The THAI Journal of SURGERY 2006; 27:93-100.
Official Publication of the Royal College of Surgeons of Thailand

Increase of the Expression of Receptors of Steroid Hormones in Patients with a Partial Androgen Deficiency of Aging Men (PADAM)

Alexander V. Pechersky[a]
Vladimir F. Semiglazov[b]
Boris K. Komyakov[c]
Bakhman G. Guliev[d]
Andrey I. Gorelov[e]
Andrey I. Novikov[c]
Viktor I. Pechersky[f]
Nikolay N. Simonov[b]
Alexey V. Gulyaev[b]
Igor A. Samusenko[g]
Maxim S. Vonsky[h]
Alexey G. Mittenberg[i]
Oleg B. Loran[j]

[a]*Department of Surgery, St. Petersburg Medical Academy of Post-Graduate Studies, St. Petersburg, Russia*
[b]*Surgical Department, N.N. Petrov Scientific-Research Institute of Oncology, St. Petersburg, Russia*
[c]*Department of Urology, St. Petersburg State Medical Academy of I.I. Mechnikov, St. Petersburg, Russia*
[d]*Department of Urology, Municipal Multi-Profile Hospital No 2, St. Petersburg, Russia*
[e]*Urology Course, St. Petersburg State University, St. Petersburg, Russia*
[f]*Problem Scientific-Research Laboratory, P.F. Lestgaft State Academy of Physical Education, St. Petersburg, Russia*
[g]*Department of Pathological Anatomy, St. Petersburg State Medical Academy of I.I. Mechnikov, St. Petersburg*
[h]*Laboratory of Genome Structural Organization, Institute of Cytology of the Russian Academy of Sciences, St. Petersburg, Russia*
[i]*Laboratory of Regulation of Gene Expression, Institute of Cytology, Russian Academy of Sciences*
[j]*Department of Urology, Russian Medical Academy of Post-Graduate Studies, Moscow, Russia*

Abstract ***Objectives:*** **To study the disruption of the normal development cycle of cells with androgen receptors by partial androgen deficiency of aging men (PADAM).**

Materials and Methods: In the current study, 15 patients were held under observation (5 with prostate cancer, 5 with bladder cancer and 5 with rectal cancer).

Results: **The levels of testosterone in the tissues of the peritumorous zone of the prostate as well as in the tumorous tissue in patients with cancer of the prostate, bladder and rectum were higher than analogous indices in the blood serum. The indices of the histochemical score of androgen (AR) in the peritumorous zone among patients with prostate cancer were higher than the analogous indices of the control group. Upon research of the peritumorous zone among patients observed groups, expressions of ER, PR, bcl-2, Ki67 and p53 were detected.**

Conclusions: **The results of this study suggest the conclusion that production of testosterone by a whole set of tumors and tissues of the peritumorous zone, which is accompanied by increased proliferative activity and disturbance of the regulation of the cell cycle, is caused by PADAM. The given changes are directed at compensating for testicular deficiency.**

Correspondence address : *Alexander V. Pechersky, MD, 41 Kirochnaya St., St. Petersburg, 193015, Russia*
E-mail: a_pechersky@msn.com

Introduction

The probability of oncological pathology significantly increases in men over 40 years old.[1] At this age men show a reduction of testosterone circulating in the bloodstream. This reduction is named partial androgen deficiency of aging men (PADAM).[2,3] PADAM leads to a disruption of the mechanisms of regulation in the system of the gonads-hypophysis-hypothalamus and in particular to an increase in the activity of the hypophysis,[4] as well as to an increase in the levels of 5α-dihydrotestosterone and 17β-estradiol.[5] A decrease in the level of testosterone induces an increase in kariomitotic activity, disruption of regulation of the cell cycle, as well as inhibition of apoptosis.[6]

An increase in proliferative activity, equally with insulin resistance and osteoporosis is a partial manifestation of metabolic syndrome. The latter reflects the complex of compensatory-adaptational reactions whose development among men of older age groups is caused to a considerable extent by a decrease in the level of testosterone.[6]

The given factors have a significant influence on the development of cancer of the prostate, bladder and rectum, as well as on several other organs.[7-9]

The malignant transformation of a whole set of tissues is accompanied by the manifestation of hormonal activity in these tissues.[10]

The cause and effect relations between PADAM, extragonadal production of testosterone and increase in proliferative activity in men of older age groups provide much interest for researchers.

Materials and Methods

Patients

In this study, fifteen patients were held under observation (5 with prostate cancer, 5 with bladder cancer and 5 with rectal cancer). The patients were men in the age ranged from 53 to 79 years. Independently from the localization of the tumor, the patients were given either radical prostatectomy, cystectomy or extirpation of the rectum. The level of testosterone was determined in the tissues of the tumor and the peritumorous zone. The transport of tissues for the ensuing measurement of testosterone was done in a thermoisolated container with dry ice (-60 °C). For histological and immunohistochemical analyses the tissues of the peritumorous zone were immobilized in a 10% solution of formalin.

Criteria for a patient to be enrolled into the study included 1) having cancer of one of the locations mentioned above, 2) being over 50 years old, 3) having a disposition to operative care, and 4) having a generally good overall state.

Patients with infectious diseases of the lower urinary tracts and large intestine, varicocele, disturbances of the liver functions (a presence of transaminase and/or bilirubin above the normal level), a presence of creatine in the serum of more than 0.11 mmol/l and those who had received medical treatment within the last three months using antiandrogen or inhibitors of 5α-reductase were excluded from the study.

The control group was made up of men ranging in age from 18 to 29 years, who had just died as a result of traumatic injuries. All of the members of the control group had a normal body shape and normal development of secondary gender attributes. Upon autopsy the members of the control group had no chronological diseases. Five samples of tissue from each of the prostate, the bladder and the rectum were taken from men of the control group. The tissue samples were immobilized in a 10% solution of formalin. The sampling of tissue material was done in a period less than 24 hours after death.

Extraction of Testosterone

Tissue samples were de-frozen, reduced in size and homogenized at 0 °C in a ground-glass Potter homogenizer in a buffered solution of TBS (10 mM Tris-HCl, pH 7.5, 150 mM NaCl). The homogenate was prepared from a calculation of 3 ml of buffered solution per 1 gram of tissue sample. Four volumes of diethyl ether were added to the aliquot of the resulting suspension, and the lipids were extracted within the next 20 minutes during intensive shaking. The starting suspension and extract were divided using a centrifuge (6600 min-1, 2 min), and the supernatant was taken out, after which the extraction was repeated.

The resulting extract was evaporated in an evaporating compartment and the precipitates were dissolved in a buffered solution of PBS (1.7mM KH_2PO_4, 5.2 MM Na_2HPO_4, 150MM NaCl, pH 7.4). The solution was cleared using a centrifuge and the amount of testosterone in the solution was then measured.

Hormonal Analysis

The analysis of the overall testosterone levels in the blood serum and in the extracted solution was done using an immuno-fermentation method. In order to measure the amount of overall testosterone in the blood serum, venous blood was extracted in the morning, on an empty stomach, at a fixed time (08.00-10.00).[11,12]

The measurement of the overall testosterone levels in the blood was done using equipment made by the company DPS (USA). The sensitivity and coefficients of variation for testosterone were 0.2 nmol/l and 8%.

Immunohistochemical Analyses

Analysis of the receptors of androgen (AR), estrogen (ER) and progesterone (PR), as well as bcl-2, Ki67 and p53, was done using a one-stage method with antigen demasking (method of high-temperature tissue preparation) on paraffin sections employing diagnostic instruments made by the company Novocastra Laboratories Ltd (Great Britain).

The results of the identification of AR, ER and PR were evaluated using the half-quantity method "histochemical score".[13] The levels of bcl-2, Ki67 and p53 were represented as a comparison of the number of positive cells to 1,000 examined cells.

Statistical analysis

A comparison between the levels of testosterone in tissues and the blood serum for each of the patients was done using a method of dispersal analysis of repeated measurements. The evaluation of the statistical significance of the differences between the values was done using paired Student criteria as a foundation.

The data of the experimental and control groups were analyzed using a method of comparison of two groups with the use of Student criteria. All data in this text and in the tables of this work are shown in the form of average values and standard deviations ($M \pm \delta$). The values of the Student criteria are also shown (t).[14]

If none of the members of a group showed a certain expression, then this expression was only described (average values and standard deviations ($M \pm \delta$) using the analogous expression among the comparison group.

Results

The levels of testosterone in the tissues of the peritumorous zone of the prostate, as well as in the tumorous tissue of patients with cancer of the prostate, bladder or rectum were 22.9%, 49.6%, 61.3% and 72.6% respectively, higher than the analogical index in the blood serum (Table 1).

Among patients with prostate cancer the levels of testosterone in the tumorous tissue were 34.6% higher than those of testosterone in the tissues of the peritumouros zone of the prostate (Table 2).

The values of the histochemical score of AR of the peritumorous zone among patients with prostate cancer were 51.7% higher than the analogous levels of the control group (Table 3).

The results of the analysis of young men of the control group showed that ER, PR, bcl-2, Ki67 and p53 were not found, while among patients with prostate cancer an expression of the given factors was found in the peritumorous zone (Table 3).

Study of the peritumorous zone among patients with bladder cancer showed an expression of PR, bcl-2, Ki67 and p53. Among the control group the given

Table 1 Amount of testosterone in tumorous and prostate tissues as compared to blood serum among patients with cancer of the prostate, bladder, and rectum

	Testosterone, nmol/l			
	Peritumorous zone of the prostate gland	Cancer of the prostate	Cancer of the bladder	Cancer of the rectum
$\mu \pm \delta$, tissue of the tumor/ peritumorous zone	24.0 ± 3.8	36.7 ± 4.2	41.3 ± 9.7	45.7 ± 15.4
$\mu \pm \delta$, blood serum	18.2 ± 3.0	18.2 ± 3.0	16.0 ± 2.7	10.7 ± 3.1
t	2.572	8.094	5.845	5.618
	p <0.05	p <0.001	p <0.001	p <0.001

N = 5

expressions were not found (Table 4).

In the peritumorous zone among patients with rectal cancer, PR, bcl-2, Ki67 and p53 were expressed. Indices of an expression of Ki67 were more than 83.8% higher in comparison with indices of the control group. Among patients of the control group, research of the rectum did not reveal a presence of ER, bcl-2, and p53 (Table 5).

Table 2 Amount of testosterone in tumorous and peritumorous prostate tissues among patients with prostate cancer

	Testosterone, nmol/l
$\mu \pm \delta$, tissue of the tumor	36.7 ± 4.2
$\mu \pm \delta$, tissues of the peritumorous zone	24.0 ± 3.8
t	3.705
	p <0.01

N = 5

Upon morphological research of the peritumorous zone in the tissues of the prostate, the submucosal layer of the wall of the bladder and the wall of the rectum, as well as in tumors of the given organs, lymphocyte and macrophage infiltrations were detected. Among several patients the infiltrate showed expressions of AR, ER, PR, bcl-2 and p53 in lymphocytes and macrophages. There was also atrophy of the epithelium of the glands around the peritumorous zone of the prostate.

Discussion

A significant part of tissues has testosterone receptors, and can be studied as a target for androgens. Testosterone also takes part in the processes of growth and differentiation of cells.[9,15] PADAM disrupts the

Table 3 Indices of AR, ER, PR (histochemical score), bcl-2, Ki67 and p53 (the number of positive cells to 1,000 examined cells) of the peritumorous zone in patients with prostate cancer as compared to the control group

	AR	ER	PR	bcl-2	Ki67	p53
$\mu \pm \delta$, cancer of the prostate (peritumorous zone)	178 ± 24	40 ± 40	26 ± 25	0.015 ± 0.019	0.002 ± 0.002	0.113 ± 0.141
$\mu \pm \delta$, tissues of the prostate gland, control group	86 ± 50	0	0	0	0	0
t	3.683					
	p <0.01					

N = 5

Table 4 Indices of AR, ER, PR (histochemical score), bcl-2, Ki67 and p53 (the number of positive cells to 1000 examined cells) in the peritumorous zone among patients with cancer of the bladder as compared to the control group

	AR	ER	PR	bcl-2	Ki67	p53
$\mu \pm \delta$, cancer of the bladder (peritumorous zone)	0	0	8 ± 16	0.029 ± 0.034	0.002 ± 0.001	0.120 ± 0.239
$\mu \pm \delta$, tissues of the bladder, control group	0	0	0	0	0	0

N = 5

Table 5 Indices of AR, ER, PR (histochemical score), bcl-2, Ki67 and p53 (the number of positive cells to 1,000 examined cells) of the peritumorous zone among patients with rectal cancer as compared to the rectum of the control group

	AR	ER	PR	bcl-2	Ki67	p53
$\mu \pm \delta$, cancer of the rectum (peritumorous zone)	0	6 ± 12	0	0.110 ± 0.195	0.037 ± 0.023	0.104 ± 0.198
$\mu \pm \delta$, tissues of the rectum, control group	0	0	0	0	0.006 ± 0.0004	0
t				2.958		
				p <0.05		

N = 5

normal cycle of development of cells which have androgen receptors. The development of androgen-independent transit-proliferative cells, which require the presence of a physiologically necessary level of testosterone, in the androgen-dependent pool of transition cells,[9] is accompanied by a disruption of the process of their differentiation.[7,16-18] The disruption of the development of cells on the testosterone-dependent stage regularly inhibits apoptosis. The given processes are a precursor to malignant growth. They are reflected by changes observed in the peritumorous zone.

In order for replacement of the shortage of endocrinal activators of division to take place, and in particular for replacement of the shortage of mitogen activity of testosterone, a whole complex of compensatory-adaptational reactions forms, which effect endocrinal, paracrinal and autocrinal levels.[6,7,19]

The given compensatory changes are expressed as, by intensification in production of peptide growth factors by the cells, increases in aromatase and 5α-reductase activity, the level of endocrinal activators of division (somatotrope hormone, insulin), vitamin D[5,6] as well as by increase of stimulation of formation of the testosterone. An increase in the level of testosterone is achieved not only by hypophysial stimulation of Leydig cells, but by the use of synthesis of testosterone by other tissues as well, for which, in normal conditions, such a function is not typical. The given conclusion is confirmed by the significant prevalence of the amount of testosterone in the peritumorous tissues of the prostate or in the tumorous tissue among patients with cancer of the prostate, bladder, or rectum as compared to the level of testosterone in the blood serum of these patients, ($p < 0.05$, $p < 0.001$, $p < 0.001$ and $p < 0.005$, respectively). Among patients with cancer of the prostate, the levels of testosterone in the malignant tissue were routinely higher than the analogous indices in the tissues of the peritumorous zone ($p < 0.01$).

This shows that partial androgen deficiency of aging men is compensated for by production of testosterone outside the gonads. The predominance of the level of testosterone in the tumorous tissue as compared to the peritumorous zone attests to the intensification of testosterone production outside the gonads together with a malignant transformation of cells producing testosterone. The largest expression of the given compensatory-adaptational reaction occurs when the level of mitotic activity of the cells is significantly increased during their malignant transformation.

The expression of AR in the tissues of the peritumorous zone among patients with prostate cancer as compared to the analogous index in the prostate of men in the control group provided evidence that adequate renewal of regulation, usually implemented by means of testosterone, didn't set in among patients with cancer, even despite extragonadal production.

The developing compensatory-adaptative reactions during a decrease in the level of testosterone are most of all directed towards an increase in the mitotic activity of the cells. Their expression is proportional to the level of the decrease in the level of testosterone. In particular, an increase of 5α-reductase and aromatase activity, which synthesizes 5α-dihydrotestosterone and estrogen, is observed in patients whose testosterone levels decrease.[5,6] Estrogens induce an intensive mitogenesis in the tissues which contain the specific receptors.[20] 5α-dihydrotestosterone and testosterone, connecting to one and the same inner-cell receptor,[10] stimulate proliferative activity of the cells.[21]

The reception apparatus, which accepts signals, as well as secreting organs, tissues and cells, form an interconnected system.[22-24] Activation of the receptors of the membrane of a cell potentiates the effect of the corresponding regulative factor.[15] The expression of AR and ER in the tissues of the peritumorous zone of the prostate and the expression of ER in the tissues of the peritumorous zone of the rectum supplement the increase in the activity of aromatase and 5α-reductase, which are observed when the level of testosterone drops.

The intensification of steroidogenesis in the tumorous tissue can be caused by the presence in this tissue of lymphocyte-macrophage infiltrate.[24,25] Lymphocytes and macrophages are capable of synthesizing testosterone from androstenedione.[24,26,27] Lymphocytes and macrophages also have aromatase activity, transforming androgens into estrogens.[24,28-30] Lymphocyte and macrophage infiltrate of tumors of the prostate gland, bladder and rectum, as well as in the peritumorous zone of the given organs, locally supplement the overall compensatory reaction directed towards raising mitotic activity. The presence of lymphocytes and macrophages in the process of steroidogenesis affirms the conception of immunal

and neuroendocrinal unity.[24,25,31,32]

Disruptions in the process of differentiation of androgen-dependent transition cells, caused by PADAM, are morphologically created by atrophy of the given cells. In particular, atrophy of the epithelium of acinar of the prostate is observed.[7,9] The given changes took place in the tissues of the peritumorous zone of the prostate. Atrophy of the epithelium in the glands of the peritumorous zone among patients with prostate cancer and the absence of atrophy in the prostate glands of the control group together point to the inadequacy of the compensatory mechanism created by extragonadal synthesis of testosterone during PADAM.

Extragonadal synthesis of steroidal hormones is stipulated by hormonal and autocrino-paracrinal factors. Prolactin,[33] insulin,[34] vitamin D,[24,35,36] insulin growth factor-1 (IGF-1),[7,36,37] basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF)[37] have a strong influence on this process. The increase in the level of the given factors is characteristic for development of metabolic syndrome (X-syndrome) and is seen when the level of testosterone decreases.[6]

A rise in the levels of STH, insulin, estradiol, 5α-dihydrotestosterone, vitamin D, bFGF, IGF-1 and EGF among men with PADAM[5,6] stimulate cell proliferation (expression of Ki67) and inhibition of apoptosis (expression of bcl-2), found in the peritumorous zone among observed patients to a considerable extent. In this way, atrophical changes in androgen-dependent cells, stipulated by PADAM, are accompanied by an increase in the risk of blastomatous transformation.

An increase in the given factors in the blood plasma involves androgen-independent tissues in the formation of compensatory reactions as a response to the development of PADAM. Thus, among the patients observed extragonadal production of testosterone by tumorous tissue of the rectum and bladder was revealed. Immunohistochemical study of the tissues of these organs among the control group, as well as in the peritumorous zone among patients with bladder or rectal cancer did not reveal the presence of AR. In the peritumorous zone of the given patients Ki67 and bcl-2 were expressed regularly.

Extragonadal production of testosterone in the patients observed in this study, as well as the results of other studies (synthesis of the analogues of hypophysic hormones by cells of the cancerous tumor of the prostate gland,[39] extragonadal production of estrogens by fatty tissue and several other types of tissue among women[24] in the menopausal period, and synthesis of renin by myocytes of the wall of the afferent arteriole, transformed into epitheloid cells, and by mesangiocytes of the kidney during expressed, long-term ischemia of kidney tissues[40] and other examples, show that potentially any cell of the organism is able to produce hormones. Hormonal activity of tissues (which are not endocrinal or neuroendocrinal by nature) is conditional upon either insufficiency of the corresponding endocrinal factor (for example, extragonadal production of androgens among men with PADAM and of estrogens during the menopausal period) or upon the assistance of the developing hormone in the chain of the compensatory-adaptational reactions, for example synthesis of prolactin by the tissue of cancerous tumors of the prostate gland,[41,42] which leads to an increase in aromatase activity.[33] Apparently, such cells, which manifest hormonal activity under certain conditions, form the so-called diffuse endrocrinal system (APUD-system).

Among the majority of patients belonging to older age groups the indices of the level of testosterone were within the normal referential interval, which can be explained by the extragonadal production of testosterone. However, the compensatory secretion of hormones by nonendocrinal tissues and cells (including tissues of the tumors) becomes unregulated[10,15,40] and inadequate. Atrophy of androgen-dependent tissues of the peritumorous zone and the expression of AR in these tissues (changes which attest to the insufficiency of testosterone regulation) among patients with prostate cancer affirm the inadequacy of the given compensatory mechanism.

The expression of p53 (which determines normalization of cell growth and stops proliferation of tumurous cells), which was shown in the peritumorous zone in patients with cancer of the prostate, bladder, or rectum, helps to control the increased proliferative activity, which develops as an answer to the inadequacy of the mitotic action of testosterone during PADAM.[6] The expression of p53 adds to the increase during PADAM of the levels of transforming factor of growth-β (TGFβ) and cytotoxic factors of anti-cancerous cell immunity: TNFα, acid phosphatase, alkaline phosphatase and serine proteinase (to which PSA belongs).[6] The TGFβ is responsible for the consequential passage

by the cell stages of the stages of differentiation and the start of apoptosis.[7,8] The cytotoxic factors of anti-cancerous cell immunity utilize the developing atypical cells and launch a program of apoptosis.[43,44] During a significant increase in the number of atypical cells, their effectiveness becomes inadequate, which was seen when tumorous tissue developed among the patients observed in this study.

The dependency of cell immunity on PADAM is affirmed by the expressions of AR, ER, PR, bcl-2 and p53 of lymphocytes and macrophages of infiltrate of the tumor and peritumorous tissues among the patients studied. The presence of AR in the lymphocytes and macrophages explains the reason of decompensation of antitumor immunity when the level of testosterone is significantly reduced.[6]

Conclusions

Extragonadal production of testosterone by a whole series of tumors and tissues of the peritumorous zone, accompanied by an increase in proliferative activity and a disruption of the regulation of the cell cycle is predetermined to a significant extent by partial androgen deficiency of aging men (PADAM). The given changes are directed at compensation of testicular deficiency (in particular at overcoming the androgen-dependent stage of the development of androgen-sensitive cells), and are the partial manifestation of metabolic syndrome (X-syndrome). The atypical cells, which unavoidably develop under metabolic syndrome, are dealt with by means of the immune process, the capabilities of which become less and less adequate in the given circumstances.

The pathological processes described in this study concern all organs and tissues of the organism, including both androgen-dependent, and androgen-independent tissues, thereby raising the risk of their tumorous transformation.

REFERENCES

1. Napalkov NP. Common oncology. Leningrad: Medicine, 1989.
2. Bremner WJ, Vitietto MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. Clin Endocrin Metab 1983; 56: 1278-81.
3. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex-hormone levels in middle-aged men: Results of the Massachusetts male aging study. Clin Endocrinol 1991; 73: 1016-25.
4. Vermeulen A, Kaufman JM. Androgens and cardiovascular disease in men and women. The Aging Male 1998; 1: 35-50.
5. Pechersky AV, Semiglazov VF, Mazurov VI, Karpischenko AI, Mikhailichenko VV, Udintsev AV. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, estradiol and prostate volume. Intern J Androl 2002; 25: 119-25.
6. Pechersky AV, Semiglazov VF, Loran OB, et al. Changes in the level of cytokines among patients with prostate cancer after orchiectomy. Terra Medica, in its special thematic edition "Laboratory Diagnostics" 2003; 2: 26-30.
7. Bershtein LM. Hormonal carcinogenesis. St. Petersburg: Nauka, 2000.
8. Fernandez E, La Vecchia C, D'Avanzo B, Franceschi S, Parazinni F. Oral contraceptives, hormone replacement therapy and the risk of colorectal cancer. Br J Cancer 1996; 73: 1431-5.
9. Lopatkin NA. Guide to urology. Moscow: Medicine,1998; 3.
10. Lavin N. Endocrinology. Moscow: Practica,1999.
11. Loran OB, Segakl AS, Supryaga OM. Andriol in the treatment secretion infertility and climacteric syndrome in men. Urol Nephrol 1999; 3: 41-4.
12. Morales A, Bain J, Ruijs A. et al. Clinical practice guidelines for screening and monitoring male patients receiving testosterone supplementation therapy. Intern J Impot Res 1996; 8: 95-7.
13. Jonat W, Maass H, Stegner HE. Immunohistochemical measurement of estrogen receptors in breast cancer tissue samples. Cancer Res 1986; 46: 4296-8.
14. Glantz SA. Primer of biostatistics. Moscow: Practica, 1999.
15. Kettyle WM, Arky RA. Endocrine pathophysiology. Moscow: Binom Publishers, 2001.
16. Farber E. Cell proliferation as a major risk factor for cancer: a concept of doubtful validity. Cancer Res 1995; 55: 3759-62.
17. Sporn MB. The war on cancer. Lancet 1996; 347: 1377-81.
18. Russo J, Russo IH. Differentiation and breast cancer. Medicina (B. Aires) 1997; 57: 81-91.
19. Vasilyev Yu. M. Social behavior of normal cells and antisocial behavior of tumorous cells. Soros Educational J 1997; 4: 17-22.
20. Burrows H, Horning E. Oestrogens and neoplasia. Springfield, Illinois: Charles C. Thomas Publ, 1952. p. 189.
21. Zazerov VG, Severin ES. Molecular mechanisms of oncogenesis of the prostate. Vestnik of the Russian Academy of Medical Sciences 1998; 5: 29-35.
22. Neveu PJ, Le Moal M. Physiological basis for neuroimmunomodulation. Fundam Clin Pharmacol 1990; 4: 281-305.
23. Besedovsky HO, Del Rey A. Immune-neuroendocrine interactions: facts and hypotheses. Endocrine Rev 1996;17: 64-102.

24. Bershtein LM. Extragonadal Estrogen Production (role in physiology and pathology). St. Petersburg: Nauka, 1998.
25. Borkovwski A, Dosogne M, Declerq P, Muquardt C, Machin D. Estrogen oestradiol conversion by blood mononuclear cells in normal subjects and in patients with mammary and non-mammary carcinomas. Cancer Res 1978; 38: 2174-9.
26. Milewich L, Whisenant MG, Sawyer MK. Androstenedione metabolism by human lymphocytes. J Steroid Biochem 1982; 16: 81-5.
27. Coddington CC, Letterie GS, Klein TA, Winkee CA. Androgen metabolism by human peritoneal macrophages. Steroids 1988; 51: 143-61.
28. Frisch RE, Canick JA, Tulchinsky D. Human fatty marrow aromatizes androgen to estrogen. J Clin Endocrinol Metabol 1980; 51: 394-6.
29. Lea CK, Ebrahim H, Tennant S, Flanagan AM. Aromatase cytochrome P450 transcripts are detected in fractured human bone but not in normal skeletal tissue. Bone 1997; 21: 433-40.
30. Mor G, Yue W, Santen RJ, et al. Macrophages, estrogen and the microenvironment of breast cancer. J Steroid Biochem and Mol Biol 1998;67: 403-11.
31. Weigent DA, Blalock JE. Interaction between neuro-endocrine and immune systems: common hormones and receptors. Immunol Rev 1987; 100: 79-108.
32. Korneva EA, Shkhinek EK. Hormones and the Immune System. Leningrad: Nauka, 1988.
33. Pankov A. Yu. Prolactin. Large Medical Encyclopedia. Moscow: Sovetskaya Aencyclopedya, 1983; 21: 134.
34. Lueprasitsakul P, Longcope C. Aromatase activity of human adipose tissue stromal cells: effects of thyroid hormones and progestogens. Proc Soc Exp Biol and Med 1990; 194: 337-41.
35. Jakob F, Homann D, Seufert J, Schneider D, Kohrle J. Expression and regulation of aromatase cytochrome P450 in THP1 human myeloid leukemia cells. Molec and Cell Endocrinol 1995; 110: 27-33.
36. Shozu M, Takayama K, Zhao Y, Simpson ER. Hormonally controlled alternative promoters regulate aromatase expression in human THP-1 cells. Proc 4th Intern Aromatase Conf. Tahoe City, California, 1996: A-15.
37. Mendelson CR, Simpson ER. Regulation of estrogen biosynthesis by human adipose cells in vitro. Molec and Cell Endocrinol 1987; 52: 169-76.
38. Ryde CM, Nicholls JE, Dowsett M. Steroid and growth factor modulation of aromatase activity in MCF7 and T 47D breast carcinoma cell lines. Cancer Res 1992; 52: 1411-5.
39. Naz RK. Prostate: basic and clinical aspects. New York: CRC Press, 1997. p. 337.
40. Tareeva IE. Nephrology. Moscow: Medicine, 1995;1.
41. Franklin RB, Costello LC. Prolactin directly stimulates citrate production and mitochondrial aspartate aminotransferase of prostate epithelial cells. Prostate 1990; 17: 13-8.
42. Costello LC, Franklin RB. Effect of prolactin on the prostate. Prostate 1994; 24: 162-8.
43. Yarilin AA. Foundations of Immunology. Moscow: Medicine, 1999.
44. Roitt I, Brostoff J, Male D. Immunology. Moscow: Mir, 2000.