC treatment with a combination of orchiectomy+antiandrogen reported by different authors diverse slightly but in general all studies demonstrate the advantages of combined treatment as compared to monotherapy. According to Flamm and Fischer (1988) in patients with terminal stages of advanced PC, $T_{3-4}N_xM_{0-1}$, a combination of orchiectomy and flutamide is effective in 25 % of cases. This data does not differ significantly from the results of combined treatment with orchiectomy and estramustine phosphate but following orchiectomy with flutamide in contrast to Estracyte complications and side effects were less frequent.

Flutamide in patients with recurrent PC stage D_2 who were orchiectomized or received LHRH agonist, LHRH ([D-Trp6] prolane B ethylamide), group I, or LHRH [D-trp6] prolane B ethylamide + diethylstilboestrol, group II, facilitates subjective improvement in both groups for an average period of 24 months and a 2-year survival in 87 % and 67 % of patients, respectively. After surgical or pharmacological castration these values were 8.1 months and 17 %. Thus antiandrogens used after castration (surgical or pharmacological) might be the method of choice in patients with PC relapse (Labrie et al., 1988 a, b).

An open non-randomized study showed that in patients with disseminated PC who had been orchiectomized and received flutamide there was a more rapid decrease of PSA and prostatic acid phosphatase levels as compared to patients who had been castrated: in 58 % versus 47 % of orchiectomized patients. At the same time there was no significant difference in the time when biological and clinical progression of the disease occurred and in the survival rate (Motore et al., 1992).

A considerable advantage of combined therapy (orchiectomy + flutamide or LHRH agonist + flutamide) as compared to orchiectomy or LHRH agonists was demonstrated in a double blind randomized prospective study which should be considered more objective. It showed that following combined therapy survival increased to 15 months versus 5.4 months after castration, quality of life improved considerably. This might be associated with a more complete androgen blockade and blockade of adrenal androgens in particular (Labrie et al., 1993 a, b).

In a similar randomized double blind placebo-controlled study results of orchiectomy + flutamide and orchiectomy + placebo were compared in newly treated patients with metastatic PC. Age, general state, bone pain, duration of the disease, prior radiation therapy were considered. The efficiency of treatment that began 7 days prior to castration and continued for 2 years was similar to those given above although there was no data on disease progression: following castration plus flutamide objective response to therapy was observed in 56 % of patients, after castration and placebo in 45 %. As to side effects, gastrointestinal disorders were in 13 % and 3 % of patients, respectively. Survival was the same in both groups though after flutamide administration there was a tendency to increased survival. So it may be concluded that both methods are equally effective in terms of survival (Zalcborg et al., 1996).

Some authors studied the effectiveness of combined therapy with orchiectomy and steroid antiandrogens. The results of the study did not differ from those given above with the use of flutamide.

The results of treating PC D₂ stage patients with orchiectomy and cyproterone acetate or fosfestrol, cortisone or placebo were compared. After orchiectomy + CPA 2-year survival was 62.2 %, 5-year survival was 4.0 %, following castration and placebo 69.6 % and 0 %, after fosfestrol and cortisone 42% and 8 %, and after cortisone 58 % and 25 %, respectively. Following administration of an estrogenic drug prolactin level increased, after CPA administration it normalized. Thus orchiectomy in combination with antihormonal therapy was more effective than mono-

therapy. CPA proved to be most effective of all drugs tested. These clinical data confirms experimental studies that prove that adrenal androgens not effected by orchiectomy play a certain role in PC relapse. Cortisone inhibits secretion of adrenal androgens, this determines the effectiveness of combined treatment (Klosterhalfen, Becker, 1987).

In a double blind study it was established that in patients with metastatic PC treated with orchiectomy + cyproterone acetate or orchiectomy + placebo and followed-up for 3 years both methods gave similar therapeutic results (Jorgensen et al., 1993).

No difference was found when therapeutic effect of orchiectomy + CPA and a LHRH agonist buserelin + CPA was compared after 2-week and prolonged treatment (the time of response to treatment, subjective reactions, progression-free time, life span and survival rate were considered).

However the advantages of combined treatment, CPA + orchiectomy, CPA + LHRH, are obvious as compared to monotherapy with CPA. In newly treated patients such treatment is more effective than in those who were treated before. It is well tolerated and rarely causes complications (Klijn et al., 1993; Tsvetkov et al., 1996 a, b).

In order to achieve a maximum androgen blockade nilutamide (Anandron) is also used with orchiectomy. After such treatment an objective improvement of the general state is observed, bone pain is relieved as well as urination disorders, the level of tumor markers decreases, progression-free time increases. It is convincingly proved by 4 double blind studies in PC D₂ stage patients that were carried out by Moguilewsky et al. (1987). A mean interval prior to objective disease progression after a combined treatment was 20.8 months (after orchiectomy alone it was 14.7 months), before a fatal outcome 37.1 and 29.8 months, respectively, objective regression was observed in 41 % and 24 % of cases, pain alleviation 1, 3 and 6 months later was reported in most patients, a decrease in PSA level with its normalization after 3 and 6 months was observed in 75 % and 28 % of patients, respectively. Some time after the onset of treatment prostatic acid phosphatase, PSA, alkaline phosphatase values improved, bone pain was alleviated, the intensity of isotope deposition at osteoscintigraphy reduced. But nilutamide caused side effects, usually moderate and reversible (delayed dark adaptation after the bright light, increased hepatic transaminase levels), sometimes they were more severe (interstitial pneumonia), and this resulted in the treatment discontinuation in some patients (Harris et al., 1993; Janknegt, 1993; Zalcborg et al., 1996).

More rapid achievement of therapeutic effect is very important in a combined treatment as compared to antiandrogen alone. In patients with advanced disease with bone and lymph node metastases a subjective effect (bone pain alleviation, decreased frequency of urination) is observed 3-4 days later while after treatment with Androcur alone this is achieved only after 2-3 weeks.

A valuable prognostic factor applied in any hormonal therapy method is measurement of prostatic specific antigen (Petros, Ariole, 1993). Normalization of blood plasma PSA 3 months after the onset of treatment is the earliest and highly correlated criterion of response to treatment. In 80-85 % of treated patients with the disease progression an increase in PSA level is observed 6-12 months earlier than any other clinical manifestation of the disease progression. An increase of PSA level with all other parameters being within normal range may indicate the coming clinical progression of the disease. Usually in an 80-90 % decrease of PSA level statistically significant prolonged remission is observed.

Blood plasma testosterone concentration decreases 1 month after the onset of treatment from 15-19 to 1.0-2.5 nmol/l after a combined treatment and to 4.2-5.3 nmol/l in Androcur-treated patients. An increase of the dose up to 350-400 mg/day results in a lowering of testosterone level to postcastration values (1-2 nmol/l), however 2 months after treatment discontinuation it increases to 5-7 nmol/l while after a combined treatment it remains on a postcastration level. At the same time 3-year survival is 22.5 % and 20 %, i.e. it does not depend on the chosen method (Kravchuk et al., 1996).

A meta-analysis of remote results in 22 clinical randomized studies where the effectiveness of surgical or pharmacological castration and a combination of castration and steroid (CPA) or non-steroid antiandrogens (flutamide, nilutamide) was compared, showed that under a mean follow-up of 40 months 3283 patients (57.5 %) died out of 5710: mortality rate in a group treated with castration alone was 58 %; in the second group it was 56 %, 5-year survival made 22.8 % and 26.2 %, respectively (Dalesio et al., 1995). Basing on these studies the superiority of a combined method as compared to castration or antiandrogen treatment is considered unproven. Still in the first case 5-year survival was slightly higher.

Orchiectomy in combination with Zoladex used to treat advanced histologically confirmed PC should also be mentioned. When patients were followed-up for 3 months, their state was assessed according to

subjective and objective parameters 2, 4, 8 and 12 weeks after treatment, then it was compared to the effectiveness of orchiectomy alone or monotherapy with Zoladex. Positive results were found in 76 % of orchiectomized patients, in 72 % of Zoladex-treated men and in 80 % of patients after orchiectomy + Zoladex. An average period preceding a distinct response to monotherapy with orchiectomy or Zoladex is 7 weeks, to their combination is 6 weeks.

It was shown that 18-30 months after combined treatment with flutamide and orchiectomy in 22.9 % of patients the disease progression is observed and despite MAB their state does not improve. It might be explained by the fact that PC tumors are polyclonal and consist of cells that respond to androgens in different ways: androgen-dependent which develop under the effect of androgen stimulation, androgen-responsive that slow down their growth in the absence of androgens and androgen-resistant that do not need androgens for their development. Under the increase of the number of androgen-resistant cells the general state worsens and the disease develops. In these cases hormonal drugs should be withdrawn, and after that many patients feel much better. This phenomenon called «withdrawal syndrome» may occur under treatment with antiandrogens (Flucinom, Casodex). It may persist for up to 4 months, and this is confirmed by numerous clinical studies, especially in patients after MAB. After monotherapy with Casodex tumor development was observed, it was diagnosed by bone scans and measurements of blood PSA level, that is why the treatment was supplemented with LHRH analogues but Casodex was withdrawn because of the persisting disease development. In 2 patients PSA content kept to a 75 % level for 3-6 months, then decreased to 42 % (Nieh, 1995; Horenrak et al., 1997). After Flucinom withdrawal in 47 % of patients PSA level decreased, in 22 % of those patients tumor size diminished (Matveyev, 1998).

The mechanism of «withdrawal syndrome» has not been elucidated so far. Some authors believe it is caused by mutations of androgen receptors and that is why hormonal drugs do not exert therapeutic effect. Other authors keep to the opinion that androgen sensitivity of tumor cells increase and as a result even residual levels of male sex hormones produce unfavourable effect and promote disease progression.

So information given above despite certain contradictions of the results obtained, shows the effectiveness of combined treatment that

consists in orchiectomy and antiandrogens and also its advantages as compared to monotherapy employing the same measures.

5.3. LHRH agonists and antiandrogens

The advisability of PC combined treatment using LHRH agonists and antiandrogens is based on the fact that therapy with LHRH agonists results in the effect of pharmacological castration which is supplemented with the curative effect of antiandrogens. Taking into account that orchiectomy is always a stressful factor negatively taken by patients, and also the fact that pharmacological castration gives the same therapeutic effect as surgical, therapy with a combination of LHRH agonists and antiandrogens might give therapeutic effect similar to a combination orchiectomy + antiandrogen being more acceptable for patients (Popko, Lokshin, 1996).

An important advantage of LHRH agonists is also associated with the fact that pharmacological castration might be reversible, (Gaillarf-Moguilewsky, 1991). If LHRH agonist alone is administered, LH and testosterone levels increase at the initial stage of the treatment, promoting disease progression. In order to prevent the disease exacerbation it is recommended to prescribe antiandrogens (CPA etc.) (Schulze et al., 1988; Ferrari et al., 1996). Such combination might be useful if a patient declines to undergo orchiectomy.

A combination of buserelin and Anadron is more effective than monotherapy with the same drugs (Labrie et al., 1983c). After such treatment remission is observed in 95 % of newly treated patients, in 50 % of those previously treated with estrogens and in 30 % of castrated patients. Positive effect of this combination is explained by the fact that buserelin desensitizes pituitary gonadotropins to the effect of endogenous GnRH, inhibits biosynthesis of testicular androgens and decreases testosterone, DHT and other androgen levels in blood. Anadron neutralizes the stimulatory effect of circulating residual androgens of adrenal and testicular origin on the prostate (Moguilewsky et al., 1986; 1987).

The necessity and effectiveness of maximum androgen blockade through combined therapy with Decapeptil, LHRH agonist, and a pure antiandrogen, flutamide (250 mg 3 times a day), was substantiated in many clinical studies. After applying the MAB scheme in patients with newly diagnosed untreated verified PC with bone metastases (D₂ stage)

objective positive response is observed for an average of 18 months after one-month treatment in 80 % of patients versus 60 % after orchiectomy or estrogen therapy. When remote results of combined therapy in newly treated patients with metastatic stage D₂ PC are being assessed for over 3 years this treatment protocol proves ineffective only in 6.5 % of patients. A mean duration of a therapeutic effect is 2.23 years, mean total survival is 3.58 years. Survival in PC patients depends on the number of bone metastases. It decreases from 8 years (1-5 metastases) to 1.76 years (multiple metastases). General symptoms and pain are stopped for an average of 5.47 and 2.71 years, respectively, functional state improves for 2.1 years. Given in time combined therapy with flutamide and LHRH agonist (or orchiectomy) in case of 1-5 bone metastases prolongs patient's life for more than 4 years and improves the quality of life as compared to advanced disease. This scheme might be method of choice in patients with PC relapse after surgical or pharmacological castration (Labrie et al., 1986, 1988 a, b; 1993 c).

When comparing the results of orchiectomy and combined androgen blockade (surgical or pharmacological castration + flutamide) in metastatic PC patients of the same age (69.9 and 70.2 years), with similar PSA levels (493.3 and 486.5 ng/ml, respectively) advantages of combined androgen blockade became obvious after 3-month treatment: PSA level decreased to 34.5 versus 52.9 ng/ml ($p < 0.01$), clinical improvement was observed in 52 versus 42.3 % of patients, biological progression was reported after 13 and 12 months, respectively, clinical progression was observed 14 and 15 months later, survival made 34 and 28 months (Fig. 5.1). In patients with metastases higher survival was observed in M₁ and is the same in M₂ and M₃ (Motore et al., 1992).

After treatment with LHRH agonists and antiandrogens (MAB) total survival in PC patients was higher ($p=0.04$), period of remission and life span after progression before a fatal outcome caused by the main disease were longer ($p=0.01$ and $p=0.008$, respectively) as well as period of remission before the first progression ($p=0.009$) than after orchiectomy alone. Normalization of acid phosphatase level is observed, and it is a favourable prognostic factor. Most frequent side effects in both treatment patterns included blood rushes, gynecomasty (Denis et al., 1998).

At the same time, conclusions that are based on results of double blind randomized studies of survival and duration of remission before disease progression in patients with disseminated PC after MAB and monotherapy with Leuprolide are contradictory. Some authors (Brogden, Clissold, 1989; Brogden, Chrisp, 1991) mention that MAB, as compared

to Leuprolide alone, considerably increases survival in newly diagnosed untreated advanced PC though emphasize that these results need further study. Other authors (McLeod et al, 1993; Ferrari et al., 1996) state that there is no significant difference in total survival, period before the first disease progression and effectiveness of treatment, and supplementing Leuprolide with flutamide in case of disease development has the same effect as other methods of treatment of progressive PC. But at the same time they recognize that in patients who were given two drugs, a clear tendency to improved general state and studied parameters was observed, and no cases of bone metastases were registered. Combined androgen blockade does not cause any severe side effects except moderate gastrointestinal dysfunction (nausea, diarrhea). In monotherapy flutamide does not cause loss of libido and impotence at least in 80 % of patients, and gynecomasty which is not frequent is observed only in its combined use with LHRH agonist or orchiectomy, that is why flutamide is indicated to patients who are concerned about their potency.

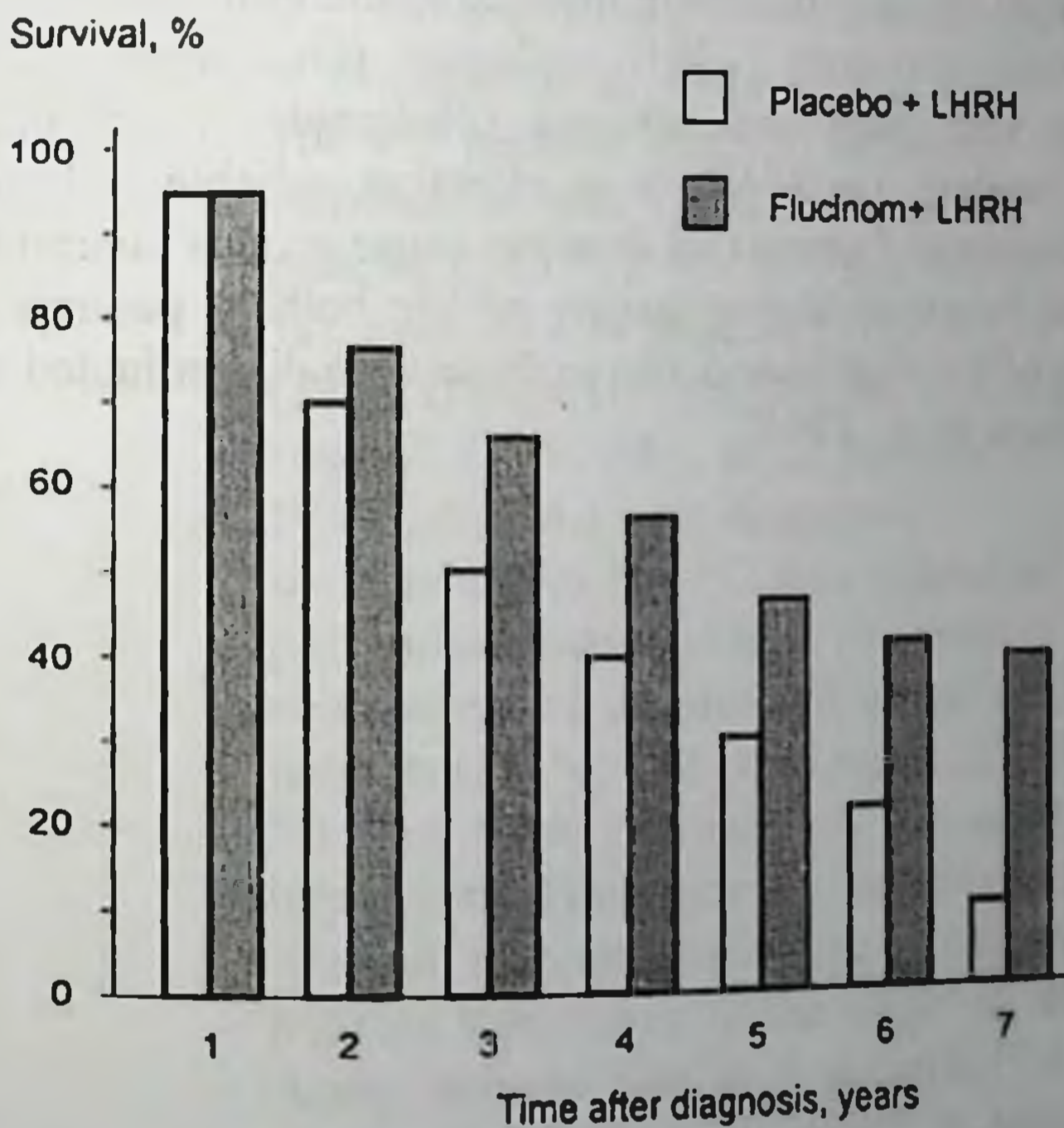


Fig. 5.1. Survival of PC patients treated with LHRH agonists or Flucinom in combination with LHRH agonists

MAB scheme might also include bicalutamide (Casodex) (50 mg once a day) in combination with goserelin acetate (Zoladex) (3.6 mg every 28 days) or leuprolide acetate (7.5 mg once in 28 days). Prospective and retrospective analyses showed that disease progression after 95 weeks, on the average, is observed in 55 % of patients treated with bicalutamide + LHRH agonist as compared to 58 % of patients who were given flutamide (250 mg 3 times a day) + LHRH agonist. A ratio of time intervals to the beginning of progression is 0.9, i.e. both patterns are equal in their effectiveness (Schellhammer et al., 1995). Later on the authors concluded that Casodex was more effective within MAB as compared to flutamide (Schellhammer et al., 1996, 1997).

In a similar study Crawford (1996) obtained higher values, 68 % and 72 %, respectively, though they also do not demonstrate a significant difference in the effectiveness of treatment. At the same time according to Simmard et al. (1997) a combination of Flucinom with LHRH agonists turned out to be the only treatment resulted in increased survival.

Thus treatment with LHRH analogues (Decapeptil, Zoladex) in combination with pure antiandrogen (Flutamide, Flucinom, Frugil, Niftolide, Casodex), i.e. MAB, is an effective, reliable and convenient method of hormonal therapy that does not cause serious complications, it allows maintenance of higher quality of life both in patients with the initial stages of the disease and also in those with disseminated advanced cancer (Alfimov et al., 1995).

LOW DOSE ESTROGEN-ANTIANDROGEN THERAPY OF PROSTATE CANCER

6.1. Clinical effectiveness

Among combined methods of endocrine therapy of PC patients a new method called low-dose estrogen-antiandrogen therapy (LEAT) is of special importance. It was developed by the authors of this book.

Chapter 3 gives theoretical and experimental substantiation of LEAT. In this very chapter we shall summarize clinical results of LEAT that have been published (Vozianov et al., 1996; Klimenko et al., 1993 a, b; 1996 a, b; 1997; Vozianov et al., 1995 b; Vozianov et al., 1995, 1998).

108 PC patients received combined LEAT. Age distribution was as follows: 50-59 years - 26 patients (24.1 %), 60- 69 years - 48 patients (44.4 %), over 70 - 34 patients (31.5 %). In 64 patients (59.3 %) stage II (T₂N₀M₀), in 22 patients (20.4 %) stage III (T₃N₀₋₁M₀), in 22 persons (20.4 %) stage IV (T₃₋₄N₀₋₁M₁) were diagnosed.

In 6 men (5.6 %) PC was diagnosed at regular preventive examination, 70 patients (64.8 %) complained of dysuria and urination disorders, 2 patients (1.9 %) had bone pains. 20 Patients (18.5 %) had been operated on for benign prostate hyperplasia. Histologically, malignant tumors were found in resected adenomatous nodules, and these patients were taken to the clinic of oncurology. Acute ischuria was in 8 patients (7.4 %). After examination PC was diagnosed. In one patient (0.9 %) the disease manifested itself with prostatic abscess.

In all cases the diagnosis was verified histologically and/or cytologically. Morphologically, small-cell and alveolar adenocarcinomas were found in 20 (18.5 %) and 22 (20.4 %) patients, respectively, tubuloalveolar cancer was identified in 30 (27.7 %), scirrhous in 10 (9.3 %), solid-trabecular in 14 (13.0 %), undifferentiated carcinoma in 12 (11.1 %) patients. None of patients had received special treatment before, there were no orchiectomized patients.

All patients underwent clinical and laboratory examination (total blood count, blood electrolytes, urea, creatinine, bilirubin, total protein, coagulogram) as well as sonography, UFM, computerized tomography, radionuclide research, blood samples for plasma androgens, LH, SHBG levels were taken.

90 patients (83.3 %) complained of dysuria, nocturia, urination disorders, pain in the perineum, in the area of the urinary bladder, 8 patients (7.4 %) had acute ischuria, 6 patients (5.6 %) in whom the disease was revealed at regular preventive examination had no complaints but at the clinic it was established that they felt discomfort at urination, 2 patients occasionally noticed blood in the urine but since it was painless and stopped without any intervention they did not consult a doctor. 2 patients (1.9 %) complained of skeletal bone pains, that is why they consulted a surgeon. At a rectal examination PC was suspected and they were referred to an oncurologist. In one patient (0.9 %) there were no signs of dysuria except pollakiuria. The disease manifested itself by prostatic abscess, and it was opened transrectally. Later, after biopsy, PC was diagnosed (histologically, undifferentiated carcinoma).

At clinical examination, in 8 patients (7.4 %) acute ischuria, in 22 patients (20.4 %) chronic ischuria was found (the residual urine volume made 100 ml and more). Total blood count showed leukocytosis up to $10.3 \times 10^9/l$ in 26 patients (24.1 %), increased erythrocyte sedimentation rate (up to 38mm/h) in 30 patients (27.8 %). In 18 patients (16.7 %) anemia (Hb=100-105 g/l) was found. Urinalysis showed leukocyturia in 100 patients (92.6 %), microhematuria in 66 patients (61.1 %). In 20 patients (18.5 %) macrohematuria and in 6 men (5.6 %) bacteriuria was observed. Blood biochemical analysis showed increased levels of urea and creatinine in 20 patients (18.5 %), other biochemical parameters were within normal range.

At rectal examination the prostate was found to be enlarged, solid with uneven contours, in 12 patients (11.1 %) the surrounding fat tissue

was infiltrated. Ultrasonically, in 72 patients (66.7 %) heterogeneity of the prostatic tissue consistency was found, in 22 patients (20.4 %) tumor focus was revealed in the left lobe, in 10 patients (9.9 %) in the right lobe, in 2 patients (1.9 %) in the middle lobe. In 6 men (11.1 %) infiltration to paraprostatic fat was observed (Fig. 6.1,6.2)



Fig. 6.1. Transabdominal ultrasonography of the prostate and the urinary bladder in a PC patient (impaired filling of the urinary bladder)

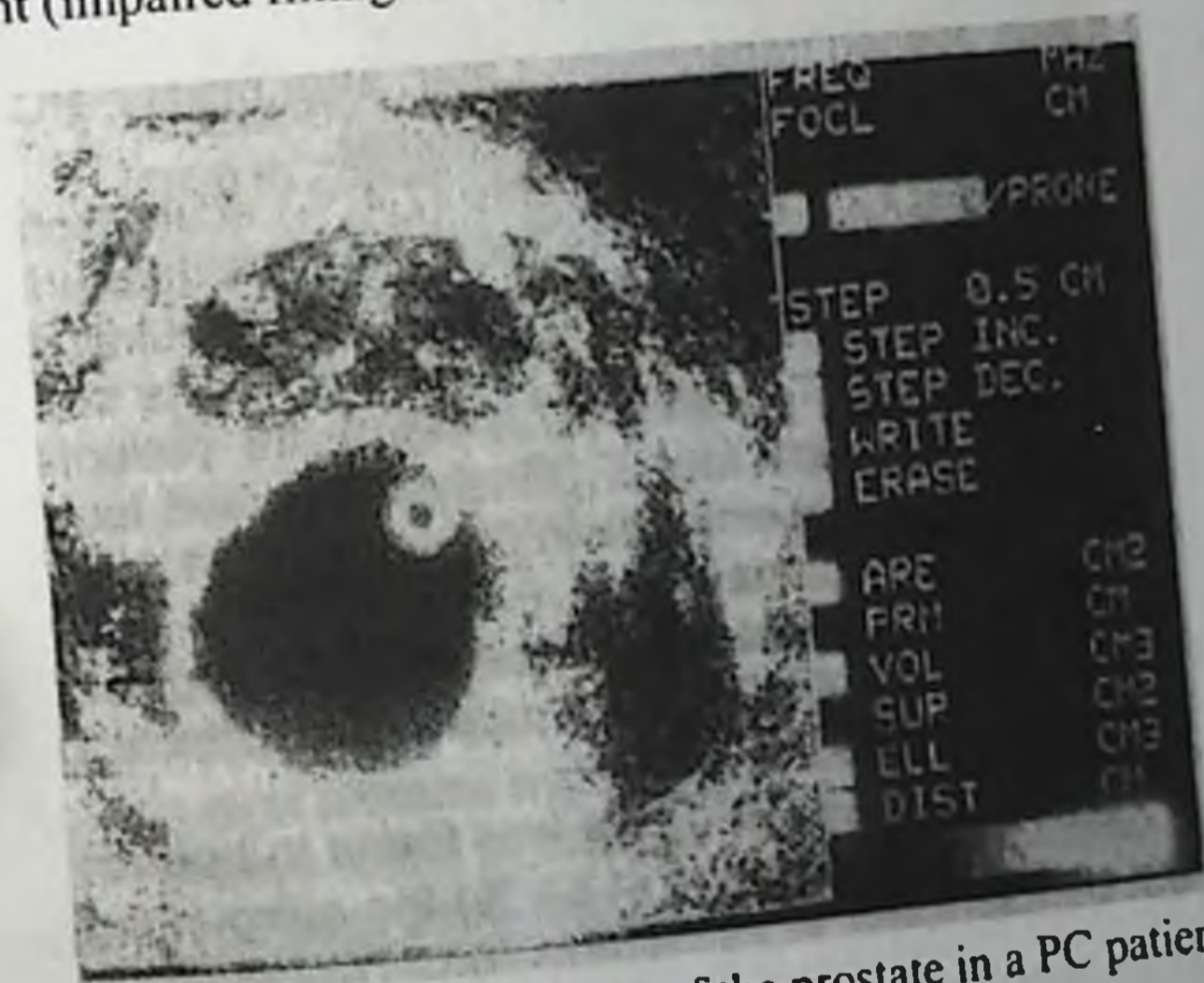


Fig. 6.2. Transrectal ultrasonogram of the prostate in a PC patient

The average prostatic size, as shown by ultrasonography, was as follows: frontal - 4.10 ± 0.21 cm, sagittal - 5.91 ± 0.23 , oblique - 4.51 ± 0.18 cm, volume 54.42 ± 0.48 cm³.

According to ultrasonography and X-ray data in 28 patients (25.9 %) the calycal-pelvic complex was enlarged, uni- or bilateral disorders of the excretory function were found (Fig. 6.3). Radioisotope renography demonstrated decelerated excretory phase in 10 cases (18.5 %). X-ray examination showed skeletal bone metastases in 14 patients (13.0 %) (Fig. 6.4). Those patients were separated into group II. In some patients descending cystography showed filling deficiency in the bottom of the urinary bladder (Fig. 6.5).



Fig. 6.3. Excretory urogram of a PC patient



FIG. 6.4. Roentgenogram of pelvic bones in a PC patient with multiple osteoblastic metastases



Fig. 6.5. Cystogram of a PC patient with filling deficiency and tumor spreading to the wall of the urinary bladder

In order to assess urination uroflowmetry was performed (Table 6.1). The table shows that maximum and minimum rates of urination are significantly less than normal values, this being a sign of subvesical obstruction.

Table 6.1. UFM in PC patients before low dose estrogen-antiandrogen therapy

Parameter	Group I	Group II
T_Q, S	22,2±5,72	28,9±4,9
$T_{Q \max}, S$	6,90±0,80	5,60±0,8
$Q_{\max}, ml/s$	9,36±1,32	5,70±1,2
$Q_{aver}, ml/s$	5,59±1,32	2,92±0,74

As to coexistent pathology, in 94 patients generalized atherosclerosis, coronary sclerosis, cerebral angiosclerosis were diagnosed, 74 patients had arterial hypertension, 2 patients had diabetes mellitus. One patient had surgery for meningioma, 14 patients had a history of gastrointestinal disorders. In all patients blood serum PSA level ranged 10-160 ng/ml.

Niftolide was prescribed in a dose of one tablet three times a day orally (a daily dose of 750 mg) half an hour before meals in combination with 0.3 ml Synestrol 2 % or 250-300 mg Honvan i.v. (i.e. in doses that are respectively 12 and 4 times less than those usually prescribed).

LEAT was given to 94 patients with stage II-III and to 14 patients with stage IV. During first 3 months Synestrol was administered intramuscularly, then the equivalent tableted dose was taken sublingually or subbuccally. Patients with $T_{1-4}N_{0-1}M_1$ were given Honvan (fosfestrol) in a dose of 250-300 mg i.v. in drops for 25 days, then fosfestrol tablets were taken (1 tablet 3 times a day).

The results of treatment were assessed separately in groups I (94 patients with $T_{2-3}N_0M_0$) and II (14 patients with metastatic $T_{3-4}N_{0-1}M_1$).

In 58 patients (53.7 %) from group I partial remission was achieved: the general state improved, urinary discharge became easier, PC size decreased by 25-50 %, UFM parameters improved; in 32 patients (29.6 %) the process stabilized (no tumor growth), in 4 patients (3.7 %) the disease aggravated.

In group II partial remission was observed in 6 out of 14 patients, 6 patients responded to therapy with improvement that persisted for 3-4 months with further aggravation. One patient died of disease progression a month after the treatment started.

UFM parameters under combined treatment are given in Table 6.2. Improved UFM parameters confirm the effectiveness of treatment (Fig. 6.6, 6.7).

Table 6.2. UFM parameters before and after a course of low-dose estrogen- antiandrogen therapy

Parameter	Group I		Group II	
	before treatment	after treatment	before treatment	after treatment
$T_{Q, S}$	22,25±2,72	24,45±3,24	28,9±4,9	28,6±5,57
$T_{Q \max, S}$	6,90±0,80	6,30±0,84	5,60±0,8	8,32±1,30
$Q_{\max, ml/s}$	9,36±1,32	14,33±1,76*	5,71±0,2	11,0±2,46*
$Q_{\text{aver}, ml/s}$	5,59±0,84	7,41±1,20	2,92±0,74	6,32±1,33*

* $p < 0.05$ as compared to pretreatment values

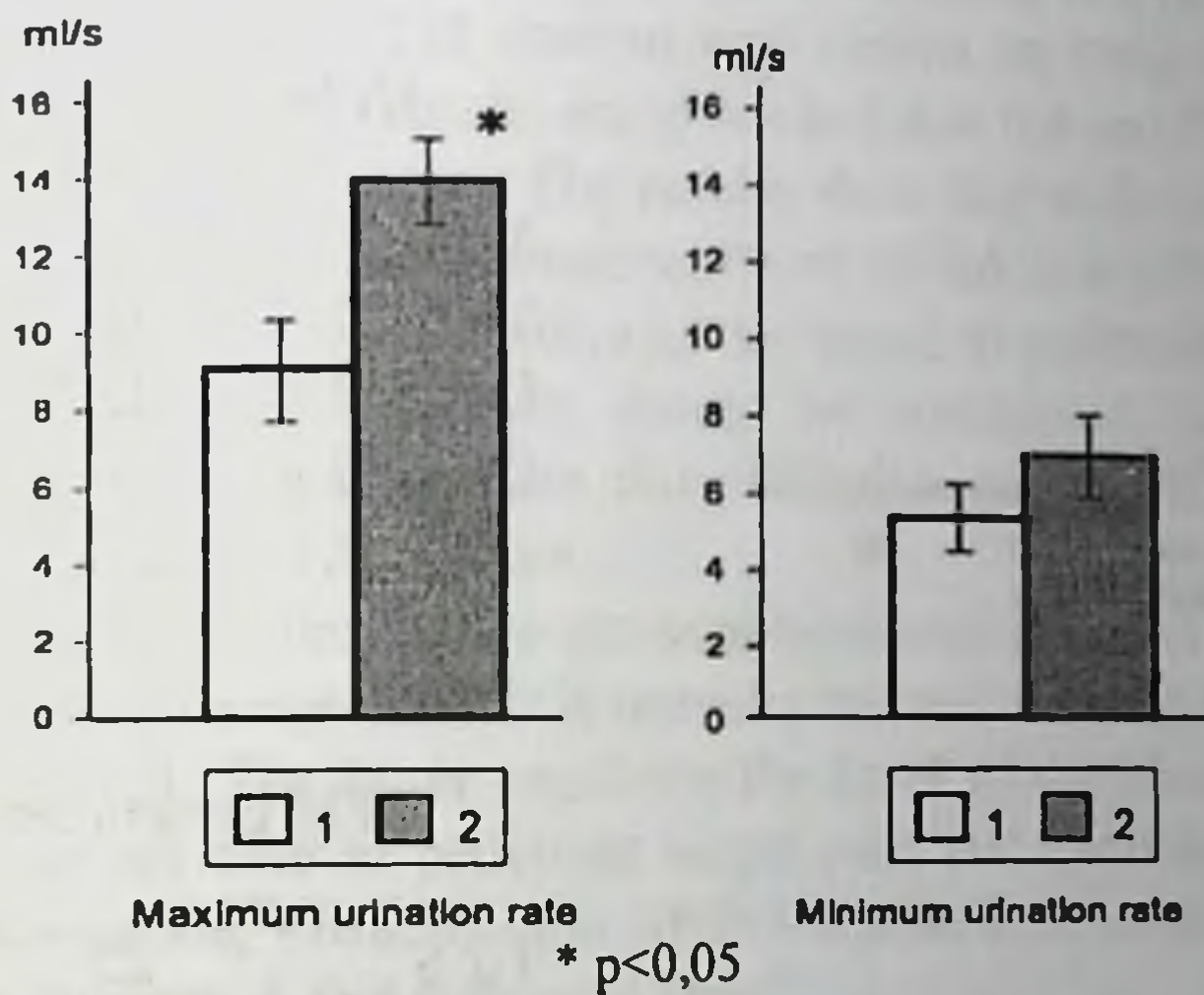


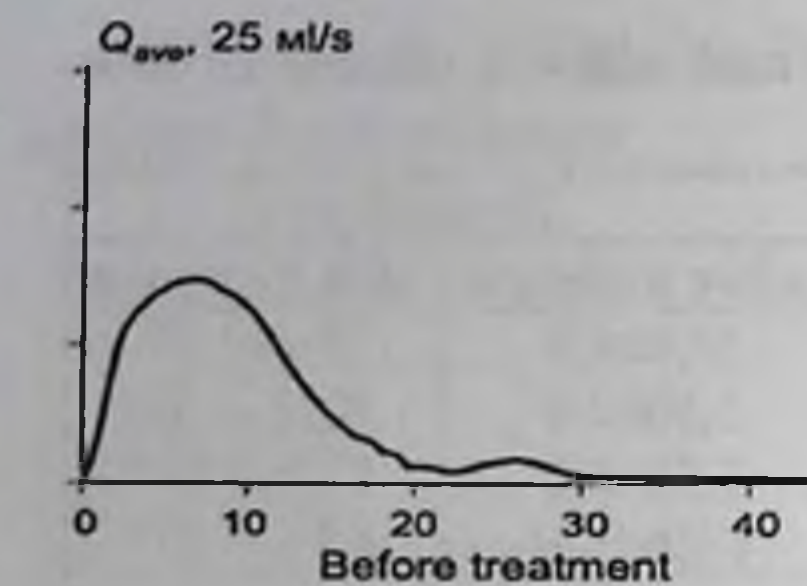
Fig. 6.6. Uroflowmetry data in PC patients before (1) and after a course of low dose estrogen-antiandrogen therapy (2)

According to ultrasonography average prostatic size decreased after 6-month treatment (Table 6.3, Fig. 6.8).

Table 6.3. Changes in the prostatic size during low dose estrogen-antiandrogen therapy

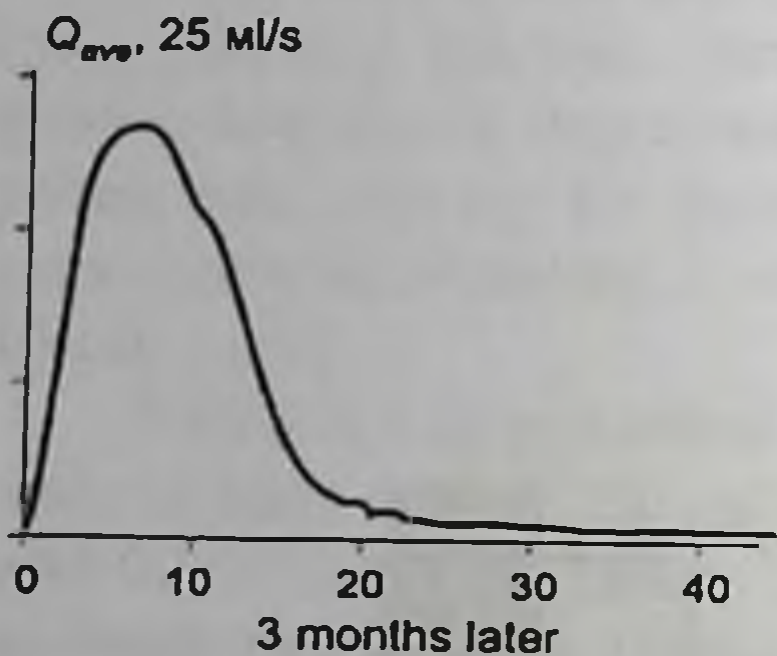
Prostatic size	Before treatment	After treatment
Linear measurements, cm		
frontal	4,10±0,21	3,72±0,18
sagittal	5,91±0,23	3,91±0,19*
oblique	4,51±0,18	4,00±0,19
Volume, cm^3	54,42±0,48	28,86±0,45*

* $p < 0.05$ as compared to pretreatment values



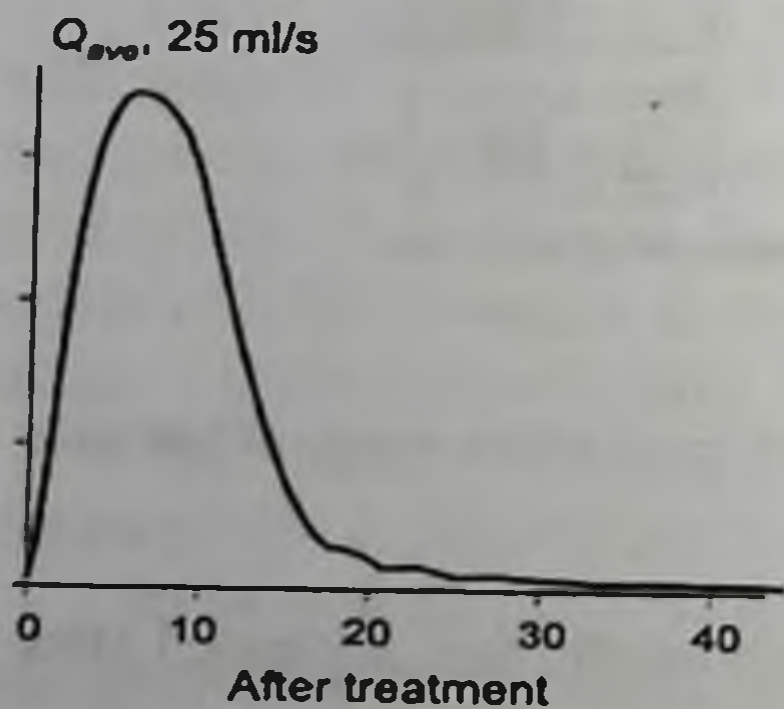
UFM parameter

T_Q, S	24
T_{Qmax}, S	5
$Q_{max}, ml/s$	9,0
$Q_{avcr}, ml/s$	4,3



UFM parameter

T_Q, S	19
T_{Qmax}, S	6
$Q_{max}, ml/s$	13,7
$Q_{avcr}, ml/s$	7,3



UFM parameter

T_Q, S	22
T_{Qmax}, S	6
$Q_{max}, ml/s$	19,1
$Q_{avcr}, ml/s$	9,0

Fig. 6.7. Changes in uroflowmetric record curve during treatment

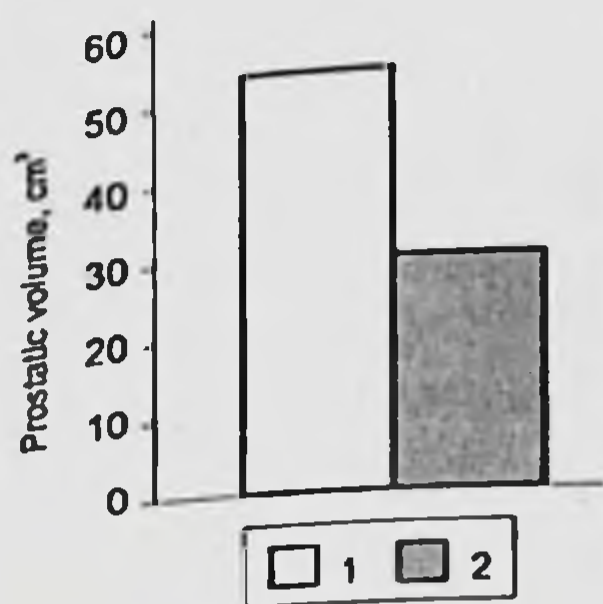


Fig. 6.8. Changes in the prostatic size in PC patients before (1) and after a course of LEAT (2)

In all patients hormonal status was studied before, during and after low dose estrogen-antiandrogen therapy. Pituitary gonadotropic function was assessed by blood plasma content of biologically active LH. The results obtained showed that under combined drug administration the level of this hormone decreased considerably during first 3 months of treatment. After 4-6 months of treatment blood LH content was similar to basal values. The results are given in Table 6.4 and Fig. 6.9.

The results show that under combined 6-month treatment with Niftolide and Synestrol LH level lowers as compared to pretreatment values. This fact should be considered as a sign of estrogen antigonadotropic effect since Niftolide exerts just an opposite effect, i.e. it increases LH content.

An important index of the gonadal hormonal function during hormonal and antihormonal therapy is testosterone and estradiol level as well as SHBG content. The latter regulates the level of circulating free sex hormones that are able to penetrate target cells and exert their biologic effect. Testosterone, estradiol and SHBG levels were measured before drug administration, 3 and 6 months later.

Table 6.4. Hormonal and SHBG levels in PC patients before and during 6 months of low dose estrogen-antiandrogen therapy (Means + S.E.)

Parameter	Pretreatment level	3 months later	6 months later
LH, IU/l	8,6±2,7	4,1 ±0,6*	6,6±1,0
ΔLH, IU/l	-	-4,9±1,0*	0,4±1,7
T, nmol/l	7,5±2,0	2,3±0,6*	7,3±2,1
SHBG, nmol ³ H- DHT/l	16,3±2,9	27,5±5,8	41,7±5,9*
FTI	55,2±6,2	14,2±6,8*	36,0±6,1*

*p < 0.05 as compared to pretreatment level

The results showed that in PC patients with the developing disease at stages III-IV 1-3 months after combined therapy estradiol level decreased moderately. A decrease in T/E ratio corresponded to lowered testosterone level.

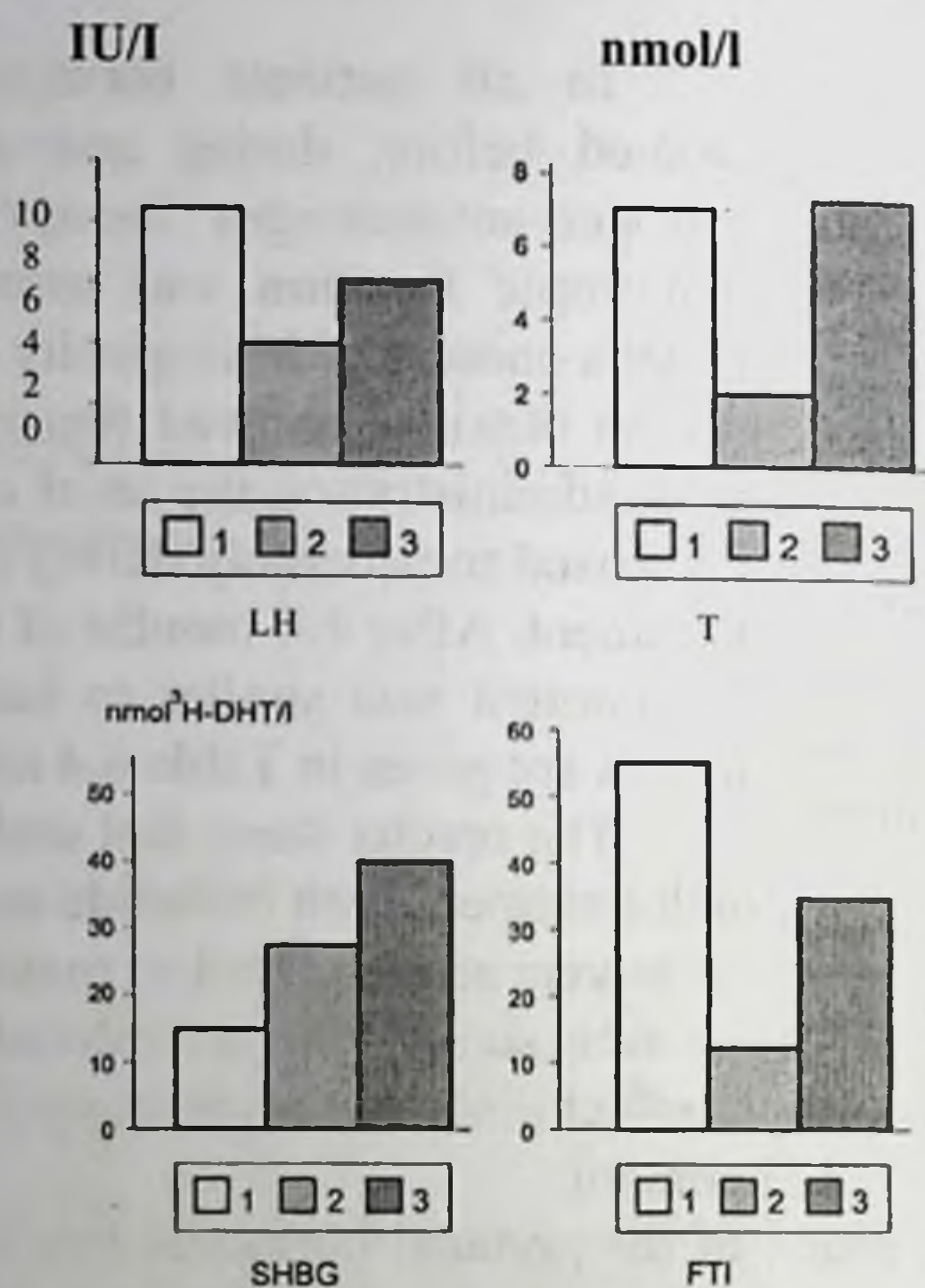


Fig. 6.9. Changes in blood plasma hormone and SHBG levels in PC patients before LEAT (1), after 3 months (2) and 6 months of LEAT (3)

Changes in blood plasma testosterone level in patients who received combined therapy were two-staged. During first three months of treatment it was considerably lower (2-3 times) than initial values and remained without changes during the following 4-12 months.

SHBG level 1 and 2 months after the beginning of combined treatment was 2.5-fold that of the initial value; after 3 months of hormonal therapy SHBG level lowered slightly, however it remained significantly higher than the pretreatment level. After 4 and 6 months of hormonal therapy SHBG content was 2.3 and 2.9 times higher as compared to the initial level. In management of PC it might be considered as a positive effect.

Free testosterone index is also worth mentioning. It is calculated basing on testosterone and SHBG levels. During the treatment FTI decreased considerably as compared to basal level. After 1 and 2 months of therapy FTI decreased 5-fold, 3 months later it was 4 times lower than pre-treatment values. It proves that owing to a decrease in blood testosterone concentration and an increase of SHBG, a free fraction of hormone available for tissues decreases dramatically.

Follow-up of these patients showed that FTI after 4-6 months of treatment was slightly higher than during first months of drug administration but it remained significantly lower than the initial values of free testosterone. During the treatment no correlation between testosterone and SHBG levels was found. Thus changes in LH and testosterone levels as well as in FTI under LEAT of PC prove its effectiveness and the fact that it in no way yields to conventional treatment. Here are some examples.

Patient D., born 1928, was taken to the Department of Urology with acute ischuria. T₃N₀M₀ PC was diagnosed, histologically, small-cell glandular carcinoma. The patient was prescribed Niftolide in a dose of 1 tablet 3 times a day for 6 months and 0.3 ml Synestrol 2% i.v. for 3 months, then 1 tablet of Synestrol 3 times a day for 3 more months.

After first 10 days of treatment following this regimen normal urination restored. After 3 months, rectal examination and ultrasonography showed diminution of prostatic size. According to UFM, urination parameters improved: Q_{max} before and after treatment was over made 8.3 and 11.5 ml/s, respectively, Q_{ave} 5.1 and 7.9 ml/s.

The patient was examined 6 and 9 months later. His state was considered stable. Now the patient is followed-up, no disease development is observed.

Patient Ch., born 1929, complained of manifested dysuria a month after prostatectomy (histologically, in resected adenomatous nodules small-cell adenocarcinoma was diagnosed). At rectal examination the prostate was enlarged, without clear-cut contours, solid, in the left lobe tuberosity was found. Ultrasonography showed irregular echogeneity, prostatic size was measured as 4.5x4.3x3.9 cm. The treatment consisted of Niftolide in a dose of 250 mg 3 times a day orally, 0.3 ml Synestrol 2% i.v. After 2 months of treatment urination improved as showed by UFM parameters: Q_{max} before and after treatment made 1.2 and 3.2 ml/s, respectively, Q_{ave} 0.8 and 2.0 ml/s. During 5 years of follow-up the patient's state remained stable without disease progression.

Analysis of LEAT-associated complications shows the absence of severe side effects that would make the doctors to give up this treatment completely. In 6 patients (5.5 %) gynecomasty developed, 20 patients (18.5 %) complained of breast tenderness or breast pain, in 6 patients (5.5 %) chronic coronary dysfunction became worse, in 4 patients (3.7 %) arterial hypertension, in 4 patients (3.7 %) gastrointestinal disorders were observed. In 2 out of 4 patients dyspepsia manifested itself in nausea and did not require the drug withdrawal. Two other patients had diarrhea twice a day. After two-week interval in Niftolide administration (treatment with Synestrol persisted) side effects were stopped, the treatment continued with the diet adjustment. These signs were not observed any more.

Two out of 6 patients with exacerbated chronic coronary insufficiency required hospitalization to the Department of Cardiology, 4 patients received ambulant treatment. In all of them these complications manifested themselves after 3-4 months of effective treatment. The drugs were withdrawn for a month, after that the treatment continued following to the initial pattern.

No severe complications associated with Honvan administration were noted. Four patients complained of burning sensation and pruritus in the anal area during first 3-7 days of treatment. Two patients complained of pain sensation in the vein where the drug was administered. It was considered to be thrombophlebitis and required respective treatment. After intravenous Honvan administration infusions were substituted with tablets in the equivalent doses and treatment continued up to 6 months.

When quality of life was scored the results were as follows: 1 in 56 persons (51.9 %), 2 in 38 (35.2 %), 3 in 10 persons (9.3 %), 4 in 4 persons (3.7 %).

After 6-month LEAT partial remission was achieved in 70 patients (64.8 %), stabilization of process was observed in 32 patients (29.6 %), progression of the disease was found in 6 patients (5.5 %).

6.2. A comparative assessment of clinical results after LEAT and conventional treatment

In order to study the effectiveness of LEAT of advanced PC, its effect and those of monotherapy with Androcur, Niftolide and Synestrol were compared. It allowed the conclusion on the action of drugs

mentioned, their effectiveness, indications for their use, side effects and complications.

When the obtained results were compared, attention was paid to the fact that in case of Androcur positive effect was more rapid and persisted longer in patients with stages I-II. When Niftolide was employed in combination with Synestroi, remission was longer and was observed both in patients with stages I-II and also in patients with stages III-IV with metastases. Fig 6.10 shows changes of prostatic size under various treatment patterns.

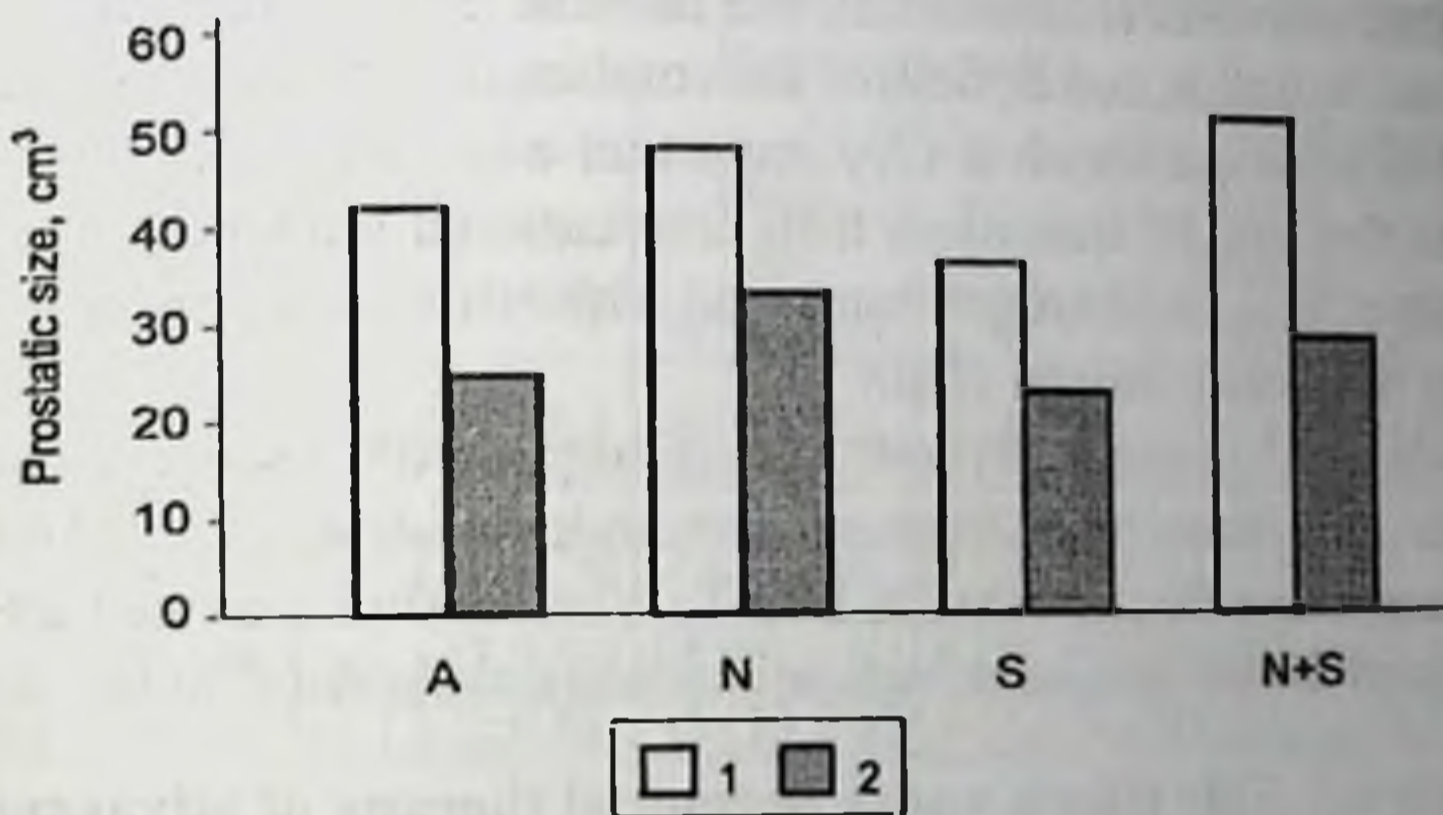


Fig. 6.10. Changes of prostatic size before (1) and after a course of therapy (2) under various treatment regimens:

A, Androcur; N, Niftolide; S, Synestrol; (N + S), Niftolide + Synestrol

Differences in the effects produced by different drugs are determined by their mechanism of action. Androcur is a steroid antiandrogen, its effect is brought about by a decrease of androgen concentration and their inhibition.

Estrogen antitumorous effect includes, first, antigonadotropic action that is manifested in decreased production of pituitary gonadotropic hormones, second, antigonadal effect, i.e. direct inhibitory effect of hormones on testicular testosterone formation and, third, perhaps, a direct antiprostatic effect.

Use of Synestroi in conventional high doses allows rapid and persistent decrease of testosterone level and positive clinical effect, tumor size diminishes, urination improves. However severe complications associated with such treatment finally bring to worsened quality of life and its duration more rapidly than the main disease, particularly at the initial

stages of the disease and in old age when all hormone-dependent processes are slow and less malignant.

Niftolide, a non-steroid antiandrogen, blocks androgen receptors in target organs and metastases thus bringing to their regression. Monotherapy with Niftolide gives a rapid clinical effect even in patients with stage IV and bone metastases. However 3-4 months later in most patients the disease progresses, it is manifested in tumor growth and generalization of the process. The matter is that as a result of blockade of androgen receptors in target organs including brain sites of feedback testosterone secretion is intensified, and this causes disease development.

When Niftolide and Synestroi are combined, a maximum androgen blockade is achieved which is very important when managing PC. Estrogen doses that are 10 times less than conventional ones help to escape severe side effects and estrogen combined with Niftolide peripheral action facilitates persistent clinical effect.

When large doses of Synestroi were used cardiovascular complications were 11.9 times more frequent than under treatment with Androcur and 6.9 times more frequent than in LEAT. When Niftolide alone was taken no associated cardiovascular complications were observed (Table 6.5).

Table 6.5. Side effects under hormonal therapy of advanced PC

Side effects	Niftolide + Synestroi (n = 108)	Androcur (n=57)	Niftolide (n = 68)	Synestrol (n = 114)
Cardiovascular disorders:	10 (9,2 %)	3 (5,3 %)	0	72 (63,1 %)
exacerbation of chronic coronary insufficiency	6 (5,5 %)	0	0	0
myocardial infarction	0	0	0	6 (5,3 %)
thrombophlebitis	0	0	0	12 (10,5 %)
arterial hypertension	4 (3,7 %)	3 (5,3 %)	0	48 (42,1 %)
acute disturbance of cere- bral circulation	0	0	0	6 (5,3 %)
Gynecomasty	6 (5,5%)	10 (17,5 %)	0	72 (63,1 %)
Decreased potency	0	3 (5,3 %)	1 (1,5 %)	36 (31,6 %)
Gastrointestinal disorders	4 (3,7 %)	1 (1,7 %)	3 (4,4 %)	0

It is worth mentioning that the severity of cardiovascular complications caused by high estrogen doses is greater than that under other treatment modalities. Attention should be paid to the fact that out of 72

cases (63.1 %) of cardiovascular complications there were 4 cases of myocardial infarction in this group. There were also 6 cases of acute disturbance of cerebral circulation. Under such treatment the number of patients who become disabled because of side effects is much higher than in other groups.

Analysis of PC development under different treatment modalities shows that it develops less intensively in the main group as compared to other groups (Table 6.6).

Table 6.6. PC development under various treatment modalities

Treatment pattern	Follow-up period					
	1 year		2 years		3 years	
	Local development	Distant metastases	Local development	Distant metastases	Local development	Distant metastases
Niftolide +Synestrol	2 (1,8%)	2 (1,8%)	6 (5,6 %)	4 (3,7 %)	18 (16,6%)	8 (7,4 %)
Androcur	4 (7,0 %)	3 (5,3 %)	7 (12,2%)	4 (7,0 %)	13 (22,8 %)	7 (12,2%)
Niftolide	10 (14,7%)	4 (5,9 %)	14 (20,6 %)	8 (11,7%)	20 (29,4 %)	10(14,7%)
Synestrol	9 (7,9 %)	3 (2,6 %)	15 (13,2%)	6 (5,3 %)	24 (21,1 %)	12 (10,5%)

The quality of life is the most important indicator of the effectiveness of treatment in any disease. It was shown that low quality of life of PC patients treated with high doses of Synestrol is caused by thromboembolic cardiovascular complications (infarction and insult), persistent arterial hypertension and repeated attacks of angina pectoris, arrhythmia.

Life quality in the majority of Niftolide-treated patients scored 3-4. It should be mentioned that in this group 25 % of patients had advanced stage IV disease with distant metastases.

After treatment with Androcur there were 6 disabled persons (10.5 %). This group consisted mainly of ambulant patients and, naturally, it effected the results of treatment.

Table 6.7 gives life quality score under various patterns of hormonal therapy. After LEAT 2 patients (3.7 %) with developing PC became disabled: in one case it was caused by the compression of the spinal cord with metastases and this resulted in inferior paraplegia, in another case it was caused by meningioma relapse (co-existent pathology). Life quality scores in these patients are the best since initially there were 10 patients

(18.5 %) who required hospital cure and in whom persistent remission was achieved.

Table 6.7. Life quality scores in PC patients under different modalities of hormonal therapy

Treatment	0	1	2	3	4
Niftolide + Synestrol	0	56 (51,6 %)	38 (35,2 %)	10 (9,3 %)	4 (3,7 %)
Androcur	0	23 (40,4 %)	28 (49,1 %)	4 (7,0 %)	2 (3,5 %)
Niftolide	0	20 (29,4 %)	30 (44,1 %)	13 (19,1 %)	5 (7,4 %)
Synestrol	0	18 (15,8%)	24 (21,1 %)	48 (42,1 %)	24 (21,1 %)

6.3. A comparison of treatment results shown by hormonal study

In Summarized data of hormonal study in PC patients before and after treatment is given in Table 6.8.

A comparison of hormonal parameters during 3-6 months of treatment showed that hormonal changes were most pronounced under treatment with Synestrol. LH, testosterone levels and FTI showed a maximum decrease (by 60-80 %) and at the same time plasma SHBG level increased by 186-209 % as compared to the initial values. It means that inhibition of LH and androgen synthesis and secretion reached its maximum. A persistent decrease of plasma hormone levels was observed during the whole treatment period.

When the effectiveness of steroid (cyproterone acetate, Androcur) and non-steroid (Niftolide) antiandrogens was compared, significant differences related to their structure and mechanism of action were demonstrated. Maximum effect of Androcur was manifested after 3-month treatment: LH, testosterone levels and FTI decreased by 32-50 %. Testosterone level remained lowered after 6-month follow-up. Niftolide, being a pure antiandrogen, during first 3 months of treatment induced an increase of LH and testosterone levels with a subsequent decrease. The matter is that Niftolide blocks androgen receptors in target tissues resulting not only in the reduction of the prostate but also in stimulation of hypothalamic-pituitary-testicular axis followed by

intensified LH and testosterone secretion. An increase of blood LH and testosterone contents is an unfavourable factor that might cause development of the disease but it is neutralized by Niftolide in the prostatic tissues. As a result Niftolide facilitates satisfactory therapeutic effect.

Table 6.8. Hormone and SHBG levels in blood plasma under various treatment patterns (Means \pm S.E.)

Treatment	Parameter	Pretreatment level	3 months later	6 months later
Androcur, 200 mg/day	LH, IU/l	14,2 \pm 1,3	11,0 \pm 1,0	15,7 \pm 11,9
	T, nmol/l	8,3 \pm 0,5	4,2 \pm 0,4	5,1 \pm 0,5
	SHBG, nmol ³ H-DHT/l	21,8 \pm 2,2	19,0 \pm 2,4	21,4 \pm 2,6
	FTI	36,6 \pm 4,4	23,3 \pm 6,0	24,2 \pm 4,8
Niftolide, 750 mg/day	LH, IU/l	6,4 \pm 1,0	12,0 \pm 1,2	11,4 \pm 1,6
	T, nmol/l	6,3 \pm 1,0	8,7 \pm 1,7	6,1 \pm 1,5
	SHBG, nmol ³ H-DHT/l	24,7 \pm 3,6	24,9 \pm 2,9	27,2 \pm 2,6
	FTI	30,0 \pm 5,3	42,1 \pm 9,4	21,3 \pm 6,4
Synestrol, 60 mg/day	LH, IU/l	12,8 \pm 1,9	6,4 \pm 2,0	-
	T, nmol/l	6,4 \pm 0,3	2,9 \pm 0,6	-
	SHBG, nmol ³ H-DHT/l	25,5 \pm 4,3	72,9 \pm 9,8	-
	FTI	36,4 \pm 7,2	7,6 \pm 4,5	-
Niftolide, 750 mg/day + Synestrol, 6 mg/day	LH, IU/l	8,6 \pm 2,7	4,1 \pm 0,6	6,6 \pm 1,0
	T, nmol/l	7,5 \pm 2,0	2,3 \pm 0,6	7,3 \pm 2,1
	SHBG, nmol ³ H-DHT/l	16,3 \pm 2,9	27,5 \pm 5,8	41,7 \pm 5,9
	FTI	55,2 \pm 6,2	14,2 \pm 6,8	36,0 \pm 6,0

A combination of Niftolide and Synestroi has certain advantages (Fig. 6.11). It prevents an increase of sex hormone levels and even lowers them as compared to monotherapy with Niftolide. LH and testosterone levels decreased by 50-70 % as compared to basal values and remained within this range with slight fluctuations for nearly 6 months.

SHBG content increased by 70 % 3 months later and reached 157% after 6 months. Changes in SHBG level induced a dramatic (75 %) decrease of FTI which remained lowered during 6-month followup. This may be considered a positive result of combined therapy.

Thus a combination of Niftolide and low doses of Synestroi in no way yields to Androcur in its effect on blood hormone levels.

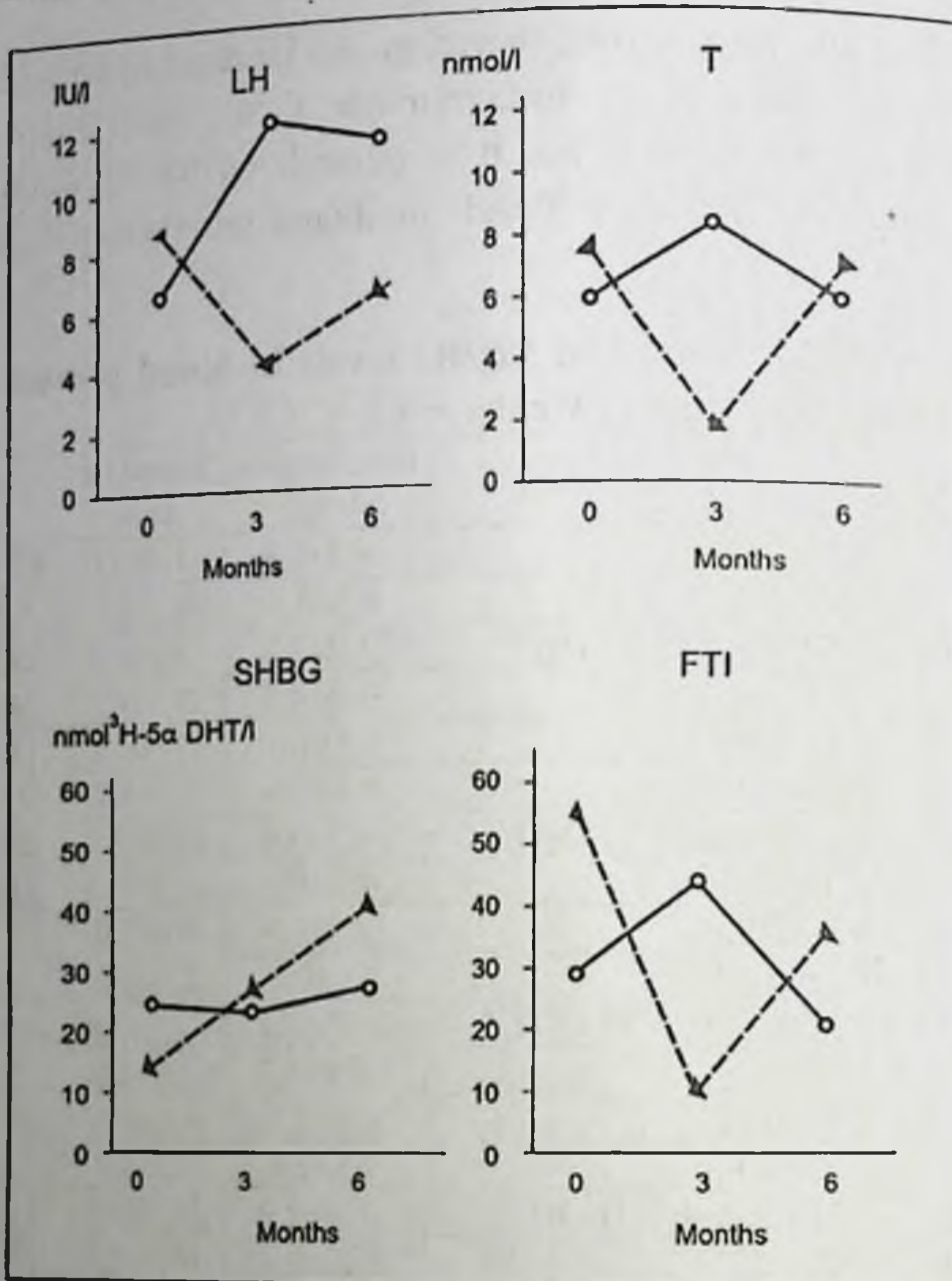


Fig. 6.11. Blood plasma hormone and SHBG levels in PC patients under low dose estrogen-antiandrogen therapy and monotherapy with Niftolide (flutamide). Solid line, flutamide (750 mg/day); broken line, flutamide + Synestrol (6 mg/day)

6.4. Long-term results of hormonal therapy

It is well known that hormonal therapy of PC patients usually continues for the whole life with short (1-1.5 months) intervals with a strict control of blood hormone levels and PSA content. It is reasonable to vary drugs in order to prevent secondary resistance. We have already cited the results of 3-6-month treatment courses of PC patients (stages I-IV) with Synestrol, Niftolide, Androcur, LEAT. We have also compared the effectiveness of different treatment modalities. When the treatment course was over an interval was made. But in case of clinical indications

the patients received hormonal therapy with other estrogenic drugs following the conventional patterns (Synestrol 2 %, 3-4 ml i.m. daily for 30 days; Chlorotrianisene, 1 tablet (0.012 g) 3 times a day during 30 days; Microfollin Forte, 1 tablet (0.05 mg) daily for 30 days; Honvan i.v., 600 mg a day for 20-25 days or 1 tablet (0.1 g) 3 times a day for 30 days) alternating them.

After such treatment long-term results were studied for up to 3 years in 108 patients who received LEAT at the first stage of treatment, in 57 patients treated with Androcur, in 68 patients who received monotherapy with Niftolide and in 114 Synestrol-treated patients. Summarized data on patients' survival is given in Table 6.9.

Table 6.9. Survival in PC patients

Treatment	PC stage	Number of patients	Survival, years		
			1	2	3
Niftolide + Synestrol	I-II	64	64(100%)	62 (96,8 %)	62 (96,8 %)
	III	22	22 (100%)	20 (90 %)	18 (81,8 %)
	IV	22	22 (100%)	18(81,8%)	14 (63,6%)
Androcur	I-II	37	37(100%)	37(100%)	34 (91,9%)
	III	16	16(100%)	14(87,5%)	10(75,0%)
	IV	4	4(100%)	0	0
Niftolide	I-II	27	27 (100%)	25 (92,5 %)	22 (81,5%)
	III	23	23 (100%)	21 (91,3%)	17(73,9%)
	IV	18	14(77,7%)	10(55,5%)	9 (50 %)
Synestrol	I-II	54	54 (100%)	51 (94,4 %)	48 (88,8 %)
	III	54	52(100%)	54 (90 %)	48 (80 %)
	IV	6	4 (66,6 %)	2 (33,3 %)	1 (16,6%)

As seen from Table 6.9 and data on the frequency and type of complications, causes of fatal outcome given above, the best results were achieved in LEAT- treated patients with advanced PC.

NEOADJUVANT HORMONAL THERAPY OF PROSTATE CANCER

Because of asymptomatic beginning of PC and difficult diagnosis only in 5-10 % of patients the disease is diagnosed at its early stages ($T_{0-2}N_0M_0$) when radical surgical treatment (prostatectomy) is possible. Though lately owing to new up-to-date methods of diagnosis (first of all blood PSA concentration) early diagnosis improved as well as the number of operable patients, the clinical experience shows that even in such patients regional metastases and tumor spreading are often found during surgery. It decreases the effectiveness of treatment or completely rules out the possibility of radical surgery. Thus there emerged an idea of hormonal therapy preceding surgery, the so-called neoadjuvant therapy (NAT). After surgery postoperative adjuvant therapy is often prescribed. NAT which has gained recognition in other fields of oncology, for managing testicular tumor and Wilms tumor in particular, was discussed (Schulman, 1994; Fair et al., 1997). At the same time many authors pay meticulous attention to this topic.

NAT is used mainly before radical prostatectomy. In this case patients are treated for 3 months with LHRH agonists Zoladex, 3.6 mg or Decapeptil 3.75 mg, once in 28 days and non-steroid antiandrogen (Flutamide, Nilutamide, Niftolide) in a dose of 750 mg/day (Fair et al., 1997). The aim of this treatment is to downstage, localize the process, make the surgery easier and less painful, slow down the disease progression and prolong the survival (Schulman, Sassine, 1993; Schulman, 1994; Graham et al., 1995).

Data on PC NAT reported by different authors diverse greatly but all of them confirm certain effectiveness of the method. A retrospective study of the NAT results showed that in patients with local PC who received 3-month therapy aimed at complete androgen blockade prostatic size decreased by 31-75 %, in 9.37 % of patients a tumorous nodule was undetectable. During surgery it was easier to dissect the prostate, intra-operational hemorrhage was less intensive. It was shown that in 14-38 % of patients the process is localized within the capsule, in one third of patients downstaging was achieved which is confirmed histologically.

A comparison of prostatectomy specimens showed a significant decrease of proliferative activity of the tumor and the amount of foci with tumorous cells at the edge of the incision, the so-called positive surgical margins.

In patients who received preoperative therapy tumorous cells are found at the edge of the incision in 7.8 - 32.0 % of cases, without treatment this figure makes 33.8-57.0 %. In 44 % of patients with T₃ stage (C) downstaging without relapse for 40 months is observed, in 56 % disease progression is observed within a year, a number of patients without disease development grows (Schulman, 1994; Villavicencio et al. 1994; Civantos et al., 1996; Lee et al., 1996; Sökeland, Engehausen, 1997).

Nevertheless there are still questions on process dissemination and disease development during this 3-month period and if the right time for radical surgery is not lost. But taking into consideration low proliferative activity of prostatic tumors (only in 2.4 % of patients they grow fast) it is believed that such danger should not be overestimated (Sökeland, Engehausen, 1997). After preoperative androgen blockade a more rapid restoration of the general state is observed postoperatively, PSA level decreases below 4 ng/ml. It was noted that in 86 % of cases with PSA level less than 0.25 ng/ml T₂ stage is usually observed while in patients with PSA level higher than 4 ng/ml it is usually T₃₋₄. Preoperatively, this phenomenon might be a prognostic factor while selecting patients for surgery.

There are also other opinions that are based on studying the results of PC treatment at stages T_{2c} (B₂) and T₃ (C) taking into consideration tumor spreading, age, PSA level and tumor type: antiandrogen therapy prior to radical prostatectomy does not result in a decrease of tumor size and changes in histopathologic staging as compared to untreated patients, it does not improve the survival and does not effect the relapse rate. PSA

cannot be considered a reliable indicator of the state of the prostate after NAT and the concept of downstaging might be misleading (Oesterling et al., 1993; Graham et al., 1995; Skardino, 1996).

Taking into account these discrepancies it seems reasonable to conduct multicentre randomized studies in order to evaluate the effectiveness of NAT. It is also important to establish if NAT is reasonable both at early (T_{0-1}) and late (T_{3-4}) stages.

One study assessed the effect of NAT by pathological process, PSA level and postoperative relapse rate. In 73 % of patients with T_0 - T_1 who received NAT a tumor localized within the prostate was found at surgery, positive margins in the prostate were discovered in 17 % of patients as compared to 56 % and 36 % of patients who were operated without NAT. Normal PSA level preserved for 28.6 months in both groups (from 6.2 to 49.5 months) in 89 % and 84 %, respectively, however this difference was not significant. It was concluded that prior to radical surgery NAT improves local state of the prostate and the results of treatment and also increases the number of patients to undergo radical surgery. PSA levels in both groups were nearly identical and usually they increased in case of tumor spreading beyond the capsule (Fair et al., 1997).

NAT is of special importance for PC patients with stages B_2 - C , $*D_1$, D_2 . When B_2 and C are diagnosed preoperatively a mistake may be made because of downstaging the disease, in this case surgery with neoadjuvant hormonal therapy or irradiation is indicated. In stage D_1 combined treatment with hormonal therapy and prostatectomy or irradiation is recommended. In case of D_2 hormonal therapy is the only method of choice. If hormonal treatment or irradiation have any priorities over surgery is still under discussion. The role of NAT before prostatectomy and irradiation as a radical method has not been elucidated yet though it has been established that blood plasma PSA level before surgery correlates with the extent to which histological changes caused by preoperative treatment, are manifested, and significant tumor regression might be expected only when PSA is undetectable (Tobisu, 1994).

Another multicenter randomized study with pathohistological assessment of resected tumors showed that 3-month NAT aimed at complete androgen blockade results in involutional changes in the prostate and its reduction, loss of glandular structure in the residual foci of adenocarcinoma, vacuolization of the cytoplasm and degeneration of tumor cells with inflammatory reaction, planocellular metaplasia, pyknosis of

the nuclei and a 35 % decrease of prostatic intraepithelial neoplastic areas. It should be noted that less pronounced morphological changes mentioned above are observed after treatment with finasteride (Proscar). Pathologists should bear it in mind studying histological specimens from finasteride-treated patients. When PSA levels, prostatic size, histopathological changes, DNA content and tumor proliferative activity were studied, it was established that following NAT PSA level lowers from the mean value of 17.5 to 4.0 ng/ml and below, prostatic size decreases on the average of 37 % (16-52 %). Highly malignant undiploid adenocarcinoma is found in 25 % of NAT-treated patients while in the control group this figure was 80 %, positive immunostaining for proliferating cell nuclear antigen was found in more than 10 % of nuclei in 33 % of patients versus 90 % in the control group. Pathohistological diagnosis of pT₂N₀ was confirmed postoperatively in 74.1 % of patients, pT₃N₀ in 22 %, pT₃N₁ in 3.7%.

Thus NAT causes manifested changes in the prostate and its tumors, decreases malignancy grade and proliferative activity of the neoplasm which is a positive prognostic factor that facilitates greater number of operable patients (Armas et al., 1994; Civantos et al., 1996).

It has been shown that the incidence of positive margins in a resected tumor depends on its type, stage of the disease and NAT duration. While in a general population of operated patients positive margins in the prostate following NAT make 11.5 % versus 35.3 % in untreated patients, in apical tumor these values are 18.6 % and 50 %, respectively. At T₃(C) stage the incidence of positive margins decreases with increased NAT duration and makes 37.5 % in 3 months and 16.7 % in 6 months. This data is of interest but it is still not clear if NAT effects the survival of patients. The answer to this question will be given only after a long-term follow-up (Solomon et al., 1993; Voges et al., 1994).

Special attention should be paid to another NAT modality when patients with localized adenocarcinoma were prescribed cyproterone acetate in a dose of 300 mg/day for 3 months before radical surgery. As in the previous method, local state of the prostate, positive margins in the prostate after surgery, initial PSA level (4 ng/ml or below, 4.1 - 10 ng/ml and over 10 ng/ml), clinical stage (T_{2c}, T_{2b} or less), histologic diagnosis of the biopsy specimen and Gleason grading (1977), the number of can-

cerous foci in biopsies were taken into account. It was shown that following NAT all mentioned parameters were much better than without NAT and were similar to those mentioned above (Rabbani et al., 1998).

There is also information that a combination of finasteride (5 α -reductase inhibitor) and flutamide, similar to combined androgen blockade with LHRH agonist and flutamide, might be effective for preoperative treatment of PC patients (Fleshner, Trachtenberg, 1993; Schulman et al., 1993). Such treatment results in a decrease of blood PSA level (on an average from 34 to 3.8 ng/ml), increase of blood plasma testosterone level and facilitates maximum androgen blockade without any significant side effects.

Diethylstilboestrol was also used for NAT (Fair, Heston, 1991). PC patients with stage C were given 3 mg of the drug for 8-10 weeks before prostatectomy. After surgery in 41.2 % of patients no positive margins and tumor cells were found in seminal vesicles and pelvic lymph nodes, in 5.9 % of patients the residual tumor was not diagnosed at all, in 11.8 % only small tumor loci were found. This NAT pattern may be recommended for preoperative treatment of patients with B₂ and C stages.

At the Institute of Urology and Nephrology 16 patients with T₁₋₂N₀M₀ (6 patients with T₁ and 10 patients with T₂ stage) received NAT prior to radical prostatectomy. The treatment consisted in radical prostatectomy with pre- and postoperative therapy with Niftolide (flutamide). Niftolide was administered orally in a dose of 250 mg 3 times a day for 10 days before surgery and postoperatively in combination with Synestroi 2 % in a dose of 0.25 ml or Synestroi 0.1 % in a dose of 3.0 ml for 3 months. After that Synestroi was taken sublingually in tablets in an adequate dose.

Intraoperative, immediate and remote results of preoperative treatment were evaluated. It was established that after such treatment prostatic size decreased as compared to that before treatment with Niftolide began. Saturation with blood was less intense, that is why the hemorrhage during surgery was less and it was easier to perform prostatectomy in terms of pure technique. No complications were noted in the immediate postoperative period.

All patients were followed-up. In one patient a relapse in the prostatic bed and skeletal metastases were found, in four patients bone metastases were discovered by the end of the first year. All other patients are considered healthy.

Blood plasma testosterone, DHT and SHBG levels and FTI were measured in all patients. Blood plasma testosterone level in patients were significantly higher (11.7 ± 1.06 nmol/l) than in healthy men (7.7 ± 1.3 nmol/l). DHT level did not show any difference and ranged 0.14-1.3 nmol/l (on average 0.42 ± 0.07 nmol/l in patients and 0.38 ± 0.14 nmol/l in healthy men). SHBG content in PC patients was higher than in the control group (26.9 ± 2.8 and 12.5 ± 1.5 , respectively). FTI was slightly lower though not significantly (42.5 ± 4.0 and 67.6 ± 14.6 , respectively).

Hormonal study carried out in these patients after surgery and hormonal therapy showed a decrease in blood plasma testosterone level with no significant changes in estradiol content. No changes in testosterone metabolism in resected tumorous tissue were observed.

When significance and effectiveness of NAT before radical prostatectomy were assessed not only its advantages but also its potential shortcomings were mentioned. These included side effects of hormonal drug therapy, its high cost, deferred radical treatment, possible cell proliferation in hormone-resistant areas of the tumor. There exist different opinions on decreased incidence of positive surgical margins in the prostate after NAT. On the one hand, after treatment prostatic size diminishes and changes occur in the periprostatic tissue, and this makes surgery easier. On the other hand, fibrosis makes it more difficult and increases the risk of remained cancerous areas. Improved results of treatment following NAT might be associated with the death of tumor cells in the prostate. But there still remains a question if it is possible to achieve downstaging through NAT effect on extraprostatic tumorous foci (Watson, Soloway, 1996). In contrast to earlier optimistic reports based on histological studies nowadays this phenomenon is evaluated with caution. The matter is that it is rather difficult to interpret pathological specimen after NAT and downstaging cannot always be achieved. Still NAT might be helpful in patients with a high risk of positive cancerous areas along the surgical incision especially in clinical T_{2b} stage, blood serum PSA level of 10-20 ng/ml and low differentiation according to Gleason (1977). This treatment is well tolerated with minimum side effects.

LIST OF ABBREVIATIONS

CAB	- combined androgen blockade
CNS	- central nervous system
DHT	- 5 α -dihydrotestosterone
FSH	-follicle-stimulating hormone
FTI	- free testosterone index
LEAT	- low-dose estrogen-antiandrogen therapy
LH	- luteinizing hormone
LHRH	- LH-releasing hormone
MAB	- maximum androgen blockade
NAT	- neoadjuvant therapy
PC	- prostate cancer
PSA	- prostatic specific antigen
SDH	- Δ^5 -steroid-3 β -hydroxydehydrogenase
SHBG	-sex hormone-binding globulin
T	- testosterone
UFM	- uroflowmetry

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Scriptum



In the monograph concerning hormonal treatment of prostate cancer special attention is paid to androgen deprivation therapy. Molecular, hormonal and cellular mechanisms of prostate cancer pathogenesis and progression are discussed. Results of animal research and clinical use of luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens and low dose of estrogens for androgen deprivation are described.

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