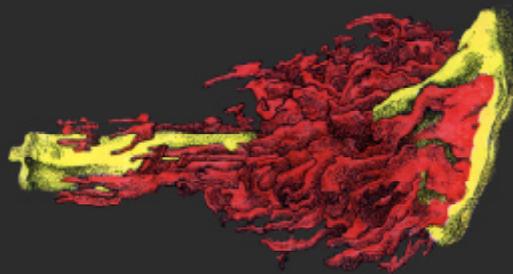


The Human Female Prostate

*From Vestigial Skene's Paraurethral Glands and Ducts
to Woman's Functional Prostate*

Milan Zaviaèiè



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Foreword

“Out of sight, out of mind”, suggested by Nicholas Bruchovsky (1990) to aptly describe the fact that while no other organ causes so much illness in men as the prostate, so little is known about its role in the body, is perhaps even more applicable to the female prostate. Morphologically incorporated into the wall of the female urethra, the female prostate, first described by Reijnier de Graaf in 1672 (de Graaf 1672), is in fact anatomically “... out of sight”.

Recognition of the female prostate has been further hindered by use of the historically acquired terminology “Skene’s paraurethral glands and ducts”, so named after Alexander Skene, who redescribed the female prostate in 1880 (Skene 1880). This terminology implies some other structure of an extraprostatic nature, rather than the prostate itself, is involved and has unfortunately until the recent studies by Zaviačič and co-workers, promulgated a vestigial notion of this female organ.

While considered in-depth herein, any doubters of the existence of the female prostate, will learn that it possesses all the components, i.e., glands, ducts, smooth musculature, characterizing the male prostate, including the cellular, enzymatic and other factors necessary for its exocrine and endocrine function.

Encouraged, while discussing the existence of the female prostate and aspects of the foregoing, including the presence of prostate-specific antigen (PSA) as an explanation for PSA in the serum of females, some 10+ years ago with the eminent urologist Willard E. Goodwin (UCLA School of Medicine), “...to put all that information together and elaborate a little more on it ...”, I am grateful that while other activities precluded my doing so, my esteemed colleague Professor Milan Zaviačič has done so and has given me the privilege of writing this “Foreword”. In this regard, the masterfully meticulous studies herein presented by Professor Zaviačič in this monograph entitled: *The Human Female Prostate*, have and will contribute immeasurably toward our further understanding and recognition of the female prostate. Commensurate with this, and from a pragmatic point of view, it is time to alert primary care physicians that women have a prostate and therefore, are affected by the same diseases as their male counterparts, including prostatitis, benign prostatic hyperplasia and carcinoma (although the latter is rare) which need to be treated appropriately, rather than as in the

past by invasive urethral dilation and/or antidepressants (the latter implying that the occurrence of such diseases in the female is a “state of mind” rather than an actual disease).

In looking to the future, it appears rational, with the demonstration by Zaviačič of the unequivocal existence of the female prostate and accompanying pathology, to apply knowledge gained from immunobiological studies of the prostate suggesting what has been termed the “prostatolymphoreticular system” (Ablin and Whyard 1990), to the female prostate. If the female prostate exhibits the similar immunopermissiveness of its male counterpart, it may also serve as a nidus for various infectious agents, inclusive of HIV. Of particular significance in this regard, as elucidated from the studies by Zaviačič, are the substantially increased number of mutually communicating ducts and intraepithelial glands with the urethra and anterior wall of the vagina vs. the male prostate, which contribute, as aptly defined by Zaviačič, to the urethro-prostatic-vaginal complex (body). Providing an environment exceptionally favorable for the long-term survival of uropathogens, it is suggested this may not explain relapses of female prostatitis, but also the recurrent episodes of urinary tract infections diagnosed as acute cystitis.

In concert with the treatise to follow and the recent editorial position statement by the *Journal of Urology* (McGuire 1999 [the official publication of the American Urological Association]) establishing a new section on “Female Urology” and the American Board of Urology’s decision to define an area of focus in female urology in program development, the female prostate should be given equal place with other female genitourinary organs and should no longer be a “mysterious female organ”!

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About the Author



Milan ZAVIAČIČ, MD, PhD, DSc is professor of pathology and forensic medicine at the Comenius University Bratislava, Slovak Republic (Slovakia). Professor Milan Zaviačič has established the updated non-vestigial concept of the prostate in the female. Based on multidisciplinary research, he has presented the female prostate as a functional genitourinary organ in the female with a specific structure, function and pathology. He has shown that the female prostate parameters are similar or even identical with those of the adult male prostate. This recent concept has been based on morphological, histochemical, forensic-medical, sexological, gynecological, urological, chronobiological and pathology research.

The results of Prof. Zaviačič's research activities have so far been presented in 431 lectures and up to 500 various scientific publications, including full papers, editorials, research reports, review articles, book chapters and contributions to proceedings of scientific congresses, symposia and conferences (40 of them concerning different aspects of the female prostate).

Professor Zaviačič joined the faculty of the Comenius University Medical School as lecturer in pathology in 1963, immediately after his graduation (MUDr.) from the Comenius University Medical School, Bratislava. After two years, he was promoted to Assistant Professor, received his CSc degree in 1975 (based on a thesis on the influence of fasting on the structure of the gastric mucosa, Zaviačič 1974). Being appointed Associate Professor in 1981 based on a thesis on the circadian biorhythms in the structure of the gastric mucosa (Zaviačič 1979), he published his functional-morphological study on the female prostate and urethra (Zaviačič 1985b) and obtained his DSc in 1986. He was appointed head of the Department of Pathology, Comenius University Bratislava, two years later, and rose to the position of full professor of pathology and forensic medicine in 1989.

Professor Zaviačič is member of the Advisory Council Board of the European Society of Pathology (ESP), member of the National Committee of the Slovak Society of Pathologists, Vice-President of the Slovak Society of Histochemistry and Cytochemistry, and elected member of International Academy of Sex Research (IASR). He has

served as President of the Czechoslovak Society of Pathologists and President of the Slovak Society of Pathologists (two terms), which is member of the World Association of Societies of Pathology (WASP).

For his work, Prof. Zavašček received several awards from Ministry of Health of the Slovak Republic (1991), State Institute for Cancer Research of Japan (1978), Japanese Society of Clinical Pathology (1995), Presidium of the Slovak Medical Society (1985, 1986, 1988), and Presidium of the Czechoslovak Medical Society (1977, 1980), and as the appreciation of his research in the female prostate, he received the 1998 Crystal Wing for Medicine and Science award.

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From Reviewers' Opinion

„This book explains excellently a new conception of woman prostate. It was formulated by Prof. MUDr. M. Zaviačič, DrSc., on the basis of his very successful 17 years lasting interdisciplinary research and careful selection of pertinent data from international publications. In contrast to the older view that Skene's paraurethral ducts and glands are rudimentary structures, the author presents them as woman's genitourinary organ with specific structure, function and pathology. This organ should be properly called „*woman prostate*“. The book is a milestone in the field and contains the newest detailed information of the anatomy, histology, ultrastructure, cytochemistry, physiology, pathology and forensic medicine of the woman prostate. Sexological viewpoints are also included“.

Professor Zdeněk Lojda, MD, DSc.,
World leading personality in histochemistry,
Founder of histochemistry in the Czech and
Slovak Republics, Histochemical Laboratory,
Charles University, Prague, Czech Republic

„In his monograph „*The Human Female Prostate*“, Professor Milan Zaviačič, MD, DSc of Bratislava introduces novel and inventive knowledge and presents the female prostate as a distinct organ which is, as far as its ontology, evolution, anatomy, physiology, clinical behaviour and pathology are concerned, fully comparable with the prostate of the man. This work is unique through its content and exceptionally important not only from the standpoint of pathological anatomy but also from the point of view of clinical practice. The introduced concept of the female prostate implies substantial clinical consequences, which may in the future bring about a change in opinions upon etiopathogenesis of functionally and organically conditioned diseases of the lower uri-

nary tract in women. This work brings a strong impulse for intensive clinical research of the female prostate“.

Professor Jan Breza, MD, DSc
Professor of Urology, President of the
Slovak Urology Society, Urology Dpt
Derer's University Hospital, Bratislava

„The monograph „*The Human Female Prostate*“ is an important landmark for our knowledge of the physiological and pathophysiological functions of woman prostate. It was written by Prof. M. Zaviačič, leading researcher in this field during the last 17 years. The text represents an excellent and inventive survey of his own experiments confronted with recent results of prominent world specialists. It contains a convincing evidence that the female prostate, similarly as the male prostate, has at least dual function: *exocrine* – production of female prostatic fluid, and *neuroendocrine* function. Therefore the term „Skene's glands and ducts as an insignificant and nonfunctional organ“ is no more correct in the light of contemporary knowledge and should be unequivocally replaced by the term „*woman prostate*“. This book helps to „bridge the gap“ in our understanding of the importance of the human female prostate not only in the basic pathology practice but in forensic medicine, gynecologic urology, sexology and chronobiology as well. It will certainly become a welcome source of up-to-date information not only for specialists but for each doctor who wants to know more about the gland on which such contradictory outlook existed, especially in the past.

Prof. Ing. Miroslav Ferenčik, DSc
Professor of Immunology and Immunochemistry,
President of the Slovak Immunology Society and
Chairman, Scientific Board of Institute of
Neuroimmunology, Slovak Academy of Science

Introduction with Acknowledgements

The two genders possess a great number of functional and structural parameters which are more or less identical, yet there are also features characteristic exclusively of one gender and missing in the other. These concern morphological and functional parameters corresponding to the basic somatic differences between the male and female of the genus *Homo sapiens*, associated with characteristic psycho-behavioral specificities typical of each gender.

In the structures of the male and female sex organs, with evidently different configurations in adulthood, homologous organs can be identified in the male and female sexual anatomy. They are sometimes given terms derived from the opposite gender to emphasize their equal importance, as used for instance by the feminist movement concerning some female genital tissues. Thus e.g. the clitoris was referred to as „the female penis“ (*penis muliebris*), presumably also in support of arguments opposing the concept of oedipism (Oedipus complex – Oedipus, Greek Mythology, Hensyl et al. 1990). As early as in 1981, the Federation of Feminist Women’s Health Center was concerned with the redefinition of the clitoris and its multiple functions, as published in *New View of Woman’s Body* (Chalker and Gage 1987). This is however absolutely not in keeping with the understanding of our emphatic recommendation to use the term female prostate as an equivalent of the designation of this gland in the male, as shown further in this monograph. Our reasoning is certainly no artificial emphasis of the equivalency of this organ in the two genders, rather the introduction of the term female prostate is based on morphological, functional and clinical evidence analyzed in this monograph, and particularly in Chapter XI concerning terminology (Skene’s paraurethral ducts and glands versus female prostate). Homologous structures develop from the same embryologic primordium. From conception to about eight weeks of gestation, the genitals of the male and female fetus are undifferentiated. At that time, due to hormonal stimulation, the genital tissue rearranges itself in characteristic male or female pattern (Francoeur 1991). The common basis of the sex-specific structures may account for the potential broad range of somatic derangements in the later definitive differentiation and configuration of the human internal and external genitals with simultaneous occurrence of elements characteristic of both sexes. Further it may also

be involved in derangements of sexo-psychological nature concerning gender identity and gender orientation.

In the fertile woman, parameters characterizing the female sex involve rhythmically recurring changes in the hormonally dependent tissues of the uterus, ovaries, tubes, vagina and breast glands. The parameters characteristic only of the female gender and absent in the male include e.g. menstruation, pregnancy and lactation.

Less unequivocal is the situation concerning certain parameters long considered typical of the male gender only and in some cultures even identified with the male sex principle. One of these controversial and long discussed parameters is the problem of the existence and role of the prostate (Skene's paraurethral glands and ducts) in the woman. Intensive morphological research and ever more broadening clinical studies of the female prostate concerning its orthology and pathology, extending over the last 50 years and particularly since the early 80s, provided evidence presenting the female prostate as an organ fully comparable and even identical with the male prostate, and that not only as to its structure and function but also as to its pathology.

Our morphological results concerning the female prostate (Skene's glands) presented in this monograph are based on autopsy findings (as well as rare biopsies) and detailed histological examinations of the urethra of 150 women, followed by histochemical, immunochemical and further examinations of normal and pathologically changed female prostatic tissue, including electron microscopic studies. Many enzymes, glycosamine glycans and glycoproteins were examined, including prostate specific antigen (PSA) and prostate specific acid phosphatase (PSAP) (Zaviačič et al. 1983; 1985b,c; 1993a, b; 1998d; Zaviačič 1987a; Zaviačič and Whipple 1993; Zaviačič and Ablin 1998 c, and references therein).

In our series including as many as 200 female patients of the 2nd University Hospital of Gynecology and Obstetrics in Bratislava, we investigated the biological phenomenon of female ejaculation, focusing on questions concerning the openings of the ducts of the female prostate and on sexological typology of women with urethral expulsions. Several results obtained in cooperation with the Hospital as well as with further medical specialities, including gynecological urology, urology, chronobiology, forensic medicine, etc., were used in developing implications concerning the function of the female prostate.

The monograph on the female prostate, with its underlying modern concept and rich, colored documentation, consists of several chapters, each focusing on a different aspect of the topics. There may be some overlap concerning some important pieces of information between the chapters for purposes of emphasis and particularly for treating the given item in the light of different relationships and points of interpretation. The reader is thus provided not only with the latest functional, morphological, pathophysiological and clinical findings but also with a broad range of implications that have appeared concerning this genitourinary organ of the woman. The basis of the individual chapters of the monograph are observations and findings derived from the series investigated by the author and his coworkers and interpreted in the light of his and their clinical expertise. The relevant morphological and clinical research was conducted in cooperation with several institutes of Comenius University and with the

support of some departments abroad. The author formed a team consisting of research workers, clinicians and technicians based predominantly at his own Institute and at the 2nd Hospital of Gynecology and Obstetrics of Comenius University Medical School. Members of the team published over 40 papers dealing with different aspects of the female prostate, with more than half of them appearing abroad in CC-covered journals.

The presented monograph is the outcome of almost 20 years of work that the author and his coworkers devoted to the study of this female genitourinary organ. Their effort can be summarized in the statement expressed in the subtitle of the book, reflecting the long way from the vestigial interpretation of Skene's paraurethral ducts and glands to the present-day non-vestigial concept of this female organ. It is the subtitle of the monograph „*From Vestigial Skene's Paraurethral Glands and Ducts to Woman's Functional Prostate*“ that best indicates the author's aim to communicate the substantiated notion of the female prostate as a functional genitourinary organ with its own orthology, pathology and a gradually developing clinical understanding, namely a female organ whose parameters are comparable or identical with those of the male prostate. The author emphasizes all important stages of research which supported and corroborated the up-to-date notion of the female prostate as presented in the monograph, yet he does not avoid mentioning also those personified controversial phases of research which for a long time influenced the issue of the female prostate to a contrary effect.

I would like to start here to express my gratitude to all coworkers from the Departments and Institutes of Comenius University Medical School and of the University Hospital in Bratislava for their contribution and assistance in the study of the female prostate and in preparing the numerous publications on this topic. The names of my coworkers appear in these papers as coauthors or they are shown in the acknowledgements. My thanks are due to the late Professor Emeritus, former Head of our Department, Prof. MUDr. M. Brozman, DrSc (1920-1993) for his support provided at the beginning of my research involvement into the problem of the female prostate, a topic considered at that time by some of my colleagues as scientifically insignificant.

My special thanks go to Ms. Mária Zajíčková and Ing. Jana Blažeková, joined later on also by other workers of the Histochemical Laboratory of the Institute, who over an almost 20-year period have been my closest coworkers. This monograph could hardly have been brought into existence without their devoted and technically demanding work in collecting and processing the material, including sophisticated histochemical examinations. Also, I would like to express my thanks to members of the Immunohistochemical and Immunochemical Laboratories, to Ms. Ivica Uhnová and Ms. Emília Kollárová, and particularly to RNDr. Mária Ružičková, whose cooperation in the immunohistochemical analysis of prostate-specific antigen in tissues of the male and female prostate and in searching for other sources of this prostatic marker in the female is being greatly appreciated. Of the doctors of our Institute who helped in collecting autopsy material, I would like to mention especially MUDr. Svetoslav Štvrtina, who assisted in determining the weight and size of the female prostate. I also wish to acknowledge the cooperation of Prof. MUDr. Ján Jakubovský, DrSc, MUDr. Štefan Polák, CSc and of workers of the Electron Microscopic Laboratory of the Institute, Ms.

Vlasta Jakubovská (Blahutová) and the late Ing. Milan Belošovič, who performed transmission and scanning electron microscopic examinations of normal and cancerous female prostate tissue and of the fluid of urethral expulsions. Ms. Vlasta Jakubovská excelled in bringing up the necessary patience in processing material for electron microscopic examination and in drawing schematic representations of the ultrastructural appearance of cells of the female prostate gland. The professionally perfect cooperation of Mr. Peter Vanerka, phototechnician of the Institute, is highly acknowledged. Further my thanks go to RNDr. Mária Ružičková, Ing. Jana Blažeková and to Ms. Gabriela Svičeková, secretary of the Institute, for retyping the text including the listing of the References. Mr. M. Škultéty, Director of the Slovak Academic Press (SAP), and MUDr M. Palkovič, Director of mpro Software, have indebted me for their assistance in publishing the manuscript in book form and as CD-ROM. The work of the Academic Painter Lucia Lišková in drawing some figures (including the cover illustration), mostly according to Huffman's wax models of the female prostate, is gratefully acknowledged.

I wish to thank Prof. MUDr. M. Kokavec, DrSc and Assoc. Prof. MUDr. M. Mego, CSc, Head of the Institute of Forensic Medicine, Comenius University Medical School, as well as the workers of this Institute, particularly MUDr. P. Fiala, CSc and MUDr. J. Oberučová, for their help in organizing the collection of female prostate gland tissue from necropsy material of the Institute of Forensic Medicine and for their cooperation in investigating secretory mechanisms of the female prostate by macroenzyme-histochemical methods on underwear in *in vivo* and *in vitro* analyses of the female ejaculate and/or female prostate secretion.

I appreciate the cooperation of Prof. MUDr. Karol Holomáň, CSc, Head of the 2nd University Hospital of Gynecology and Obstetrics, and of his coworkers MUDr. V. Brázdil, CSc, MUDr. P. Štencl, CSc, MUDr. T. Zaviačič, and particularly that of Ing. S. Doležalová, at that time Head of the Biochemical Laboratory of the Hospital. They helped me in performing some functional-clinical examinations of the complex of the female prostate and urethra and biochemical analyses of the female ejaculate. Our cooperation devoted to the study of the female prostate started in the early 80s and is still continuing. Concerning the problem of carcinoma of the female prostate, I look gratefully back to our cooperation with Assoc. Prof. MUDr. M. Borovský, CSc, Head of the 1st Hospital of Gynecology and Obstetrics, Comenius University School of Medicine.

Our cooperation with Prof. MUDr. J. Breza, DrSc, Head of the University Department of Urology, has proved equally successful. With the consent of the Transplantation Committee, he obtained for our studies otherwise hardly available material of the female urethra with normal female prostate tissue during organ harvesting for transplantation. The material provided met the requirements for successful electron microscopic examination.

My thanks go also to the former Head of the 1st Department of Medicine, Comenius University Medical School, Prof. MUDr. M. Mikulecký, DrSc, for biometric analysis of the female ejaculate in dependence on days of the menstrual cycle and of some further data obtained in investigating the female prostate.

My sincere thanks are due to my wife, MUDr. Alexandra Zaviačičová, physician at the Economic University in Bratislava, my first coworker and coauthor of several papers and lectures on the female prostate. Thanks for her help and support all over my work on the project and on this monograph and for her invaluable assistance that helped in solving some specific problems concerning the function of the female prostate.

Last but not least, I wish to acknowledge the cooperation of my colleagues from abroad, their contribution to the research on the female prostate and their support in establishing and defending the non-vestigial concept of the female prostate in medico-biological, andrological, sexological, psychological, and sociological sciences in their environment.

Dr. Richard J. Ablin, PhD, occupies a special position among my collaborators abroad. To name at least his most important distinctions, he is Scientific Investigator, Director of Innapharma, Suffern, NY, USA, President of the Robert Benjamin Ablin Foundation for Cancer Research, Mahwah, USA, and Honorary Lifetime President of the International Society of Cryosurgery. Our scientific contacts started in 1985 and have continued ever since. They resulted in co-authored papers on the female prostate, published or in press in important CC-covered journals. Based on the results of enzyme histochemical and immunohistochemical studies on the female prostate published in the early 80s, it was already in 1989 that Dr. Ablin suggested that the female prostate may be a potential source of PSA (Ablin 1989) and in further studies he has been proved right. The scientific personality of Dr. Ablin (see Cover Legend, *Int J Oncol* 14:611-613, 1999), renown as the discoverer of PSA and a distinguished author of several original andrological papers, has promoted our findings on the female prostate in penetrating a broader circle of medically, clinically, yet also more generally biologically oriented scientists. I am most grateful and feel greatly honored that Dr. Ablin wrote the Foreword to my present monograph on the female prostate. I thank him also for his kind help in completing a certain part of urological and andrological literature cited in the monograph which was not available in Slovakia.

Of the sexologists involved, I would like to mention particularly the renown American sexologist Professor Beverly Whipple, PhD, acting President of the American Association of Sex Educators, Counselors and Therapists and member of the Executive Committee of the World Association for Sexology (WAS), distinguished co-author of a book on the G spot (Ladas et al. 1982). Professor Beverly Whipple was one of my first coworkers abroad and our intensive scientific contacts resulted in co-authored publications in *J Sex Res* (1993) and in *Slovenský Lekár* (1993b). I wish to thank her also for providing sexologically oriented publications, some of which have been cited in the monograph.

Further, let me mention the Austrian sexologist Dr. Karl F. Stifter, Head of the Institut für die Therapie psychogener Sexualstörungen in Vienna. He is the author of the book *Die dritte Dimension der Lust. Das Geheimnis der weiblichen Ejakulation* (Stifter 1988). The chapter on the female prostate is predominantly based on our studies published before 1988, the year of appearance of his book.

The non-vestigial concept of the female prostate has found its promoters also among other sexologists and psychotherapists, as Desmond Heath, MD, Mt. Sinai Hospital

Medical Center, Child Psychiatry, New York; Dr. John D. Perry, Perry Research Institute, Portland, Maine; Dr. Joseph Bohlen, Southern Illinois University, Springfield, Ill.; Edward W. Eichel, MA, Director of Heterosexual Education Research Council of the US, New York; Nilton César da Silva, MSc, Adjunct Professor of Human Sexuality, Universidad Federal de Santa Catarina, Santa Catarina, Brazil; Gary Schubach, Ed D, Institute for Advanced Study of Human Sexuality, Novato, USA; Dr. Janneke van der Velde, Dpt. of Clinical Psychology, Amsterdam, The Netherlands; Dr. F. Cabello, Instituto Andaluz de Sexologia, Malaga, Spain; Prof. Dr. Stanislav Kratochvíl, CSc, Psychiatry Hospital, Kroměříž, Czech Republic. Our forensic-sexological studies concerned with the phenomenon of female ejaculation and of the female prostate have met with the interest of such renown scientific personalities as Dr. John Money, Baltimore, USA; Stephen J. Hucker, MB, BS, FRCPC, FRC Psych., Division of Forensic and Correctional Psychiatry, Kingstone, Canada; Dr. Sune M. Innala and Dr. Kurt E. Ernulf, Psychologiska Institutionen, Göteborg Universitet, Sweden, and several other scientists.

Our research into the problem of the female prostate met with a positive response also in the great authority in pathology, Professor F.K. Mostofi, MD, FRCPA, Dpt. Genitourin. Path., AFIP, Washington, DC, USA, who wrote me „... I congratulate you on your research on prostates in female patients.“ I wish to thank him for his appreciation of our papers on the female prostate.

To all those mentioned above, yet also to those whose names do not appear explicitly, I am most grateful for their cooperation of a rather varied nature and for the support I received during my reserch on the female prostate and in preparing the relevant publications.

I History of the Female Prostate

As early as in 1672, De Graaf presented the first description of the female prostate and he was also the first to use this term. In his work „*De mulierum organis generationi inservientibus...*“, Reijnier De Graaf (1641-1673), a Dutch physiologist and histologist, described one year before his death the structure of the female prostate amazingly exactly for his period of time as being formed by glands and ducts around the female urethra. De Graaf was also the first to attempt to formulate the role of the female prostate on writing „The function of the prostate (*corpus glandulosum*) is to generate a pituitoserous juice which makes women more libidinous with its pungency and saltiness and lubricates their sexual parts in agreeable fashion during coitus (Jocelyn and Setchell 1972). Although De Graaf's idea on the homology of the female para(urethral) glands and ducts with the male prostate was basically but of intuitive nature, nevertheless he is undoubtedly the discoverer of the female prostate.

The American gynecologist Alexander J. C. Skene (1838-1900) played a rather controversial role in the problem of the female prostate. His idea, voiced 200 years after de Graaf and identifying the female prostate with two paraurethral ducts (two important glands of the female urethra) opening on the sides of the urethral orifice (Skene 1880), has exerted an inhibitory effect on further advances in the problem of the female prostate, and that despite the fact that dating back as many as 50 years, Huffman expressed his disagreement with several conclusions drawn by Skene (Huffman 1948; 1951). Even to date, the female prostate is known to many urologists (gynecological urologists) and gynecologists under Skene's name, and this term (Skene's eponym) is still commonly used to designate the female prostate, though the substantiation of this use has long been defuted.

In a separate chapter of this monograph, treating problems of terminology in detail, we present the reasons justifying only the use of the term female prostate in designating prostatic tissue, similarly as in the male. The reasoning is based on repeated substantiated recommendations which appeared in previous publications (Zaviačič et al. 1985b; 1997a, b; Zaviačič 1987a; Zaviačič and Whipple 1993; Sesterhenn et al. 1998; Zaviačič and Ablin 1998a, b).

In the past, the problem of the female prostate interested such authorities in medicine and biology as Astruc (1737), Virchow (1853) and several others, as presented by Huffman (1948) and later by Stifter (1988). It has to be emphasized that the epoch of the great pathologist Rudolf Virchow (1821-1902) was rather supportive of the study of the female prostate and Prof. Virchow himself considered it to be a genitourinary organ of the female in its own right, to which he gave his considerable attention. He was first to describe in the glands of the female prostate concretions „corpora amylacea“ (Virchow 1853), which had before been known to occur only in the male prostate. Despite the great interest and the favorable attitude of Rudolf Virchow and of his time towards this field of study, there was no breakthrough in the research into the problem of the female prostate since at that time autopsy and macrodiagnostics were predominant in pathology, while biopsy and histological methods were in research activities rather at their beginning. Yet the outstanding scientific authority of Prof. Virchow promoted the study of the female prostate for many years even after his death. The clinical interest in the female prostate was at that time and also later on less intensive than that of morphologists.

At present we witness an increasing interest of urologists and gynecologists in the female prostate, associated to a great deal with the new information on the female prostate-specific antigen and its potential implications in the female. Similarly as the prostate in the male, the female prostate is considered to be the main producer of this prostatic marker in the woman (Zavlačič and Ablin 1998a, b, c; Zavlačič et al. 1998c), and that even in light of considerable research attention that has been given to the search for extraprostatic sources of PSA. The lack of clinical interest may be accounted for by the fact that compared to the male prostate, the female is far less affected by diseases, and those which do occur are usually of minor severity. As yet, however, exact clinico-pathological data on diseases of the female prostate and on their actual incidence are not available.

The term female prostate was commonly used till the beginning of the 20th century. At that time the term was based mainly on embryological data showing that Skene's glands and the male prostate arise from the same embryonic primordium, the urogenital sinus. Even to date, many textbooks present these embryological findings as the sole argument in favor of the homology between Skene's glands (female prostate) and the male prostate (Campbell 1954; Egloff 1972; Kurman 1994). Unfortunately, and apparently justifiably, for the majority of scientists embryological findings supporting the notion of homology of the two genitourinary structures have been insufficient for accepting unequivocally the existence of the prostate in the woman.

On the other hand, from the early years of our century, we can trace an opposite trend considering the female prostate referred to as Skene's paraurethral ducts and glands as an insignificant, rudimentary, vestigial female organ, which does not play any role in the life of the woman. The vestigial concept of the female prostate has been based mainly on gross macroscopic differences between the size of the prostatic glands in the two genders. The difference in size, in disfavor of the female prostate, provided for many a welcome implication that it would be unable to function, or at least to function comparably to the male prostate. The human body provides several examples

of small organs defuting this hypothesis. Thus e.g., the pituitary is despite its small size a central endocrine organ controlling the function of other endocrine glands and through them the body as a whole. On the other hand, the female prostate was considered to be clinically rather unproblematic and this notion has apparently supported the vestigial concept, though even this favored and often repeated statement fails to be based on objectively established evidence.

The male prostate presents a classical example of an androgen-dependent organ, while the question whether, and if then to what extent is the function of the female prostate hormonally dependent has not been fully answered as yet. Nevertheless, our first electron microscopic study of the ultrastructure of the normal female prostate indicated that in the function of the female prostate and particularly in its secretory cells, estrogens may play an equally significant role (Zaviačič et al. 1998d) as do androgens in the maturation and function of the male prostate. The relationship between the prostate and androgens, which andrologists have so far even uncritically considered to be an absolute one, does not appear to apply biologically in general. As far as the woman is concerned, female sex hormones will probably turn out to play a far greater role in prostate function than do androgens. In urologists, endocrinologists and gynecologists, this assumption should stimulate a greater interest in studying the relationship between the female prostate and sex hormones, which has so far received but little attention, and even that goes as far back as the late 30s (Korenchevsky 1937).

The history of the study of the female prostate extending from the vestigial position to the present-day non-vestigial concept developing since the early 80s was treated of in our previous publications which presented evidence on the unequivocally non-vestigial position of the female prostate. Attention of those interested in this topic should be directed especially to the DSc Thesis of the author of this monograph and a number of earlier publications (Zaviačič 1985b; 1987a; Zaviačič and Whipple 1993; Zaviačič et al. 1983; 1985b) as well as some recent ones (Zaviačič and Ablin 1998a, b, c; Ablin and Zaviačič 1999). A historically broadly conceived overview on the female prostate and its function in the female ejaculation phenomenon, along with different attitudes on female ejaculation as observed in individual sex cultures, including those of ancient India and Japan, can be found in Stifter's work (Stifter 1988).

Huffman's publications (Huffman 1948; 1951) provide important data concerning specifically the orthology and pathology of the female prostate but dealing also with historical aspects. Earlier studies, dating back to the first half of the 20th century, deserve also to be mentioned (Evatt 1911; Johnson 1922; Korenchevsky 1937; Petrova et al. 1939; Caldwell 1941; Folsom and O'Brien 1943; 1945; Deter et al. 1946). They have contributed to the gradual shaping of views on this female organ and influenced Huffman's conclusions with their lasting impact on the problem of the female prostate.

The present intensive research on the female prostate, which started in the early 80s, has succeeded in presenting this small organ of the genitourinary system of the woman as an organ with defined structure and function. Ever more morphological and clinical parameters keep accumulating which are shown to be identical or at least well comparable with those of the male prostate.

Our monograph is concerned with morphological, functional-morphological and clinical aspects of the normal and pathologically changed female prostate. In pathology, the main focus is on carcinoma, benign hyperplasia and inflammation of the female prostate. The value of several prostatic markers and especially of prostate-specific antigen (PSA) in the study of the normal and pathologically changed prostate is being emphasized. Further updated findings concern clinical, sexological, forensic-sexological, gynecologic-urological, chronobiologic and forensic-medical aspects.

The major part of the monograph is focused on research carried out over the last 20 years, i.e. over a period of intensive advances and increasing clinical interest in this female genitourinary organ. The intensive research and publication activities of these last two decades have affected our opinion on this organ, as documented by different views of the same authors expressed in publications that appeared within a relatively short period of time. Thus e.g. Sesterhenn co-authored the study of Wernert on the female prostate (Wernert et al. 1992) with the following conclusion: „They“ (glands of the female prostate) „remain immature throughout life from the fetal period up to the advanced age No indications can be found for a proper biological function“. Six years later, the same author wrote in Congress Abstracts (Sesterhenn et al. 1998): „The female prostate is not a myth and is not equivalent to Skene’s glands. ... It does explain detectable serum PSA levels in females“. We are confident that such shifts in opinion occurred also due to the considerable influence of our numerous studies on the female prostate published over the last 15 years, as well as our recent contributions published with Dr. R. J. Ablin, PhD in „Correspondence“ of the Journal of the National Cancer Institute (Zaviačič and Ablin 1998a), in „Letter to the Editor“ of the Journal of Urology (Zaviačič and Ablin 1998b), in the Invited Review in the Journal of Histology and Histopathology (Zaviačič and Ablin 1998c), and in „Commentary“ of the journal *Lancet* (Ablin and Zaviačič 1999).

II

Weight, Size and Macroanatomy of the Female Prostate

Weight and size of the female prostate

Over long years, the dimensions and the weight of the female prostate would remain unknown variables, although they represent the basic data shown for every human organ. Certainly, this also supported the perception of this female organ as a vestigial one compared to the same organ in the male the dimensions and the weight of which have been well known since long. Size and weight data of the female prostate have been published but recently (Zaviačič et al. 1998a).

In determining the weight of the male prostate, the individual structural components (glands, ducts and smooth musculature (the musculofibrous part) are not separated and the prostatic portion of the urethra is not removed; consequently, the total organ is weighed. Thus, the weight of the male prostate represents the sum of the weights of the individual parts of the prostatic components, including the prostatic portion of the urethra. Its size (in cm) is given by the length (measured along the axis of the urethra), width (transversal diameter), and height (vertical diameter from the base of the prostate to its cranial top) of this chestnut-shaped organ (Fig.II/2).

A similar principle has been applied to the determination of the weight of the female prostate, being the sum of the entire organ including the female urethra. The size of the female prostate (expressed in cm) is given by the length, width and cranio-caudal height of the female urethra (see Fig.II/4). The whole female urethra corresponds to the prostatic part of the male urethra (Egloff 1972; Zaviačič 1987a).

Based on data from our own series involving histologically verified normal male prostates, as well as based on literary data, the weight and size parameters of the normal female prostate were compared to the corresponding measures of the adult male prostate (Zaviačič et al. 1998a).

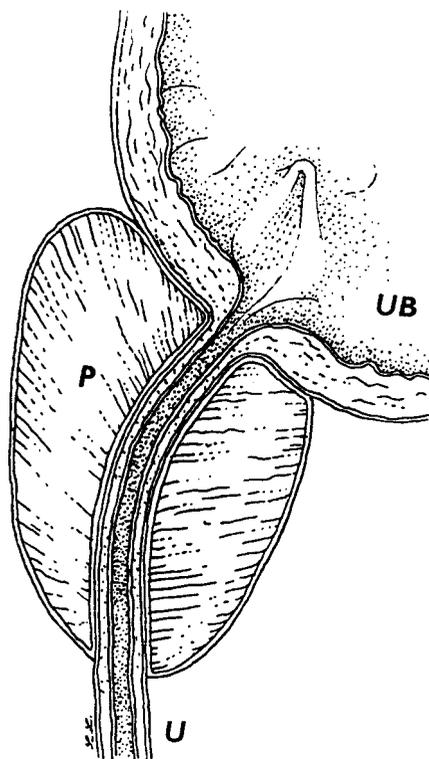


Fig.II/1 Normal male prostate (P) and its relationships to the urethra (U) and the urinary bladder (UB). The male prostate surrounds the prostatic portion of the urethra which is sited approximately in the center of this male organ.

We present data obtained from the determination of weights and sizes of 20 normal male prostates (obtained at necropsy) and data concerning the female prostate obtained from 15 necropsy cases (Zaviačič et al. 1998a).

Measurements of male and female prostates showed that the normal prostate of the adult woman weighs 5.2 g in average, whereas the corresponding figure for the normal adult man is 23.7 g (Zaviačič et al. 1998a). The mean size of the female and male prostate is 3.3 cm x 1.9 cm x 1 cm (length x width x height)(Fig.II/4) and 3.4 cm x 4.5 cm x 2.9 cm (Fig.II/2) respectively. For results of a more detailed non-parametric biometrical analysis, see Table 3 of the above mentioned paper (Zaviačič et al. 1998a).

Compared to the mean weight and size of the normal male prostate as usually ascertained in our necropsy material, which is in keeping with the majority of the relevant literary data (Thackray 1978; Sinelnikov 1981; Williams et al. 1989; Petersen 1994), the female prostate achieves about one fifth to one fourth of the male prostate weight. If we agree with the generally accepted finding that, in the majority of women, the richest

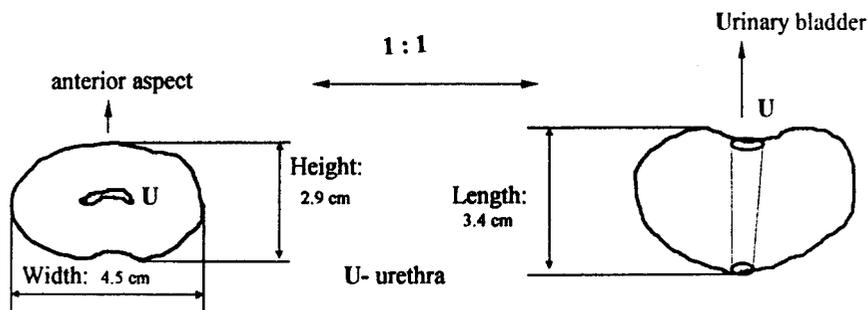


Fig.II/2 The size of the male prostate (in cm) is given by the length, width and height of this male organ.

prostatic tissue is in the anterior urethra behind the urinary meatus, as already reported by Huffman (1948) and later by Zaviačić et al. (1985b) and Wernert et al. (1992), namely in the anterior distal half of the urethra (the meatal type of the female prostate; Zaviačić et al. 1985b; Zaviačić et al. 1987a), a potential correction concerning virtually 70% of women seems to be plausible. The weight of the female prostate would then vary within the 2.6 – 5.2 g range, and its size would be 1.7 cm x 1.9 cm x 1 cm (L x W x H). Thus, the prostate of the adult female would roughly reach one tenth to one fourth of the mean weight of the normal adult male's prostate. These specifications replace the rather vague formulation used so far, stating that the female prostate (Skene's glands and ducts) is „much smaller than the male prostate“ (Zaviačić et al. 1998a).

Macroanatomy of the female prostate

The principal macroscopic difference between the male and the female prostate lies in the localisation of the prostatic tissue. In the male, the prostate surrounds the prostatic portion of the urethra, with the urethra being approximately in the center of this organ (Fig.II/1), whereas the female prostate is situated in the wall of the urethra (the whole female urethra corresponds to the prostatic part of the male urethra (Egloff 1972; Zaviačić 1987a), and there is no prostatic tissue beyond the urethra in the female)(Figs.II/ 3 and 4). The thickness of the urethral wall and the length of the female urethra thus limit the size of the prostate, which has to be – and actually is – smaller than the male prostate. This even macroscopically evident difference in appearance between the male and the female prostate (Figs. II/1,3,4) has proven to be the handicap of the female prostate, running through the whole history of the attempts to understand this organ (Zaviačić et al. 1998a).

It nevertheless has to be emphasized that, despite the smaller space available for the female prostate, this organ in the female possesses all the components (glands,

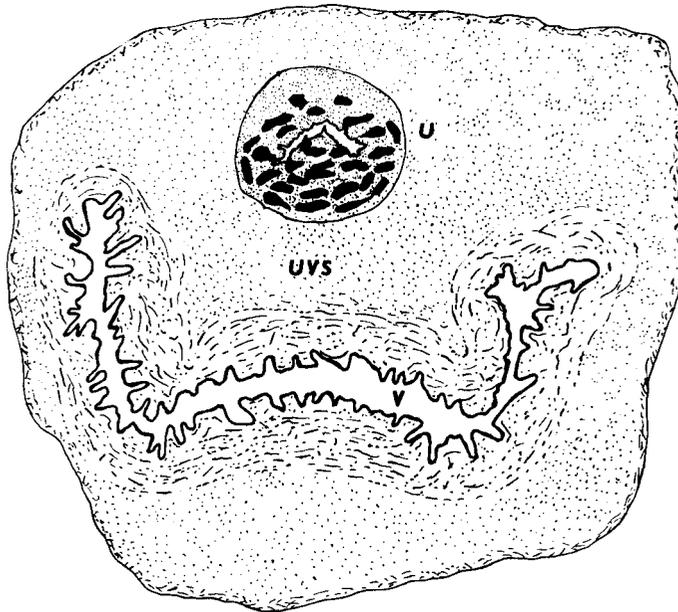


Fig.II/3 The female prostate in the wall of the female urethra (U). The relationship is shown between the female urethra with the prostatic tissue, the urethro-vaginal septum (UVS) and the vaginal canal (V).

ducts, smooth musculature) which characterize the male prostate, including the cellular, enzymatic and other equipment necessary for its exocrine (production of female prostatic fluid) and neuro-endocrine function (Zaviačić et al. 1985b; Zaviačić et al. 1987a; Zaviačić and Whipple 1993 and references therein; Zaviačić et al. 1997b and references therein). These findings have implications with respect to several medical disciplines (Zaviačić et al. 1985b; Zaviačić 1987a; Zaviačić and Whipple 1993; Zaviačić and Ablin 1998a, b, c).

The individual parts of the female prostate can be visualized on cross sections using both conventional histological methods and selected enzyme-histochemical methods, as well as by immunohistochemical identification of prostate-specific antigen (PSA) and epithelial markers. Some assays only visualize a single prostatic component, e.g. PSAP only identifies prostatic glands (Figs. IV/1, 2, 3), yet no prostatic ducts (Zaviačić 1984b), other enzymes, such as glycerol-3-phosphate dehydrogenase, are able to visualize both the ductal and the glandular parts of the female prostate (Zaviačić 1984a). Similar results were obtained concerning the immunohistochemical expression of PSA (Figs. VIII/1, 3) (Zaviačić and Ablin 1998c; Zaviačić et al. 1998c). Expression of cytokeratins, particularly the mixture of AE₁/AE₃ provides optimal possibilities to study the epithelial components of the female prostate (Figs. III/8, 9). This can be an advantage in demonstrating the difference in the abundance of prostatic tissue between

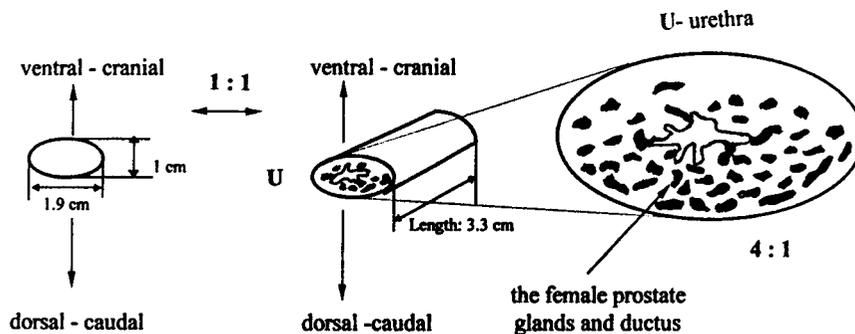


Fig.II/4 The size of the female prostate (in cm) is given by the length, width and height of the female urethra. Schematic representation of the female prostate structure in the wall of the urethra.

the anterior and the posterior urethra in the meatal type of the female prostate. Wernert and coworkers (1986; 1987) reported on their good experience with using cytokeratins, epithelial markers (AE_1/AE_3) to visualize structures of the male prostate, only to find later that the same approach yields excellent results also in studying the female prostate (Wernert et al. 1992).

The spatial representation of the female prostate on wax models (Huffman 1948) can be considered a milestone in the study of the detailed spatial anatomy of the female prostate and the onset of its modern history. The three-dimensional representation of this small organ provides a plastic picture which has not been overcome even after fifty years, although virtual computer programs could presumably offer further insight into the structure of the female prostate. A considerable part of Huffman's conclusions (1948; 1951) has gained general acceptance, and we are able to confirm several of them on a far larger autopsy material than available to Huffman (1948).

In our material, the whole urethra removed at autopsy was transversally divided into 6 – 8 segments, depending on the overall length of the organ, and the segments were embedded in paraffin. More than 20 paraffin sections were prepared from one block.

On assessing the presence or absence of ductal and glandular components of the female prostate in the individual segments of the entire urethra examined at autopsy, we could distinguish, with certain simplification, several „types“ of the female prostate which do not have counterparts in adult individuals of the opposite sex (Zaviačič 1987a; Zaviačič et al. 1998a).

Among all the types, the „anterior (meatal) type“ of the female prostate is the richest in prostatic tissue which is located in the distal half of the female urethra in segments of the anterior urethra behind the urinary meatus (Fig.II/5). This type occurred most frequently in our material (66%) and, in our opinion, it represents the most characteristic appearance of the female prostate (Zaviačič et al. 1998a), see also cover illustration in



Fig.II/5 „Anterior (meatal)“ type of the female prostate (according to Huffman’s wax model (1948)).

this Monograph and on the CD-ROM cover.

Huffman (1948) and Wernert et al. (1992) arrived at the same conclusion emphasizing that the distal part of the female urethra is most abundant in prostatic tissue. It has to be noted, however, that the musculofibrous tissue forms a much larger part of the female prostate than is the case in the male prostate. The ratio between the glandulo-ductal and the muscular component exhibits considerable inter-individual variations, yet the musculofibrous component invariably exceeds the glandulo-ductal one. In exceptional cases, conglomerates of prostatic glands could be seen along with corpora amylacea(?) (Fig.III/4), so that the tissue might have been mistakenly considered on histological examination to be male prostatic tissue (Zaviaèiè et al. 1985b). Prostatic calculi in the female prostate were first described by Virchow (1853).

The „posterior type“ of the female prostate can be characterized by prostatic tissue being most abundant in the wall of the posterior urethra extending to the neck of the urinary bladder (Fig.II/6). This type could be identified in 10% of autopsies (Zaviaèiè et al. 1998a). In concordance with our experience with gynecological examination of female patients at Department of Gynecology (Zaviaèiè et al. 1988b) and with the detection of the G spot in the vagina during autopsy at Department of Pathology, only in this relatively low number of cases was there a relation between the main portion of the female prostate tissue and the localisation of the Graefenberg (G) spot (Perry and Whipple 1981) on the anterior wall of the vagina. Eichel et al. (1988) and Eichel (1997) pointed out the importance of the meatal type of the female prostate with respect to the

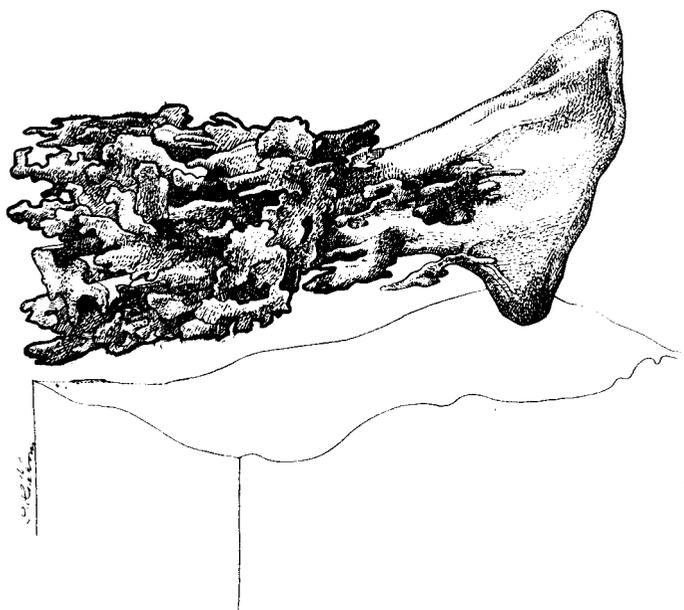


Fig.II/6 „Posterior“ type of the female prostate with prostatic tissue mostly located in the wall of the posterior urethra.

achieving of coital orgasm in the female, when the anterior portion of the female urethra containing the greatest amount of prostatic tissue is directly stimulated by pressure and counterpressure of the male and female genital regions. Eichel (1997) thus shifted the attention from the classic G-spot, an erotic zone on the anterior wall of the vagina (Graefenberg 1950; Perry and Whipple 1981; Ladas et al. 1982), corresponding to the posterior urethra and the neck of the urinary bladder (Zaviačič et al. 1985b; Zaviačič 1987a), to the vaginal introitus where the urethral meatus and the onset of the anterior urethra are projected. In the majority of women, it is the wall of the anterior urethra, and especially its dorsolateral parts facing the anterior wall of the vagina that contains the greatest amount of prostatic tissue (Huffman 1948; Zaviačič et al. 1985b; Zaviačič 1987a; Wernert et al. 1992). In this respect, Eichel (1997) speaks of „relocation“ of the G-spot.

The type of the prostate distributed „over the whole length of the female urethra“ (Fig.II/7) was present in 6% of the autopsy cases (Zaviačič et al. 1998a). Although this type of the female prostate is rather rare, it is this configuration shown in the paper by Huffman (1948, Fig.1) that has often been considered the classical model of the female prostate and presented as such in several papers. In the same study (Figs.2 and 4), Huffman showed the configuration of the female prostate now referred to as the „meatal type“, actually the most frequently occurring configuration of the female prostate (Zaviačič et al. 1985b; Zaviačič 1987a; Zaviačič and Whipple 1993).

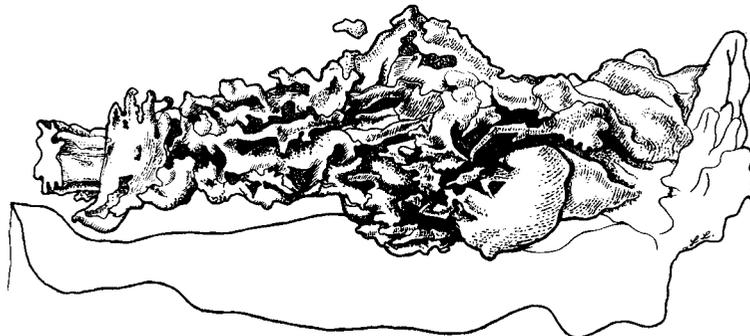


Fig.II/7 Type of the female prostate extending „over the whole length of the female urethra“ (according to Huffman’s wax model (1948)).

In the female prostate, paraurethral glands and ducts were reported to be located under the luminal surface and in deeper parts of the urethral wall dorsally and dorsolaterally rather than ventrolaterally. A corresponding localisation, predominantly in the dorsal and lateral part of the female urethra was also reported by Wernert et al. (1992). In this context, Sesterhenn et al. (1998) speak of „the glands (of the female prostate) deep in the posterior wall of the urethra“. This location of prostatic tissue in close vicinity of the ventral wall of the vagina enables mechanical expulsion of the contents of the glands and ducts of the female prostate by pressure of the penis during penocoital friction or by contractions of the muscles around the urethra during orgasm. Similarly, the discharge of the contents of the female prostate can be enhanced by congestion on excitation at the onset of the female’s sexual response, and even by non-sexual stimuli eliciting a local effect, such as micturition, defecation and physical and motor activity (Zaviačič et al. 1983; 1988a).

The „rudimentary“ female prostate in our material was characterized by scarcity of glands and ducts in the majority of sections evaluated. This picture was seen in 8% of the cases (Zaviačič et al. 1998a). Yet, when examining all segments of the urethra along its entire length in detail, thorough examination of the female urethra wall invariably revealed at least one or a few small ducts and paraurethral glands. If these findings are also taken as representing the presence of the female prostate, then any woman evidently has prostate, the richness of the structure of which may cover a broad range, including the „rudimentary“ form. Leaving the 8% cases of „rudimentary“ female prostate seen in our material out of consideration, we can say that the rate of successfully identified female prostate is 90%. Wernert et al. (1992) demonstrated PSA and/or PSAP immunohistochemical positivity of the female prostate in 22 out of 33 cases of their small series, i.e. in 66.7% (actually, this means 48-82% with 95% CI; Zaviačič et al. 1998a). The figures reported by these authors are thus statistically comparable with the data published by Tepper et al. (1984) and Pollen and Dreilinger (1984) who identified female prostatic tissue in 70% and 80% of the examined cases, respec-

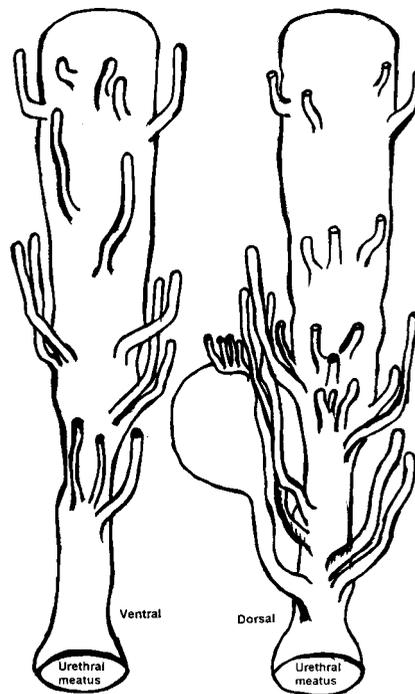


Fig.II/8 Numerous (paraurethral) ducts of the female prostate. The ducts have no separate openings on the sides of the urethral orifice (urethral meatus), and effectively enter the urethra along its whole length (according to Huffman's wax model (1948)).

tively, although their series were even smaller than that of Wernert et al. (1992). Sesterhenn et al. (1998) claimed that female prostate can be identified in as many as 80% of women. Interestingly, the above authors observed discrepancies in PSA and/or PSAP immunohistochemical positivity between the investigated samples.

The rarely occurring „middle“ and „dumbbell“ configurations of the female prostate described with a certain simplifying abstraction (Zaviačič et al. 1985b; Zaviačič 1987a) are presumably of no practical relevance. Their occurrence rates are even lower than that of the „rudimentary“ type. It has to be emphasized that the meatal type is the most frequent one (66%; 95% CI 58-74%), while the posterior type occurs in about 10% of women. The two latter types are thus to be found in more than three quarters of adult women (Zaviačič et al. 1998a). For pathologists, anatomists and other researchers interested in the understanding of the female prostate's structure, the best approach is to study the distal half of the female urethra (the first two to three segments of the anterior urethra) where most of the prostatic tissue is to be found in the majority of women.

Huffman's (1948) wax models of the female prostate (cf. Fig.3 in his paper, in particular) clearly show that the female prostate does not have two (paraurethral) ducts

as claimed by Skene (1880), and that they do not open on both sides of the urethral orifice (Fig.II/8) as incorrectly presented in anatomical (Rauber and Kopsch 1929; Schaeffer 1944; Moore 1980; Williams and Warwick 1980; Williams et al. 1989) and specialized gynecologico-urological literature (Novak and Woodruff 1979; Kurman 1994). On the contrary, the ducts of the female prostate (paraurethral ducts) have been shown to have no separate openings into the vulva on the sides of the female urethra; rather, they effectively enter the urethra behind the meatus along the whole length of the former (Huffman 1948; Zaviačič et al. 1983; Wernert et al. 1992). Similarly as in the man, the female prostate discharges its contents through the urethra by mechanism of continual secretion or upon urethral expulsions (Zaviačič et al. 1988b, c). Both in the male and female, the urethra represents the common passageway for urine and prostatic secretions. In our series which included as many as 200 female patients of the 2nd University Hospital of Gynecology and Obstetrics, Bratislava, we have not seen a single instance of female prostate (paraurethral) ducts opening on the sides of the urethral orifice. Only in multiparous women, where the urethral meatus can be considerably distended, spot-like openings of the female prostatic ducts could occasionally be seen, yet always behind the orifice, in the depth of the urethral lumen. These observations only concerned 5 multiparas, and the findings were not unequivocal even in these cases (Zaviačič et al. 1983). Gynecologists and urologists must nevertheless continue to look for openings of prostatic ducts in female patients to broaden our clinical understanding of this female organ. Autopsy material does not lend itself for the identification of female prostatic duct openings. The issue of female prostate ducts opening thus remains a hot clinical topics. Our observations of the female prostate ducts not opening on the sides of the female urethra meatus as has been erroneously claimed so far in the literature but rather penetrating the lumen behind the urethral meatus along its entire course, as postulated by Huffman (1948) followed by other authors, including ourselves (Zaviačič 1987a; Zaviačič et al. 1983; 1985b; Wernert et al, 1992) have been supported by clinical papers dealing with urethroplasty and urethrolisis for the treatment of the urethral syndrome and for the correction of distal urethral resistance to urination in the female (Richardson 1969; 1972; Richardson and Stonington 1969). These surgical procedures are designed to interrupt the continuity of fibroelastic tissue which surrounds the distal third of the urethra resulting in increased resistance to the free flow of urine. In Figure 1 of the Richardson and Stonington's (1969) paper, showing the anatomical relationships of the urethra to the surrounding tissues, there are no ducts or any other structures of the female prostate seen; at the same time, no ducts of the female prostate are shown to open to the vulva on the sides of the female urethra meatus as assumed by Skene (1880). Neither do Richardson and Stonington (1969) mention that the surgeon should pay any special attention to female prostate ducts (paraurethral ducts) during the intervention which would be necessary did the ducts open to the vulva on the sides of the female urethra meatus. With respect to the external urethroplasty technique, Richardson (1969) literally states: „No attempt is made during resection either to include or avoid Skene's glands“.

III

Histology and Ultrastructure of the Female Prostate

Histologically, the female prostate is composed of the same elements as the prostate of the male: prostatic glands, ducts and smooth musculature. The ducts of the female prostate are more numerous – not only two ducts as Skene (1880) maintained -, and the glands are less numerous, i.e. the glandular and the ductal components are in an inverse ratio compared to the male prostate. These historical statements concerning the female prostate were analyzed in detail in our material by investigating prostatic tissue over the entire length of the female urethra, from the meatus of the anterior urethra to the orifice of the posterior urethra in the urinary bladder.

The ducts of the female prostate (paraurethral ducts) are a more substantial component than the prostatic (paraurethral) glands, while this relation is inverse in the male prostate. The male prostate has some 12 – 20 excretory ducts (Williams and Warwick 1980; Williams et al. 1989). The number of ducts in the female prostate is not known, it undoubtedly exceeds several times that of the male prostate. When counting the dorso-lateral and the ventrolateral ducts on Huffman's (1948) wax model I, representing the total length (2.8 cm) of the urethra of a 20-year-old virgin, we arrive at a number of ducts exceeding 40, and this only with respect to large and medium-sized ducts, as the small-caliber ducts are not represented on the model (Fig.II/8)(also see our mini-review Zaviačič et al. 1998a). The ducts of the female prostate are long tubular formations with the walls consisting of pseudostratified columnar epithelium (Fig.III/1). Similarly as the glands, they also sometimes contain female prostatic secretion (Fig.III/2). Stratified squamous epithelium was observed in the large paraurethral ducts, often at the site of their opening into the urethra (Fig.III/3)(Zaviačič et al. 1983); this is one of the epithelium types lining the female urethra (Zaviačič et al. 1985a and references therein). The paraurethral ducts, the ducts of the female prostate cannot be considered a passive component the role of which is just to transport the female prostatic secretion, the product of the female prostatic glands, into the urethra. The wall of the ducts was found to be richly equipped with neuroendocrine cells (Zaviačič 1986a, b; Zaviačič et al. 1997b and references therein) indicating that the ducts may be responsible for the

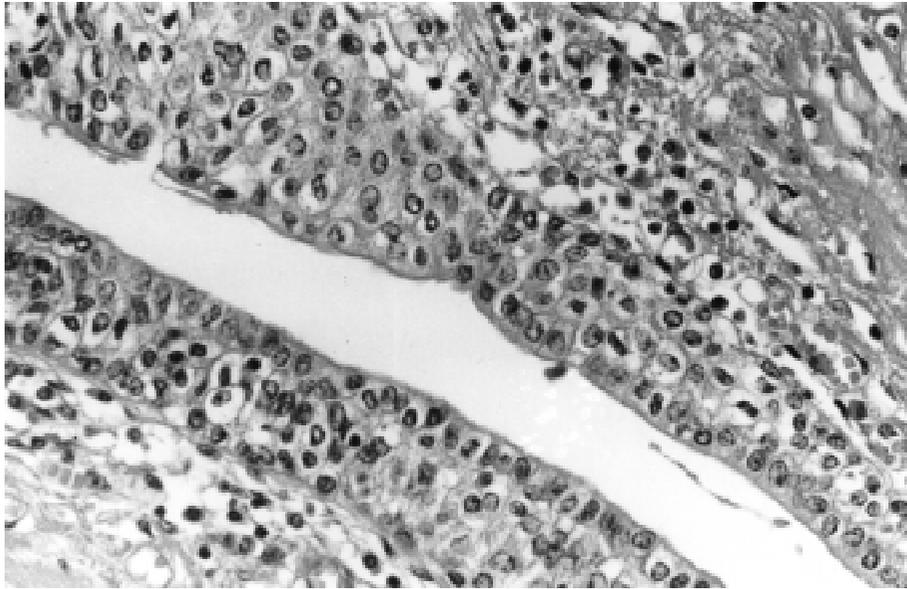


Fig.III/1 A large empty duct of the female prostate with pseudostratified columnar epithelium in the duct's lining. Female, 58-year-old, HE x 360



Fig.III/2 A large duct of the female prostate with pseudostratified columnar epithelium in the lining of the duct. Dense prostatic secretion can be seen in the lumen. Female, 31-year-old, HE x 175



Fig.III/3 A large duct of the female prostate close to the opening to the urethra, with stratified squamous epithelium in the lining (left margin). Intraductal prostatic glands with acid phosphatase activity. No enzyme in the ductal epithelium. Female, 33-year-old. Naphthol ASBI phosphate, hexazonium-p-rosaniline, x 90

major portion of the neuroendocrine function of the female prostate. The presence of these cells has been known since the early 40s (Pretl 1944), and has been repeatedly confirmed (Zavjačić 1986a, b; Wernert et al. 1992; Zavjačić et al. 1997b and references therein). Compared to the knowledge on the male prostate that concerning the female prostate as a neuroendocrine gland, a part of the female's diffuse neuroendocrine system, and the knowledge on the hormonal polypeptides produced by the female prostate remains rather insufficient.

In our series, prostatic (paraurethral) glands were seen as solitary alveolar or tubulo-alveolar glands, sometimes occurring in variously dense glandular conglomerates (Figs.III/4, 5). They either formed the terminal endings of the female prostate ducts or were localized directly in the epithelial lining of the prostatic ducts as so-called intraepithelial prostatic glands, already demonstrated by Huffman (1948). In Fig.III/6, a detail can be seen of a female prostatic gland containing secretory and basal cells. Sometimes, problems may arise in distinguishing female prostatic glands from mucinous Littré's glands. Littré's glands are strikingly bright, weakly PAS positive, diastase-resistant mucinous cells which can be distinguished from the finely granulated somewhat darker cells of the female prostatic glands even by conventional staining methods (Fig.III/7). Contrary to the data reported by Elgamal et al. (1994) on PSA

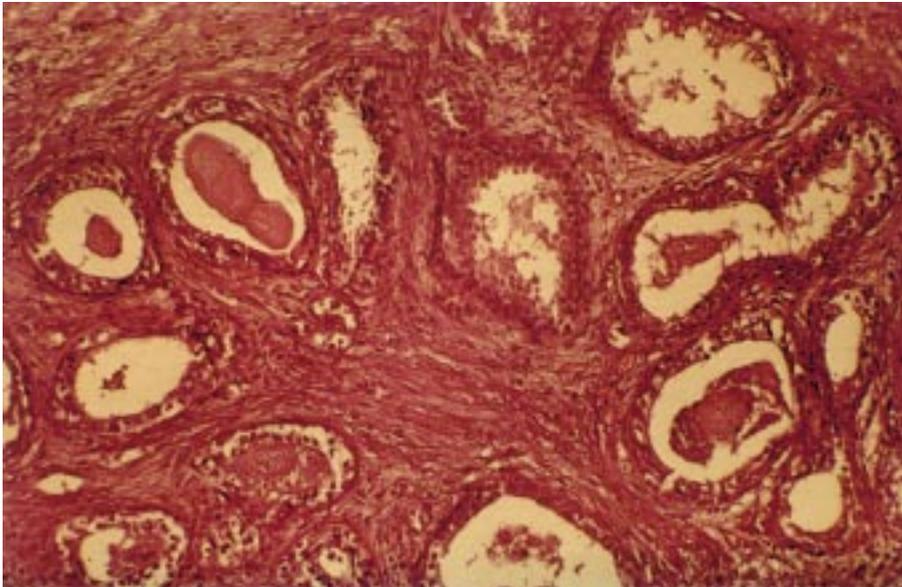


Fig.III/4 Unusually rich glands in the female prostate with thickened prostatic secretion (*corpora amylacea?*) in some glands. Smooth musculature (musculofibrous) tissue can be seen surrounding the glands. Female, 27-year-old, HE, x 175

positivity of male Littre's accessory sex glands, female urethral Littre's glands do not express PSA (Zavlačič et al. 1998a), whereas female prostatic glands typically express this prostatic marker (Pollen and Dreilinger 1984; Tepper et al. 1984; Zavlačič et al. 1994; Zavlačič and Ablin 1998a, c; Zavlačič et al. 1998c; also see Chapter VIII and Figs. VIII/1 – 3 of this Monograph). Female prostatic ducts (Fig.III/8) and glands (Fig.III/9) are easily identified and contrasted on immunohistochemical examination of the AE1/AE3 epithelial marker mixture.

Glands of the female prostate (paraurethral glands) are lined with columnar, cuboidal or moderately tall cylindrical cells. Even light microscopy enables to differentiate between secretory and basal cells in the female prostate glands by the shape of the cells, the appearance of their nuclei and their localization (Fig.III/6). Some paraurethral glands and ducts were empty, others contained eosinophilic homogeneous or finely vacuolized secretion which expressed PSA and showed diastase-resistant PAS positivity (Zavlačič et al. 1983). Interestingly enough, the finding of retained secretions in glands and ducts of the female prostate would in the past, be sufficient for the assessment of the secretory activity of the female prostate, and even conclusions would be drawn on this basis of the female prostate as being a functional genitourinary organ in childhood in contrast to the male prostate which at this age remains unfunctional (MacKenzie and Beck 1936; Moore 1936; Andrews 1951). Naturally, the evidence for

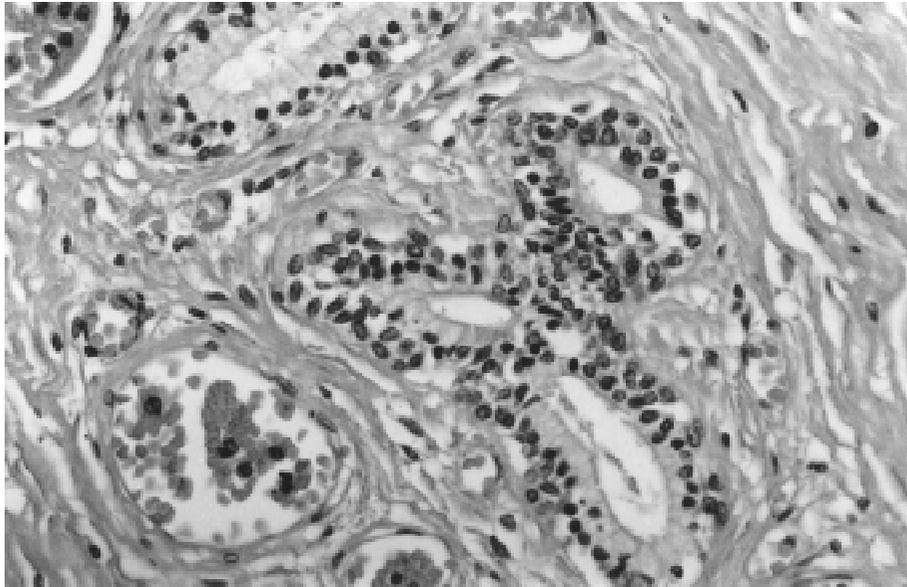


Fig.III/5 Groups of glands of the female prostate embedded in vascularized musculofibrous tissue. Female, 52-year-old. HE, x 360

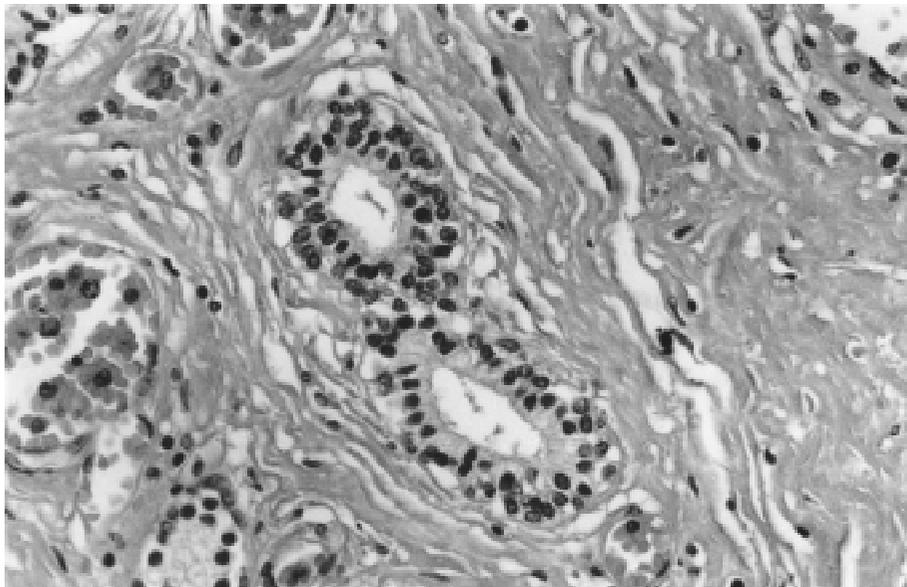


Fig.III/6 Two female prostatic glands lined with columnar secretory cells. The basal (reserve) cells are located below the secretory cells. The shape and the appearance of the nuclei of the basal cells differ from those of the secretory cell nuclei. Female, 52-year-old, HE, x 360

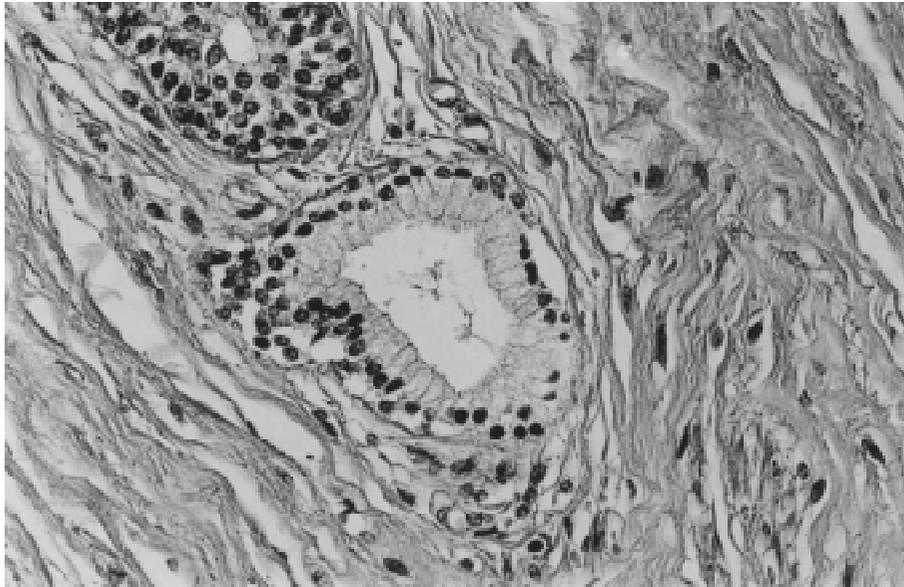


Fig.III/7 Littré's gland with strikingly bright mucinous cells containing uniformly basally located dark nuclei. A portion of female prostatic gland in the vicinity. Female, 34-year-old, HE, x 360

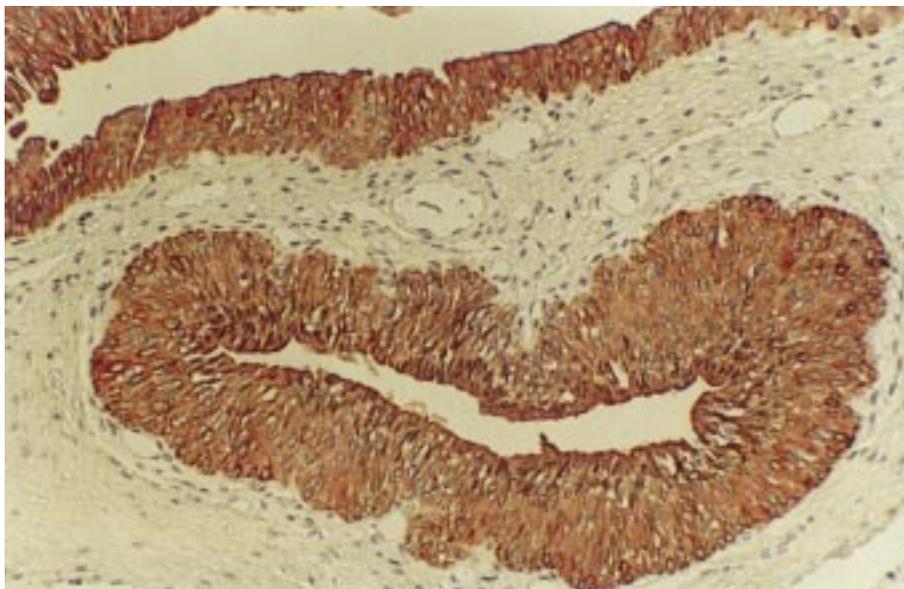


Fig.III/8 Large ducts of the female prostate with pseudostratified columnar epithelium in the lining, with expression of AE1/AE3 epithelial markers in the cell membranes and on the surface of epithelial cells bordering the duct lumen. Female, 63-year-old, x 360



Fig.III/9 Female prostatic glands expressing AE1/AE3 epithelial markers. Female, 39-year-old, x 90

the secretory activity of the female prostate is currently based on much more objective parameters, including, a.o., the observation of active secretory configuration of secretory prostatic cells under electron microscopy of female prostatic glands (Zaviačić et al. 1998d). Nevertheless, the female prostatic glandular and ductal contents need to be paid attention to even today. The female prostatic secretion seems to stagnate in the cavitory system of the female prostate unless mechanisms helping the female prostate to empty are involved. Female prostates of bed-ridden patients after prolonged hospital stays examined at autopsy frequently contained more stagnating prostatic secretion than seen at forensic-medical analyses in the same structures in „fully healthy“ women who died suddenly. In these latter cases, the mechanisms helping the prostate to empty could have been operating up to the death without any restriction (unpublished observations). Also, a layer on the surface of secretory cells of the prostatic glands and on the luminal surface of the urothel of prostatic ducts and the female urethra showed the same diastase-resistant PAS positivity as did prostatic secretion. This clearly configured layer on the luminal surface and in the apex of secretory cells of prostatic glands in both sexes as well as on the surface lining of the cavitory system of the female prostate and urethra appears to present a complex interplay of glycosamine glycans, glycoproteins (including PSA and (human) urine protein 1) and enzymic proteins. Thus, in addition to the secretory role of urine protein 1 as indicated by the association of this layer with the female and male secretory cells, it may also have a protective role, espe-

cially in the ureoepithelium, against the aggressive effects of urine (Zaviačič et al. 1997a).

Female prostatic (paraurethral) glands have been known since mid-80s to manifest high acid phosphatase (PSAP) activity on various enzyme-histochemical (Zaviačič 1984b) and immunohistochemical methods (Tepper et al. 1984; Pollen and Dreilinger 1984), as well as proteosynthetic enzymes activity (glucose-6-phosphatase, E-600-sensitive esterase)(Zaviačič 1984a). The identification of female secretory prostatic cells under light microscope has been promoted by both histochemical and immunochemical studies of PSAP and by immunohistochemical findings of PSA expression in the apical part and the surface of these cells (Pollen and Dreilinger 1984; Tepper et al. 1984; Zaviačič et al. 1994; Zaviačič 1997; Zaviačič and Ablin 1998c). Further insight could be gained by immunohistochemical demonstration of human protein 1 in female prostatic glands which, compared to conventional staining methods, provided better possibilities to distinguish secretory from basal cells of female prostatic glands under the light microscope (Zaviačič et al. 1997a; and Fig. 1).

The ultrastructure of the normal prostatic gland in the adult woman

The first electron microscopic study of the female prostate concerned a case of female prostate carcinoma in inadequately fixed material (Sloboda et al. 1998). This ultrastructural study nevertheless confirmed the immunohistochemical and histological conclusions made on the existence of secretory (luminal) cells in the female prostate (Zaviačič et al. 1997a; 1998a). Sloboda's paper (Sloboda et al. 1998) showed the tumor cells to possess the basic ultrastructural parameters of secretory cells: numerous secretory elements (secretory vacuoles and granules) in the apical cytoplasm, and short stubby microvilli on their surface. Thus, carcinoma of the female prostate appears to develop from the same cells as does male prostate cancer (Sloboda et al. 1998 and references therein).

Over prolonged periods of time, the investigation of the female prostate's ultrastructure using transmission electron microscopy would be hindered by problems concerning the obtaining of optimally fresh material of the female urethra which would lend itself for electron microscopic investigations. Suitable material (of the female urethra – female prostate) could only be obtained recently during harvesting of other organs for transplantation purposes. Ultrastructural parameters of the normal adult human female prostate gland were published only recently (Zaviačič et al. 1998d).

Also, Gittes and Nakamura (1996) obtained several specimens of the female urethra and its surrounding soft tissue en bloc from brain-dead donors from whom multiple organs were harvested for transplantation. This optimally fresh material was only used to immunohistochemically determine PSA in the glands of the female prostate, no electron microscopic investigation of the female prostatic tissue was however done.

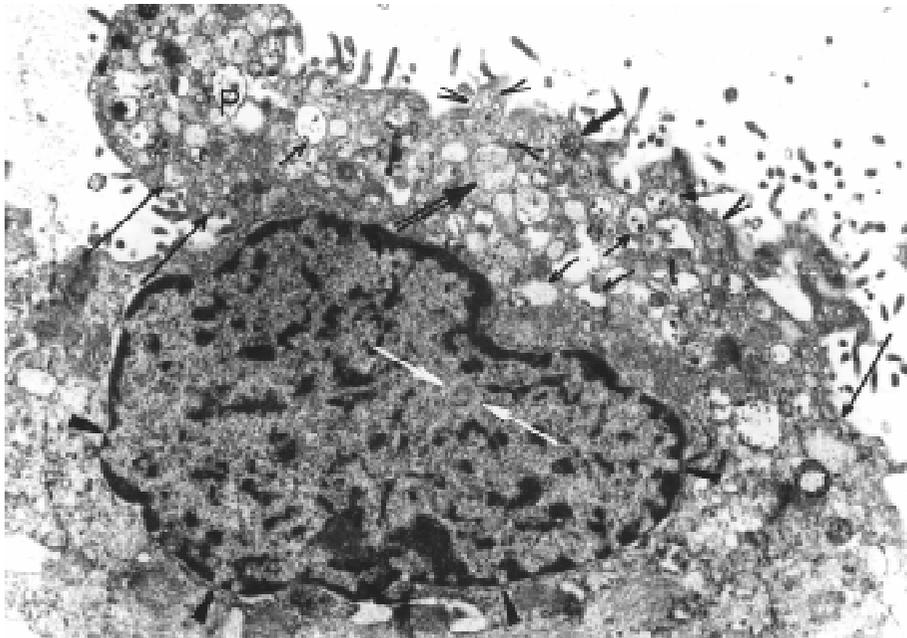


Fig.III/10 A secretory cell with the typical bizarre appearance of secretory vacuoles (SV). Longer microvilli can be seen on the cell surface, with irregular orientation towards different directions. The short arrows point to polymorphous SV in the cytoplasm. Some of them are in contact with the cell membrane (long arrows). Some SV contain 2 – 4 dense microgranules, others contain wisps of little electron-dense material (long double arrow). In some SV, lysosome-like particles and pinocytic vacuoles (arrowheads) can be seen in close vicinity to the cell membrane. The cytoplasmic protuberance (P) also contains SV. Moderately dilated sacs of the perinuclear cisterna are in direct contact with RER. Nuclear pores of varying density (thick arrowheads) and a simple nuclear body (between the arrowheads) can be seen. Uranyl acetate and lead citrate (UALC), x 18,000

In our electron microscopic study (Zavlačič et al. 1998d), the female urethra containing prostatic tissue was obtained from three brain-dead female patients aged 19, 34 and 47 years. They all had suffered cranio-cerebral trauma during traffic accidents, and were pronounced dead after the cerebral blood circulation had stopped (as confirmed by cerebral panangiography). The systemic blood circulation was however maintained within normal limits until permission could be obtained to harvest several organs for transplantation purposes. The urethra was removed first by transvaginal / perineal approach. Immediately after the removal, the distal urethra containing most prostatic tissue (meatal type of the female prostate; Zavlačič et al. 1998a and references therein) was cut under a drop of 3% glutaraldehyde solution into small blocks

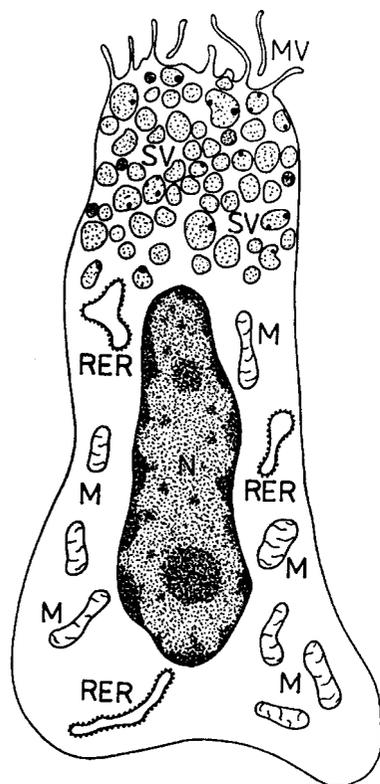


Fig.III/11 Schematic representation of the ultrastructure of a secretory (luminal) cell with an abundant population of polymorphous secretory vacuoles.
 Symbols: SV, secretory vacuole; MV, microvillus; M, mitochondria; RER, rough endoplasmic reticulum; N, nucleus

with an edge length of approx. 0.2 mm, and fixed in 3% glutaraldehyde for 2 hours. For details of further steps of the fixation procedure, see Zaviačič et al. (1998d).

Glands of the female prostate are formed by tall cylindrical secretory (luminal) cells limiting the lumen of the female prostate gland. Basal (reserve) cells are located below the secretory cells or between their base and the basement membrane. Epithelial cells may occasionally be seen interposed between basal and secretory cells or in their vicinity; in our study they have been referred to as intermediary cells (Zaviačič et al. 1998d).

The ultrastructure of the normal female prostate gland was compared with the available information on the ultrastructure of the normal adult male prostate reported by several researchers (Brandes et al. 1964; Fisher and Jeffrey 1965; Mao et al. 1966; Tannenbaum et al. 1967; Fisher and Sieracki 1970; Sinha and Blackhard 1973; Brandes 1974; Dermer 1978; Srigley et al. 1988). In their monograph on the prostate, Fitzpatrick and Krane (1989) devoted a chapter to the ultrastructure of this organ.

In our material (Zaviačič et al. 1998d), secretory cells resting on a layer of basal cells were found to be the predominant cell type of the female prostatic gland. The

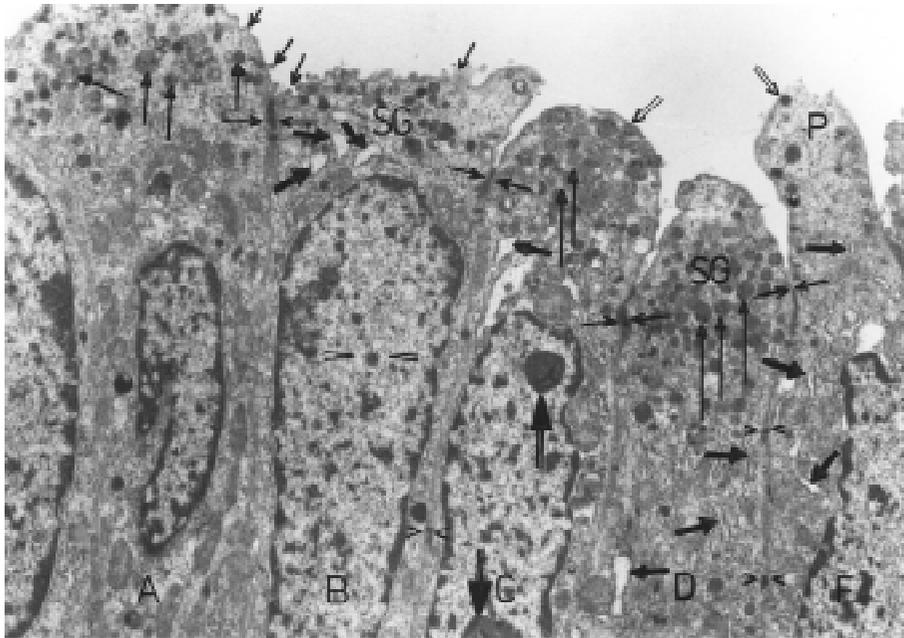


Fig.III/12 Secretory cells (A,B,C,D,E) with secretory vacuoles (SV) and secretory granules (SG). Numerous polymorphous SV (long arrows) of varying structure and content density can be seen in cell A. Cell B contains denser SG and some RER profiles (thick arrow). A nuclear body can be seen in the nucleus (between the arrowheads). Stubby microvilli on the surface of cells A and B (arrows). Cells C and D contain mostly uniform SG of medium density with peripherally located flakes of electrodense material. Some of them are within the surface membrane (double arrow). Abundant RER in both cells. Cell C has a nucleus with two striking nucleoli (double thick arrow) and contains supranuclear optically empty vacuoles. Cell E has a large apical cytoplasmic protuberance (P) and contains much RER and few secretory elements. Zonulae occludentes in the apical part between the cells (between arrows). Somewhat below, zonulae adherentes (between the arrowheads). The nuclei of all cells have numerous nuclear pores. UALC, x 12,000

basic structure of the female prostate acinus and the location of prostatic secretory and basal cells were in conformity with the structural pattern of the prostatic glands of the adult male (Fisher and Jeffrey 1965; Fisher and Sieracki 1970; Brandes 1974; Dermer 1978; Srigley et al. 1988).

Similarly as in the adult male prostate (Fisher and Jeffrey 1965; Brandes 1974; Srigley et al. 1988), the columnar secretory cells of the female prostate are characterized by polymorphous secretory elements in the cytoplasm: secretory vacuoles and secretory granules, lending these cells a special appearance. The secretory vacuoles

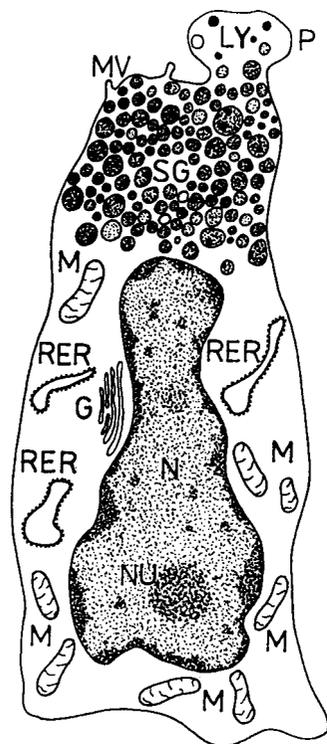


Fig.III/13 Schematic representation of the ultrastructure of a secretory (luminal) cell with secretory granules.

Symbols: SG, secretory granule; MV, microvillus; P, protuberance of the apical cytoplasm; LY, lysosome; RER, rough endoplasmic reticulum; G, Golgi complex; M, mitochondria; N, nucleus; NU, nucleolus

mostly had a similarly bizarre appearance (Fig.III/10) as seen in mature male secretory cells with rather polymorphic structures within the vacuoles. In some instances, they contained remnants of mitochondria or other organelles. Some female secretory prostatic cells also contained homogeneous medium-dense granules with flakes of more dense material (Fig.III/12). A mixture of polymorphous populations of secretory elements, secretory vacuoles as well as secretory granules was seen in other secretory cells (Fig.III/14).

The merocrine content-releasing mechanism of the secretory vacuoles (secretory vacuoles fuse with the luminal plasma membrane and the contents get dissolved) and the apocrine discharge of apical blebs into the lumen of female prostatic glands observed in our studies was consistent with the known secretory mechanism of the same cells in the adult male prostate (Brandes 1974). Lysosomes and lysosome-like dense bodies were often seen in the supranuclear parts and in blebs of secretory cells in our samples. Our ultrastructural findings support the results of numerous enzyme-histochemical studies which identified high activities of lysosomal and cytoplasmic PSAP in the apical parts of the female secretory cells (Pollen and Dreilinger 1984; Tepper et al. 1984; Zaviačić 1984b; Aumüller and Seitz 1985). The appearance of

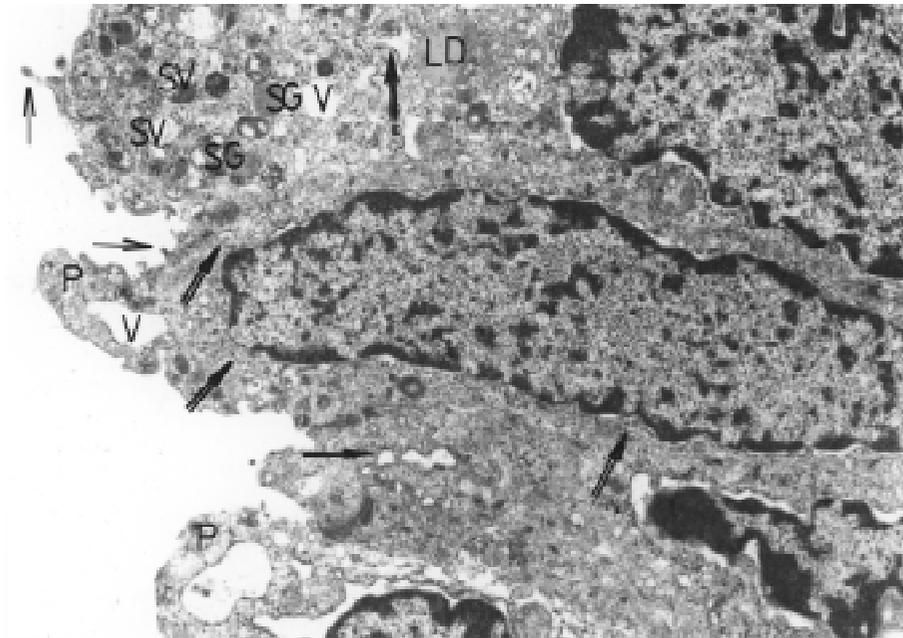


Fig.III/14 Secretory cells of the female prostate with a mixture of secretory granules (SG) and secretory vacuoles (SV). Individual short microvilli (arrow) on the surface. Occasional para- and supranuclear RER profiles (double arrow). A lipid droplet (LD) and empty vacuoles (V) above the nucleus. Protuberances (P) and V and RER profiles in the apical cytoplasm. ULAC, x 18,000

other cell organelles of female prostate secretory cells also corresponded to that of mature secretory cells of the male prostate. Besides apical protuberances of the cytoplasm and blebs, the surface of these cells was also covered by numerous short stubby microvilli, similarly as seen on the surface of secretory cells of the male prostate (Brandes et al. 1964; Fisher and Jeffrey 1965; Brandes 1974; Srigley et al. 1988). A comparison of the normal fine structure of secretory cells of the female and male prostate showed that the secretory cells of the adult female prostate were consistent in appearance with the prostatic secretory cells of the adult male. The present focus on female PSA (Borchert et al. 1997; Diamandis 1998; Zaviačič and Ablin 1998a, c) has increased the interest in the female prostate, which produces the major part of this prostatic marker in the healthy female and which has several functional implications (Sesterhenn et al. 1998; Zaviačič and Ablin 1998a, b, c; Zaviačič et al. 1998c). The ultrastructural organization of female secretory cells in our material suggests an active secretory function as judged upon by the presence of abundant secretory elements – secretory vacuoles and secretory granules, rough endoplasmic reticulum, developed Golgi complexes, numerous mitochondria and apical blebs. The subcellu-

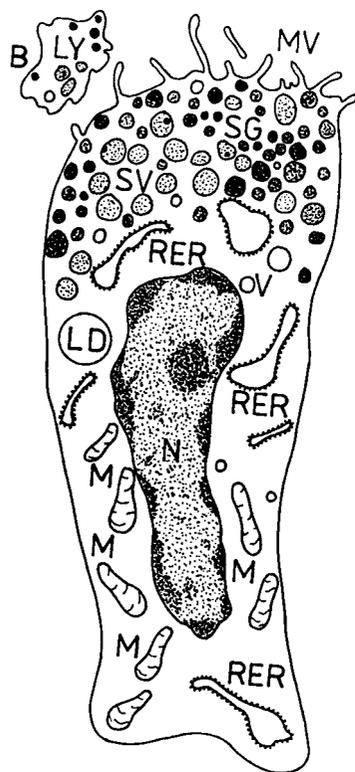


Fig.III/15 Schematic representation of the ultrastructure of a secretory (luminal) cell with a mixture of secretory elements (secretory vacuoles together with secretory granules in one secretory cell). Symbols: SV, secretory vacuole; SG, secretory granule; B, bleb; LY, lysosome; MV, microvillus; RER, rough endoplasmic reticulum; LD, lipid droplet; V, empty vacuole; M, mitochondria; N, nucleus

lar equipment of female and male secretory cells with „secretory“ organelles is comparable. In the light of the exocrine function of the male prostatic glands (Abtin 1997 and references therein) and of the same function of female prostatic glands (Zavlačič and Whipple 1993 and references therein), the secretory (luminal) cells play an exceptionally important role in both these organs.

The other basic cell type seen in the female prostate, i.e. the basal (reserve) cells, was found to be identical with the basal cells of the adult male prostate as to the location and the appearance of the cytoplasm (Fisher and Jeffrey 1965; Dermer 1978; Srigley et al. 1988). In the cytoplasm of female prostatic basal cells, dilated profiles of the rough endoplasmic reticulum and moderate numbers of mitochondria could be visualized (see the schematic representation in Fig. III/16). Besides these organelles, Srigley et al. (1988) also described a poorly developed Golgi complex in male prostatic basal cells. Neither us nor other researchers did find any secretory vacuoles or granules either in female or in male prostatic basal cells. Their absence provides the most characteristic difference between mature basal cells and secretory prostatic cells (Fisher and Jeffrey 1965; Dermer 1978; Srigley et al. 1988). Both the appearance of prostatic basal cell nuclei and the distribution of their chromatin in the female and male prostate

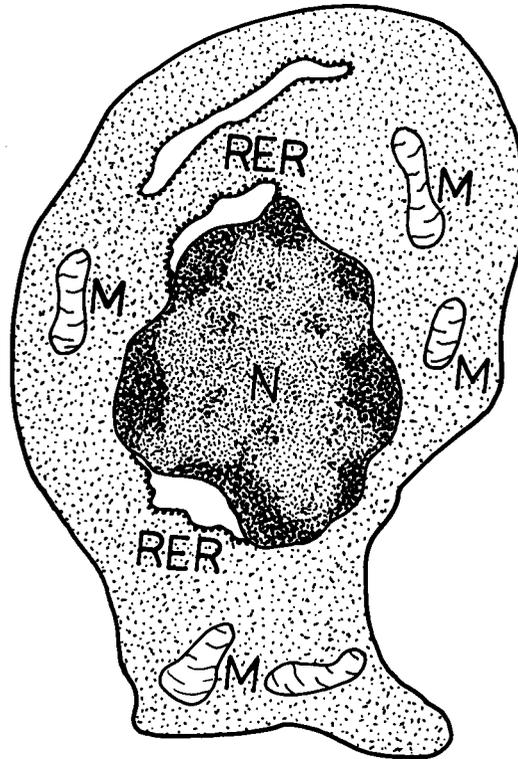


Fig.III/16 Schematic representation of the ultrastructure of a basal (reserve) cell of the female prostatic gland. Swollen mitochondria and profiles of the rough endoplasmic reticulum can be seen in the dense cytoplasmic ground substance.
 Symbols: M, mitochondria; RER, rough endoplasmic reticulum; N, nucleus

were comparable (Fisher and Jeffrey 1965; Dermer 1978; Strigley et al. 1988). Since female basal cells rest on the basement membrane of female prostatic glands, their potential myoepithelial nature may be considered as tentatively discussed in the case of male prostate basal cells (Fisher and Sieracky 1970). Unlike breast and salivary glands where myoepithelium is present, the female and the male prostate contain a non-glandular contractile system composed of smooth muscle cells and/or musculofibrous tissue (Huffman 1948; Dermer 1978; Zaviačič et al. 1983; Zaviačič 1987a; Wernert et al. 1992). In keeping with this, we did not find structures suggesting contractile function in female basal prostatic cells. Besides sexual stimuli, the tonus and the congestion in musculofibrous tissue surrounding the glands and ducts of the female prostate, which change during micturition and defecation, may well contribute to the evacuation of the female prostate (Zaviačič et al. 1983).

Glandular epithelial cells with little differentiated cytoplasm, seen along with secretory and basal cells, were termed by us type 1 and 2 intermediary cells. The most pronounced difference between them is the virtually complete absence of secretory granules and vacuoles in type 1 cells (Fig.III/17) and their appearance in the little differentiated cytoplasm of type 2 intermediary cells. In the female prostate, intermediary cells may represent cell forms between basal and secretory cells, demonstrated by some authors under electron microscopy in the male prostate only (Mao and Angrist 1966). Dermer (1978) and Srigley et al. (1988) suggested that male prostate basal cells may be a source of secretory cells. Xue et al. (1998) developed a prostatic stem cell model in which both exocrine and neuroendocrine cells of the male prostate are derived from a subpopulation of basal cells that give rise to luminal (secretory) cells through intermediate cells (pluripotent amplifying cells). Our findings support the opinion on the similar role of basal cells in the renewal of exocrine (secretory) elements in the female prostate glands.

The principal structural parameters of secretory (luminal), basal (reserve) and intermediary cells of the adult human female prostate gland are schematically shown in Figures 11, 13, 15, 16, and 18.

In the male prostate, immature stratified glandular epithelium differentiates during puberty into two principal cell types of the adult prostate glands: the secretory columnar epithelium and the basal cells. This differentiation process of the male prostate during puberty is obviously initiated by the commencing testicular androgen secretion (Wernert and Dhom 1989; Wernert et al. 1992). These andrological findings are in accordance with the earlier anatomical observations by Andrews (1951) that the male prostate gland remains without any secretory activity between about 4 months and thirteen years of age. Heath (1984; 1987) believes that the female prostate begins functioning very early, nevertheless erotic and orgasmic functional sequences are gradually inhibited and, as hypothesized by Money (1987), also societal prohibition plays a role in the inhibition. In spite of the fact that under normal conditions, there are no androgenic stimuli either during puberty or throughout life of a woman, the epithelium of female prostatic glands gets clearly differentiated into mature secretory and basal cells. It seems to be justified to address the question whether it actually is androgens only that are involved in an important manner in the processes of differentiation and maturation of prostatic glandular cells and whether estrogens may not be called into play in the differentiation of glandular cells of the female prostate, which is equipped with receptors for this hormone. Estrogen-receptor-associated protein (ER-D5) was found in the cytoplasm of cells lining female prostate glands, yet not in ductal cells (Wernert et al. 1992). Our considerations concerning the potential participation of estrogens in the differentiation of the glandular epithelium of the human female prostate are strongly supported by the findings of Merck et al. (1980). These authors observed regressed glandular cells in the male prostate to acquire a new phenotype after the administration of estradiol-17-beta-17-cyclopentylpropionate to castrated and hypophysectomized dogs. The characteristic features of these cells included newly formed secretory granules. The authors suggested that androgens and estrogens have an equal capacity to control the expression of prostatic secretory granules.

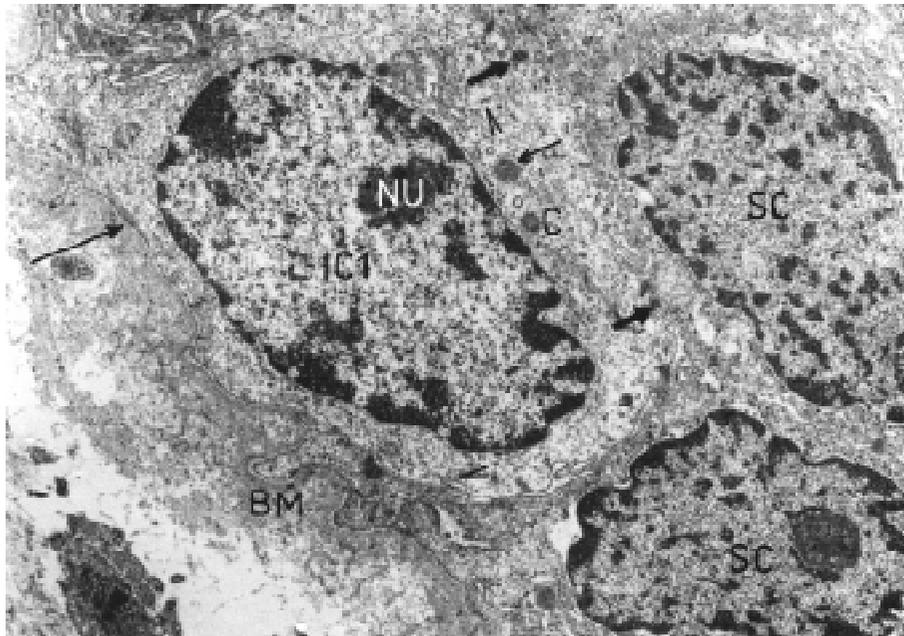


Fig.III/17 Intermediary cell type 1 (IC1) between two secretory cells (SC). The nucleus with a smooth surface, inconspicuous simple nucleolus (NU) and much disperse chromatin. Only one or two small SG (arrow), profiles of undilated RER (arrowhead), free ribosomes and centriole (C) in the cytoplasm. The cell rests on the basement membrane (BM) and is attached to it by separate hemidesmosomes (long arrow). Zonulae adherentes connect the cell with the cytoplasm of the neighboring SC (thick arrow). UALC, x 18,000

Our results concerning the female prostate (see references in this Monograph) including our electron microscopic study (Zaviačič et al. 1998d) with the discussion presented in the latter paper and in this Monograph substantiate our disagreement with the skeptical conclusions voiced in the study by Wernert and coworkers (1992) that „these glands (of the female prostate) resemble strongly the male prostate glands before puberty ... glands (of the female prostate) remain immature throughout life (of the female) from the fetal period up to advanced age... No indications can be found for a proper biological function...“ On the contrary, our electron microscopic analysis of the normal female prostate showed that, similarly as in the male after puberty, prostatic glands in the adult female form morphologically mature secretory and basal cells. There is no ground to believe that these cells would not play the same role in the pathophysiology of the female as they do in the male prostate. Supporting evidence has been provided by several implications of the exocrine function of the female prostate in forensic medicine, gynecologic urology, chronobiology and sexology (Zaviačič

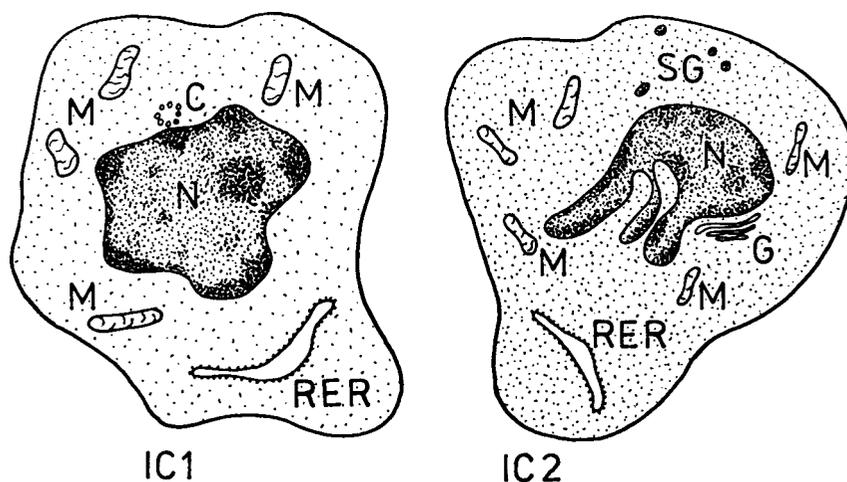


Fig.III/18 Schematic representation of the ultrastructure of type 1 and 2 intermediary cells of the female prostatic gland. The cytoplasm of type 2 intermediary cell (IC2) is more differentiated than that of IC1, and contains sparse secretory elements (secretory granules).

Symbols: SG, secretory granule; G, Golgi complex; M, mitochondria; C, centriole; RER, rough endoplasmic reticulum; N, nucleus

1987a; Zaviačić and Whipple 1993; Zaviačić and Ablin 1998a, b, c). On giving equal consideration to ultrastructural parameters of the glands of the human male and female prostate, it might be appropriate to mention some rodent species with comparable structures of prostatic glands in males and females, observed at the ultrastructural level (Ichihara 1976; Gross and Didio 1987).

The recent ultrastructural observations further support the justified view that prostate should be seen as woman's specific functional genitourinary organ. Increasing evidence substantiates the notion that the woman's prostate is an actually functional gland in its own right rather than an afunctional vestigial Skene's gland. Its structure has been well defined and the adult woman prostate's ultrastructural equipment also corresponds to that of the glandular cells of the adult male prostate. Comparability with the male prostate has not only been established with respect to the exocrine and probably also neuroendocrine function, but also with regard to the pathology of the female prostate. The occurrence of pathologic conditions may be less frequent in the female, yet there is increasing evidence indicating that the female prostate can be affected by the same diseases as does the male prostate, including cancer, benign prostate hyperplasia and prostatitis (Folsom and O'Brien 1943; Zaviačić et al. 1985b; 1993a; 1994; 1995; Zaviačić 1987a; Zaviačić and Whipple 1993; Gittes and Nakamura 1996; Sloboda et al. 1998 and references therein; Sesterhenn et al. 1998; Zaviačić and Ablin 1998a, b, c).

The prostate can thus be considered as another organ exhibiting different size and weight (certainly, depending on additional parameters such as body stature and weight, and age as do most human organs and as evident from tables showing the parameters of human organs; Thomas 1990) and different functional capacity in man and woman, yet the same qualitative parameters in both genders. Sandritter's *Macropathology* (Thomas 1990) however does not show any data concerning the weight of the female prostate since such data have only been published very recently (Zavjačić et al. 1998a).

Differences in somatic organ parameters between the genders may become important with respect to transplantation medicine, e.g. in looking for adequate replacement of male organs by female organs. The heart of a 40- and 50-year-old woman is 35 g lighter and smaller than that of a man of the same age, stature and almost the same weight (Thomas 1990). Then, such differences may become a serious or even determining indication criterion with respect to the selection of the donor for human heart transplantation. Naturally, the differences in organ parameters between males and females should not be an adequate argument to support the simplistic view that some organs in women are inferior to those of men. A similar conclusion also applies to the female prostate: it cannot be considered inferior just because it is smaller and has a smaller weight than the male prostate.

IV.

Enzyme Histochemistry of the Female Prostate and its Functional Implications

The first enzyme histochemical papers dealing with the female prostate (Skene's glands) appeared in early 80s, at a time, when homology between vestigial Skene's glands and the male prostate was essentially based on the embryology-derived knowledge of both tissues originating from the same embryonal urogenital sinus. Suddenly, evidence could be brought for Skene's glands having a typical enzyme equipment comparable with that of the male prostate (Zaviačič 1985a), including the presence of prostatic and lysosomal acid phosphatase (Zaviačič 1984b), other hydrolases and numerous oxidoreductases (Zaviačič 1984a).

Enzyme-histochemical investigations, and among them and due to understandable reasons, the evidence for acid phosphatase in Skene's glands but not in paraurethral ducts, were the strongest reason for the recognition of the existence of the female prostate in early 80s, prior to the PSA era. At a time, when identification of female prostatic glands faced some problems, in particular when located intraepithelially in the prostatic duct walls, azo-coupling and precipitation techniques according to Lojda et al. (1976) were an easy approach to resolve the problem. Acid phosphatase activity established by the azo-coupling (Fig.IV/1) and Gomori's precipitation method (Fig.IV/2) most probably demonstrated „lysosomal“ acid phosphatase (EC 3.1.3.2) rather than its isoenzyme, cytoplasmic „prostatic“ phosphatase (Vries et al. 1980). Also, the lysosomal fraction can be assumed with a high probability to be released to the female ejaculate along with cytosolic prostatic acid phosphatase, as suggested by macro-enzyme-histochemical studies providing evidence for a high activity of the former enzyme in association with continual secretion and ejaculation-induced emptying of the female prostate (Zaviačič et al. 1987a, b; 1988a, b, c). As determined biochemically, acid phosphatase activity was several times higher in the fluid of female urethral expulsions than in the urine (Addiego et al. 1981; Belzer 1981; Longo 1982; Stifter 1988).

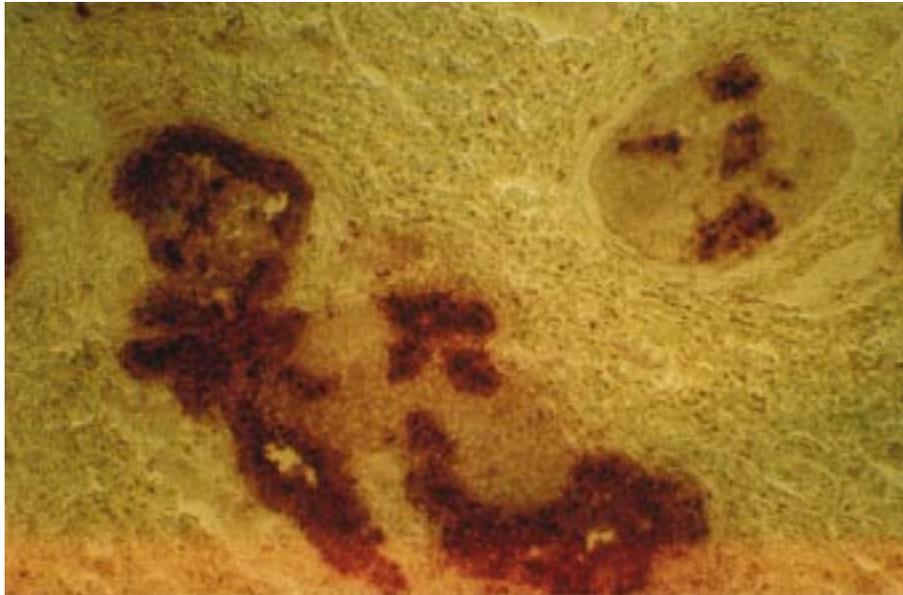


Fig.IV/1 High activity of acid phosphatase in the glands of the female prostate and in intraductal prostatic glands. The enzyme is absent in the ductal epithelial lining. Female, 17-year-old. Naphthol ASBI phosphate, hexazonium-p-rosaniline, cryostat section, semipermeable membrane technique, pH 5.4, x 175

Formaldehyde (Pearse 1968; Jöbsis 1990) and tartrate-resistant but fluoride-sensitive acid phosphatase (EC 3.1.3.2) exhibited a high activity in the glands of the female prostate (paraurethral glands), in glands located directly in the epithelial lining of the prostatic (paraurethral) ducts (Fig.IV/1) as well as in cells of neuroendocrine nature (Zaviačič 1984b). In the prostatic glands, acid phosphatase was localised in the apical parts and the surface of lumenally located (secretory) cells. A weak activity could also be seen in the epithelium of the paraurethral ducts, but not unless semipermeable membrane technique and long-term incubation in the cold (overnight at 6°C) was introduced. The histochemical reaction to determine acid phosphatase by the azo-coupling (Fig.IV/1), Gomori's precipitation technique (Fig. IV/2) or the technique developed by Serrano et al. (1977) using phosphorylcholine (Fig.IV/3) to demonstrate „specific“ prostatic acid phosphatase allow to readily distinguish the glandular components (paraurethral glands) of the female prostate (where the reaction is very pronounced) from the ductal parts of the prostatic tissue (paraurethral ducts) with no or only minimal activity (Zaviačič 1984b). The specificity of Serrano's (Serrano et al. 1976) histochemical technique to visualize „prostatic“ acid phosphatase alone, has however been intensely criticized (Lojda 1987). In the early 80s, the very evidence for the presence of the enzyme in the female prostate glands suggested the existence of female secretory pro-

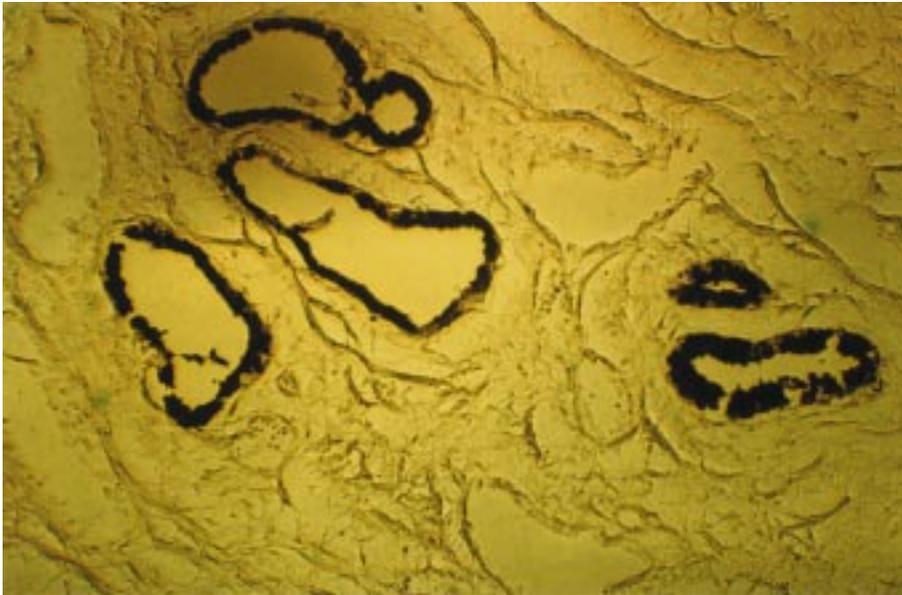


Fig.IV/2 High activity of acid phosphatase in the glands of the prostate of a 15-year-old female. Sodium beta-glycerophosphate, Gomori's method, pH 5.4, frozen section, x 175

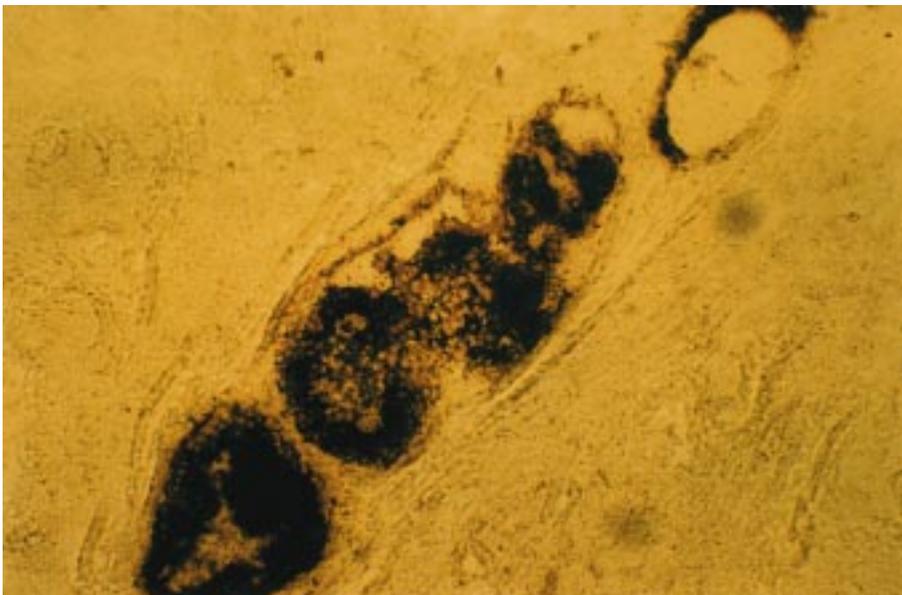


Fig.IV/3 High activity of prostatic (specific) acid phosphatase in the glands of the prostate of a 37-year-old female. Method according to Serrano et al. with phosphorylcholine, x 180

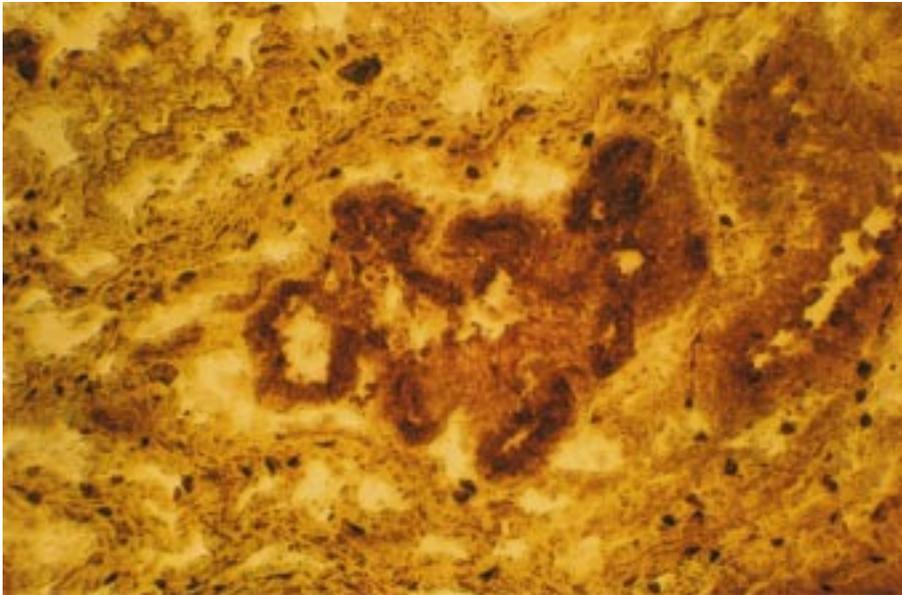


Fig.IV/4 Markedly high activity of E-600 sensitive esterase in the cytoplasm of prostatic gland cells. The activity is considerably weaker or missing in the pseudostratified columnar epithelial lining of the ducts. Female, 17-year-old. Alpha-naphthyl acetate and hexazonium-p-rosaniline, x 175

static cells and thus an exocrine role for the female prostate. Prostatic ducts do not have a similar role. However, they are far from being a mere passive ductal part of the prostate since (as will be shown below) they are equipped with cells for neuroendocrine function. In addition to secretory cells of female prostatic glands, also occasional cells and nerve fibres of cells showed reaction, which corresponded well with argyrophilic cells as seen when using the Grimelius' method (Zaviačič 1986a) or when using polyclonal antibodies against human protein 1 (urine protein 1) and other neuroendocrine markers to study female prostate (Zaviačič et al. 1997b). The findings concerning acid phosphatase and some other phosphatases repeatedly confirmed the existence of neuroendocrine cells in the female prostate, although their presence in the female and the male prostate urethra has been known since the late 50s (Koch and Engelhard 1959) and even early 40s (Pretl 1944) respectively.

The determination of acid phosphatase, naphthyl esterase and glucose-6-phosphatase helps to distinguish the glandular component of the female prostate (where relatively high activities are observed) from the epithelial lining of the ducts, where these enzymes are missing. The secretory function of the female prostate glands has been supported by the findings of E-600 sensitive naphthyl esterase (Fig.IV/4) and glucose-6-phosphatase (Fig.IV/5) in lumenally located secretory cells of female prostatic glands.

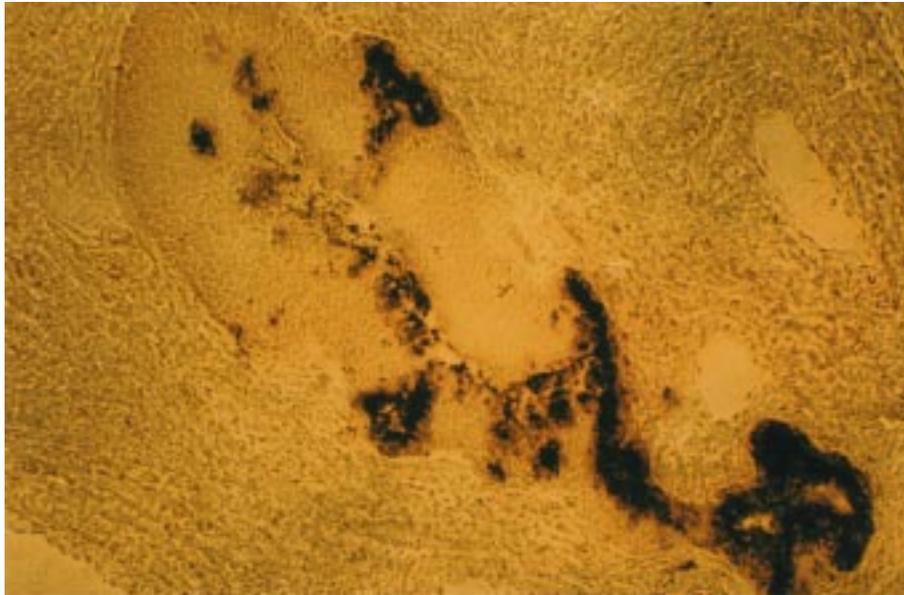


Fig.IV/5 High activity of glucose-6-phosphatase in female prostatic glands and in intraductal glands of the female prostate. No activity in the pseudostratified columnar epithelium of the epithelial lining of ducts. Female, 17-year-old. Glucose-6-phosphate, x 180

The exocrine secretory role of the female prostate (production of female prostatic fluid) is being suggested by the enzyme equipment of the prostatic glands marking organelles of cells involved in proteosynthesis.

Differences have been demonstrated in the enzyme equipment of the prostate in women of childbearing age compared to post-menopausal women. The latter show a reduced activity of naphthyl esterase (Fig.IV/6) and, in some cases, also of glucose-6-phosphatase. On the other hand, there was a marked increase in the activity of lysosomal acid phosphatase in the prostatic ducts with „prostatic“ acid phosphatase activity being maintained or reduced in the glands of the prostate. In some women of advanced age, a majority of the dehydrogenases showed reduced activities in prostatic glands and ducts (Fig.IV/7). During early menopause, no such decrease in dehydrogenases activity could be observed, the activities being as high as those measured in samples of prostatic tissue of women of childbearing age (Fig.IV/8)(Zavlačič 1987a, b; Zavlačič et al. 1989).

Comparative enzyme-histochemical studies of the female and male prostate (about 20 different enzymes) revealed similar distribution and virtually similar activities of the enzymes in the glands of the male and female prostate. Not a single enzyme of the group of enzymes examined was observed to be typically present in the cells of the



Fig.IV/6 Low activity of E-600 sensitive esterase in the glands and ducts of the prostate of a 73-year-old-female. Alpha-naphthyl acetate and hexazonium-p-rosaniline, x 180

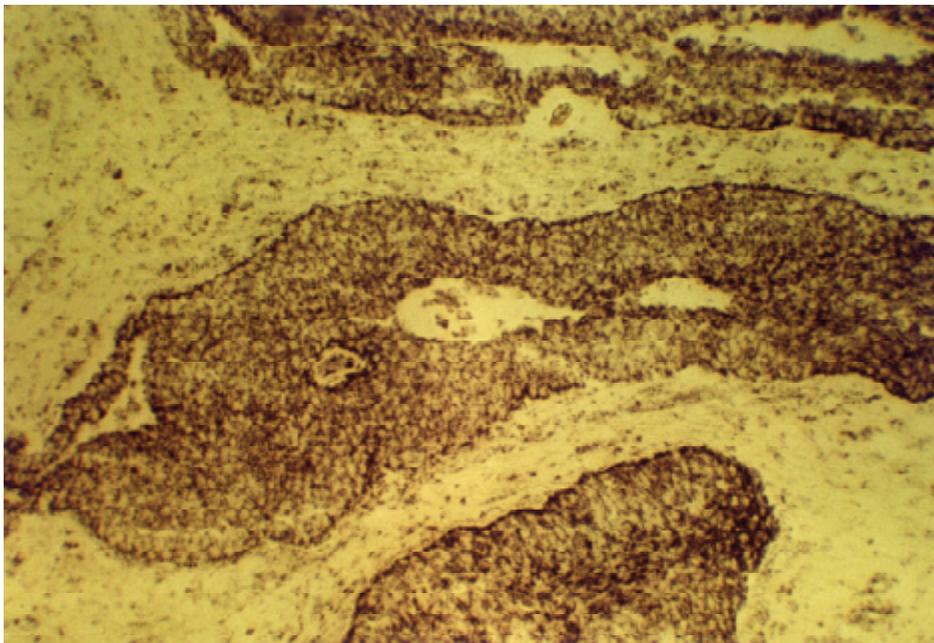


Fig.IV/7 Low activity of mitochondrial glycerol-3-phosphate dehydrogenase in the epithelium of the female prostate ducts. Female, 71-year-old, x 180

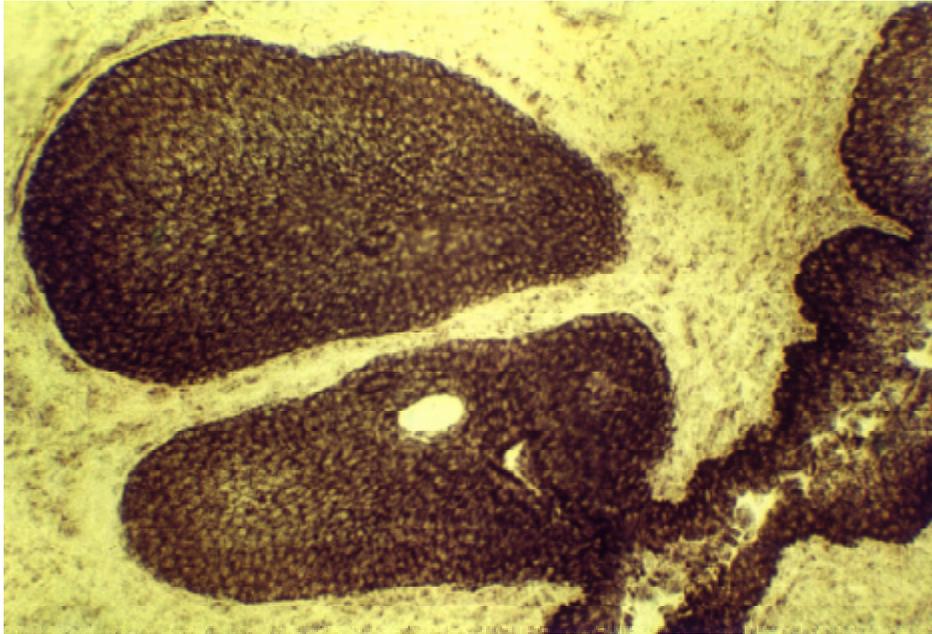


Fig.IV/8 High activity of mitochondrial glycerol-3-phosphate dehydrogenase in the epithelium of the female prostate ducts and urethra. Female, 38-year-old, x 180

male prostatic glands while being absent in the female prostate structures (Zaviaèiè 1985a).

At the same time when the first papers concerning the enzyme equipment of the female prostate started appearing (Zaviaèiè 1984a, b; 1985a), also the first immuno-histochemical works were published providing evidence for the presence of prostate-specific antigen (PSA) in female prostate structures, in particular in glands which could also be easily identified (Mallon 1983; Tepper et al. 1984; Pollen and Dreilinger 1984), similarly as in selected enzyme-histochemical studies.

Being an important component of the male prostate secretion, acid phosphatase participates in the hydrolysis of phosphorylcholine in seminal plasma, and is considered to be a marker of the development of the secondary sex characteristics in the male (Spring-Mills and Hafez 1980). The role of the high activity of acid phosphatase in the female prostate is not clear, it nevertheless cannot be ruled out that female prostatic acid phosphatase plays a similar role as in the male with respect to the female secondary sex characteristics. This enzyme could be demonstrated in a woman aged over 80 as well as in early childhood long before the onset of puberty (Zaviaèiè et al. 1983; 1989). Kellokumpu-Lehtinen (1980) used light and electron microscopy to study acid phosphatase distribution in the urogenital system of 7-13-week-old human fetuses of both sexes. At this young age already, the lining of the female urethra displayed acid phosphatase activity comparable with the activity of the same enzyme in the urethra of

male fetuses. The same author could observe lysosomal acid phosphatase activity in the prostatic epithelium upon its appearance in week 10, and a few epithelial cells showed acid phosphatase-positive apical granules suggestive of the appearance of secretory acid phosphatase. We believe that (lysosomal?) acid phosphatase may have a similar significance in the prostate as in some other secretory active cells in removing exhausted cell organelles during the active and resting phase of their metabolic involvement (Zavjačič et al. 1980).

Contrary to acid phosphatase, the equipment of lysosomes with beta-D-glucuronidase and acetyl-beta-D-glucosaminidase in the female prostatic gland is but very poor. E-600 sensitive naphthyl esterase and glucose-6-phosphatase have been demonstrated in cells of female prostatic glands; similarly as acid phosphatase, this enzyme is of help in differentiating between female prostate glands and ducts. Together with other enzymes, the finding of the above enzymes represents the expression of secretory activity of the cells. The equipment of glandular cells with granular endoplasmic reticulum (Figs.III/10, 12, 14) is indicative of the secretory role of the female prostate gland.

The high activity of glycerol-3-phosphate dehydrogenase in the ducts and glands of the female prostate which invariably yields the highest activity of all dehydrogenases examined (Fig.IV/8)(the same holding true for the male prostate) may indicate synthesis of triglycerides and phospholipids in these parts. It has not yet been determined whether these substances are components of female prostatic secretion. Being a non-polar lipid, cholesterol is a component of the male prostatic fluid, and is presumed to support sperm stabilisation, protecting it from environmental shock and heat damage (Spring-Mills and Hafez 1980).

Assessing, from a different angle, the value of histochemical works dealing with the enzyme equipment of the female prostate (Skene's glands), which has been shown to be comparable with that of the male prostate (Brandes and Bourne 1956; Kirchheim et al. 1964; Brandes 1966; Aso et al. 1968), those works can be said to become, at the time when published in mid-80s, the basis for the „histochemical concept of male and female prostate homology“, and all this at a time when it was only embryology-derived knowledge on the origin of Skene's glands and the male prostate that pointed to such a homology.

Differences in the enzyme equipment of the prostate between women of childbearing age and post-menopausal women (concerning a decrease in the activities of naphthyl esterase, glucose-6-phosphatase and a majority of dehydrogenases in elderly women, and a marked increase in the activity of „lysosomal“ acid phosphatase in the prostatic ducts in elderly individuals) support the possibility of hormonal dependence in this female genitourinary organ function (Zavjačič et al. 1989). This important issue has not been dealt with in detail so far, and our assumptions in this matter have not been either supported or confirmed by other methodological approaches. There are however some sexological reports showing that some of the patients which could be considered female ejaculators lost this ability at higher age (Ladas et al. 1982). This issue is of importance since the male prostate is a classical hormone-dependent organ the epithelium of which starts differentiating under the influence of the commencing production of sex hormones, and which is substantially dependent with respect to its function on a

sufficient level of male sex hormones throughout life of the man. The same issue in the female prostate should be treated with caution because of relatively little information available in this respect. Nevertheless, estrogens seem to play the same role in the female prostate as do androgens for the male prostate. This is suggested by the finding of typical secretory vesicles and granules in female prostatic secretory cells. Also, additional ultrastructural parameters of these cells of the female prostate correspond to those of the secretory cells of the adult male prostate, and this despite the fact that androgens said to be the key factor for the formation of secretory elements in male prostatic secretory cells, are lacking in normal females. However it may be, secretory elements (secretory vacuoles and secretory granules) are seen in the secretory cells of the female prostate, and their numbers and appearance is even comparable to those seen in the same prostatic cells of the adult male (Zaviačič et al. 1998d).

V Exocrine Function of the Female Prostate: Implications for Gynecology, Urology, Chronobiology and Forensic Medicine

The exocrine function of the female prostate consists of the production of prostatic fluid, and this role is equally a major one as it is the case in the male prostate. Similarly as prostatic glands in the adult male, female prostatic glands are equipped by mature secretory (luminal) cells (Zaviačič et al. 1998d) responsible for the production of prostatic fluid in both genders. Unlike male's fluid, pure female prostatic fluid could not have been isolated as yet. So far, female prostatic fluid has been studied but as a part of the female ejaculate, a fluid released during the phenomenon of female ejaculation, and it has been investigated with respect to the demonstration of continual secretion of the female prostate. If urologists and gynecologists succeeded in isolating pure female prostatic fluid, it would significantly speed up the identification of additional components considered to be typical components of male's prostatic fluid, the production of which by the female prostate is uncertain.

According to our experience, the volume of the fluid obtained after a single G-spot stimulation ranged between 1 – 5 mL. A distinct layer of whitish opaque cellular component appeared on the bottom of the test tube 10 – 15 minutes after collection, covered by urinous layer. A thin layer of transparent mucosubstances was sometimes seen at the borderline between the two above layers (Zaviačič et al. 1984a, c; 1988c).

The cellular component of the female ejaculate is formed by squamous cells of the vaginal type originating from the lining of the female urethra, large ducts of the female prostate (paraurethral ducts), and the bladder trigone. During the proliferative and ovulatory phase of the cycle, typical flat squamous cells with pycnotic nuclei were seen in Shorr-stained smears of the cellular component of the female ejaculate (Fig. V/1). Scanning electron microscopy showed clusters of flat squamous cells with overlapping edges

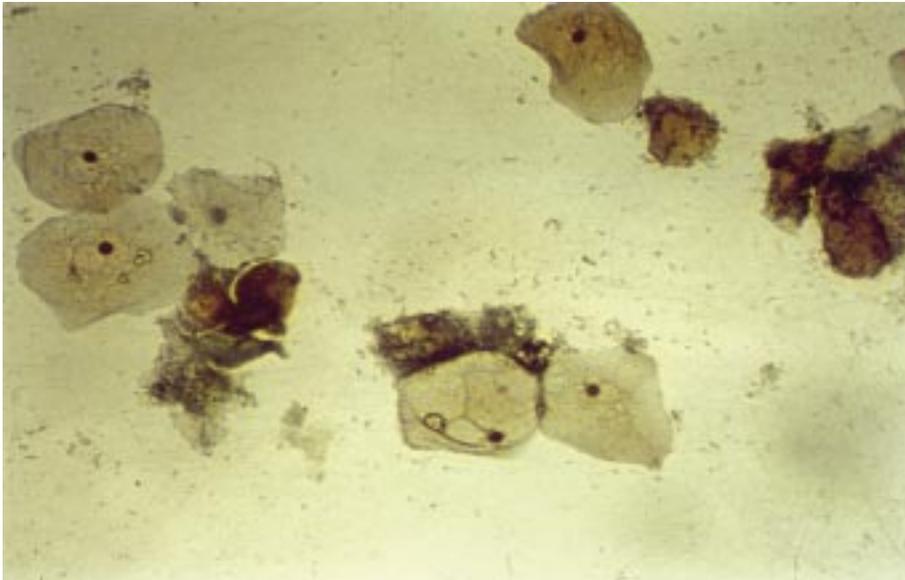


Fig.V/1 During the proliferative and ovulatory phases of the cycle, typical flat squamous cells with pycnotic nuclei were seen in smears of the Shorr-stained cellular component. Day 14 of 28-day cycle

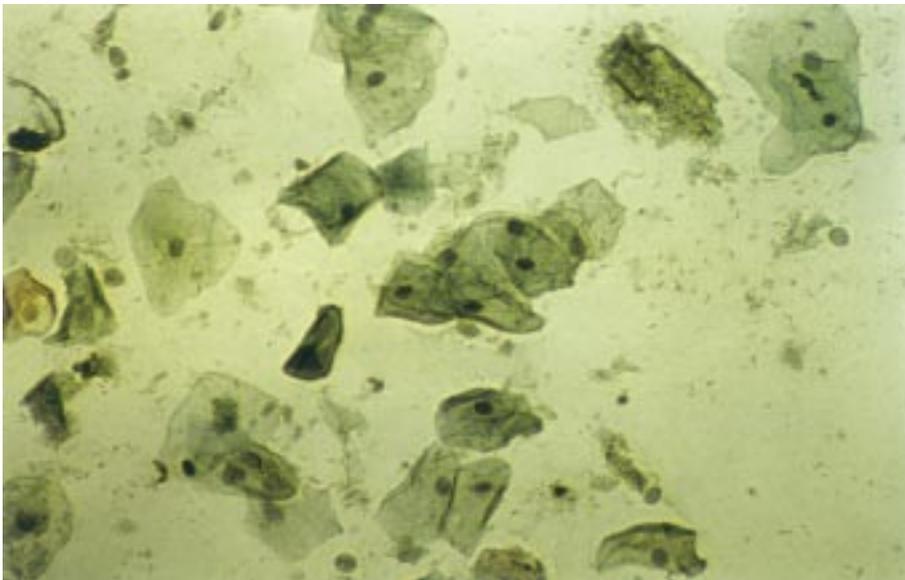


Fig.V/2 During the secretory phase of the cycle (late luteal phase), squamous cells were frequently seen on Shorr-stained hormonal urocytology, shrinking and curled up, with their edges bent. Day 27 of 28-day cycle

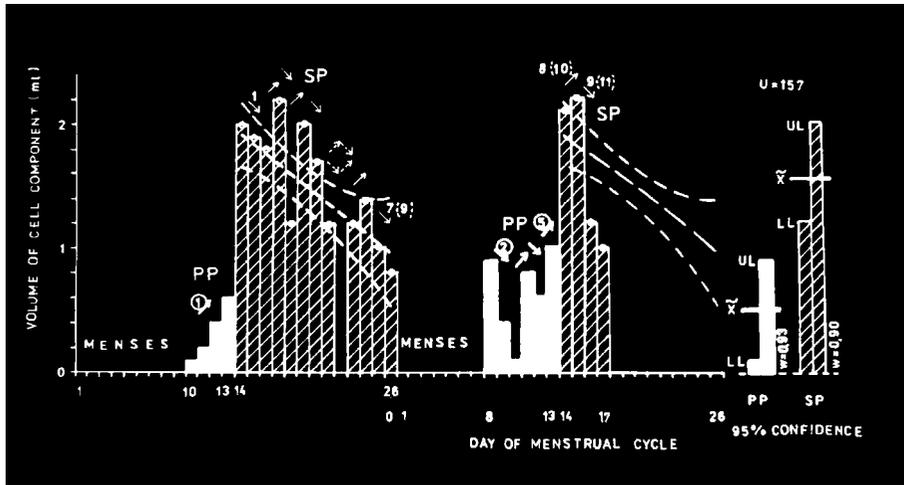


Fig.V/3 Daily volumes of the cell component during one-and-half menstrual cycle, multipara volunteer, 37-year-old. PP, proliferative phase (white columns); SP, secretory phase (hatched columns and circles). Runs shown by arrows (dashed for missing data); some their ranks are given in numbers (in parentheses including missing data). Global linear trend for all SP data and its 95% confidence corridor (dashed straight lines and hyperbolas). Right panel: The median (\tilde{x}) and its 95 % confidence lower (LL) and upper (UL) limit both for PP and SP. Random variable of the Mann-Whitney test (U) and Shapiro-Wilk test (W).

and knob-like nuclei in the cell center. During the late luteal (secretory) phase of the cycle, squamous cells were frequently seen under Shorr hormonal urocytology staining, shrunken, curled and with bent edges (Fig.V/2). Scanning electron microscopy showed regressively altered squamous cells at different stages of folding-up. Thus, a qualitative rhythm can be distinguished with respect to the uroepithelial squamous cells pattern (cell component) in female ejaculate during the menstrual cycle. This cell component pattern can be used for hormonal urocytology in cases when vaginal smears cannot be obtained (Zavaičić et al. 1984a, b; 1988c).

The typical cellular changes during the menstrual cycle seen under light microscope represent the basis for functional urethral and urinary cytology (Langreder 1961; O'Morchoe and O'Morchoe 1967; Lencioni and Staffieri 1969; Egloff 1972; Hermosa 1978; Bernhard et al. 1979) which are more preferred in South America (Hermosa 1978) than in other parts of the world (Koss 1979). The drawback of the urinary sediment cytology from centrifuged urine is the small amount of cells which can be evaluated in urine cytograms, as well as artifacts which may develop during urine centrifugation. The squamous cells of the female ejaculate are perfectly preserved, remain unaltered by centrifugation, and are present in amounts that cannot be obtained by any other similar method, including the procedure used to collect



Fig.V/4 Markedly high acid phosphatase activity in a spot of 3 mL ejaculate, 46-year-old male. Naphthol ASBI phosphate, hexazo-p-rosaniline, cotton, 2:1

material for urethral cytology. The cellular component of the female ejaculate can be preferred for hormonal urocytology over urinary sediment cytology from centrifuged urine.

Quantitative data on the amounts of uroepithelial squamous cells released into the fluid of urethral expulsions were obtained from a 37-year-old female ejaculator from a group with „easily induced expulsions“ (Zaviačič et al. 1988b). Digital stimulation of the G spot was repeated consecutively five times every day over the period of one and a half menstrual cycle. As shown by the quantitative biometrically analyzed data, the proportions of the cellular component were far higher during the secretory phase of the cycle than during the proliferative phase (Fig.V/3). The quantitative circatrigintan rhythm (30 ± 5 days) of the cell component volume of the female ejaculate (female urethral expulsion fluid) with the acrophase during the secretory phase of the menstrual cycle reduced the height of the urethral epithelium, this weakening the sphincteric closing mechanism of the female urethra. In contrast to the first half of the cycle when far fewer cells were released into the ejaculate, the epithelium remained in situ, and the sphincteric closing mechanism of the urethra could operate effectively (Zaviačič et al. 1984c; Mikulecký et al. 1986).

Gynecologists and sexologists are familiar with the rhythmic menstrual cycle of women in terms of phases. However, there are additional rhythmic components during the menstrual cycle. The rhythm of the cellular component of the female ejaculate (Zaviačič et al.



Fig.V/5 Acid phosphatase in a spot of female ejaculate determined by azo-coupling method. Female ejaculate (1.2 mL) obtained on day 8 of cycle. Naphthol ASBI phosphate, hexazo-p-rosaniline, cotton, 2:1

1984c) is of practical value for gynecologic urology and with respect to problems of urinary incontinence in women. With respect to the role of the urethral epithelium in the closing mechanism of the female urethra it may be assumed that conditions for the development of incontinence in women are more favorable during the secretory phase of the menstrual cycle (Zaviačič et al. 1984c; Mikulecký et al. 1986). The treatment of urinary incontinence by estrogens is thus justified as estrogens positively influence the thickness of both the urethral epithelium and the urethral wall (Bhatia et al. 1989). The closing mechanism of the female urethra important from the viewpoint of urine incontinence is however even more complicated: also, striated muscle fibers around the smooth musculature (musculofibrous tissue) in the urethral wall around the spongy body and the glands and ducts of the female prostate participate in this mechanism. All these structures are involved in the mechanism of continence, and play a role in sexual reactions of the female (Graefenberg 1950; Ricci et al. 1950; Langreder 1956; Hutch and Rambo 1967).

Female ejaculate as a phenomenon of the exocrine function of the female prostate (the fluid of the female urethral expulsions) and female ejaculation have important practical implications for the practice of forensic medicine.

The forensic-medical expertise has used determination of spermatozoa as the most sensitive and most reliable method for the identification of semen. However, when due to whatever reasons no spermatozoa could be determined in the individual investigated (e.g. in azoospermic male or after vasectomy), the evidence of acid phosphatase (Fig.V/



Fig. V/6 Markedly high acid phosphatase positivity in a spot on lingerie in urethral projection (U). Girl, 11-year-old, cotton lingerie worn for 4 days. Naphthol ASBI phosphate, hexazo-p-rosaniline, 2:1

4) alone would be considered adequate to identify a semen spot in the past (Rusfeld 1946; Kaye 1947). The quantitative aspects of the enzyme determined were emphasized as early as in the 70s (Schumann et al. 1976; Findley 1977). Later on, this test in combination with positivity of other components (spermine, fructose) would only be accepted as reliable proof in forensic-medical expertise.

With respect to expert evidence of rape in women, the acid phosphatase test was found to have no forensic relevance in identifying sperm spots which contain no spermatozoa, since the same acid phosphatase activity can be established in *in vitro* formed spots of female ejaculate (Fig.V/5) (Zaviačič et al. 1987b) and in *in vivo* produced spots on worn female lingerie (Figs. V/6, 7) (Zaviačič et al. 1988d). Thus, positively reacting spots may originate from the woman herself, without any male involvement. Macro-enzyme-histochemical findings of acid phosphatase on underwear (Figs. V/6,7) in parts in constant contact with the female genitals are indicative of the existence

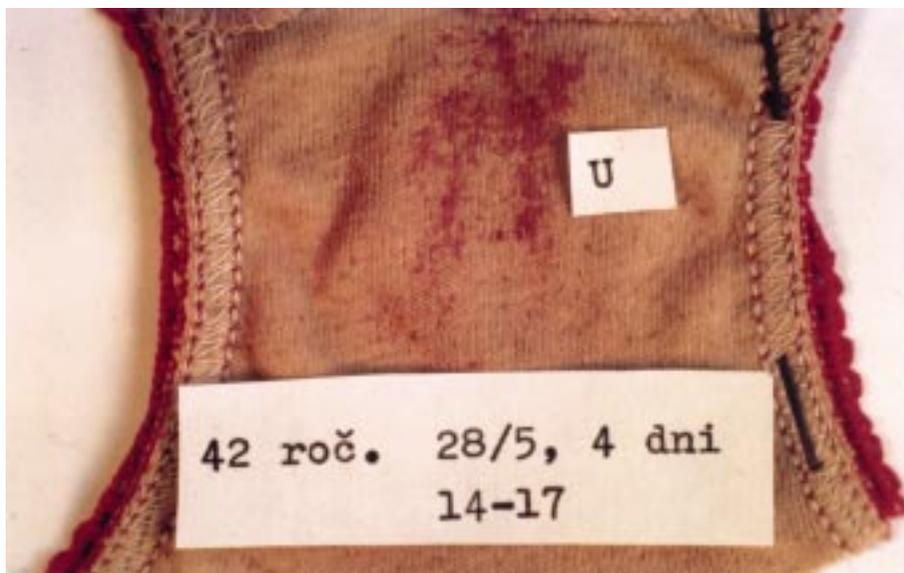


Fig.V/7 Markedly high acid phosphatase positivity in a spot on cotton underwear in the area of urethral projection (U). Female, 42-year-old (28/5). Underwear worn for 4 days (between days 14 and 17 of cycle). Naphthol ASBI phosphate, hexazo-p-rosaniline, 2:1



Fig.V/8 Acid phosphatase positivity in a spot on cotton underwear in the urethral projection area. Spot spreads distally because the underwear had been worn for several days. Girl, 7-year-old, death of asphyxia (suffocation) due to lung compression by elevator cage. Ejaculation due to asphyxia. Naphthol ASBI phosphate, hexazo-p-rosaniline. 2:1

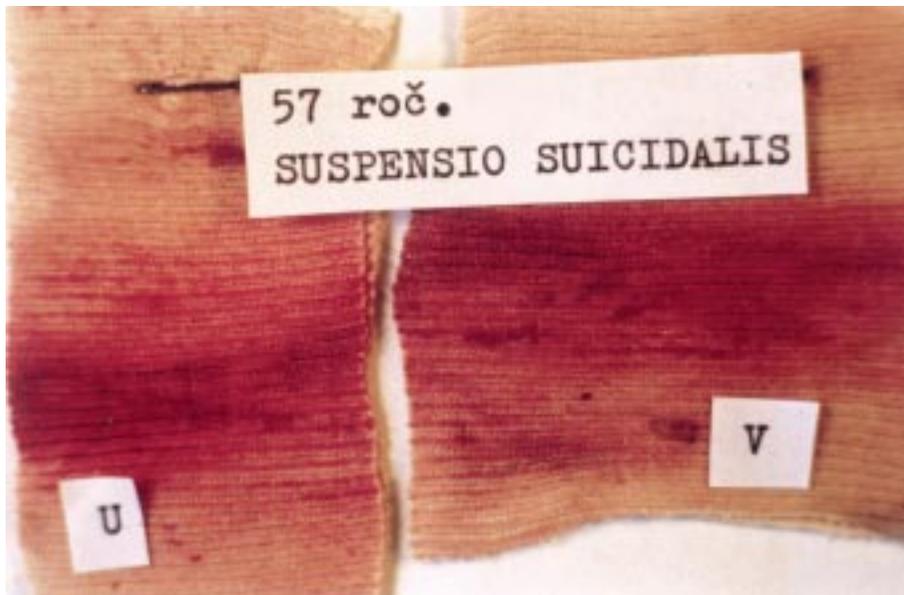


Fig.V/9 High acid phosphatase positivity in a large spot on underwear, extending distally (V) from the urethral projection (U). New, not worn cotton underwear. The transversal section is artificial. Female, 57-year-old, suicide by hanging. Agonal ejaculation due to asphyxia. Naphthol ASBI phosphate, hexazo-p-rosaniline, 2:1

of continual secretion by the female prostate (Zaviačič et al. 1988d). Initiation of the female prostate secretion precedes the onset of puberty (Zaviačič et al. 1989), similarly as is the case in the male (Aumüller et al. 1983).

Asphyxia can evoke agonal urethral expulsions (ejaculation) in the woman, e.g. upon strangulation, suffocation (Fig.V/8) and hanging (Fig.V/9)(Zaviačič et al. 1987a; 1988d), similarly as it occurs under the same circumstances in about 30% of men (Resnik 1972). It has been hypothesized (Zaviačič 1994) that the phenomenon of the female ejaculation may play a role as a motivation in sexual asphyxiophilia (Kozcwarism) in women. According to this hypothesis, women of the ejaculatory type (female ejaculators) desire to induce ejaculatory orgasm (orgasm with ejaculation) by asphyxia. This kind of female orgasm is usually assessed as a sensation of greater delight than orgasm without ejaculation, and this may be the reason for repetitive, life-threatening deviant sexual practice.

As suggested above, forensic medical studies of the female prostate and female ejaculation not only focussed on special forensic medical problems but also on the associated possibilities to study the secretory mechanism of the female prostate. We could show that, besides the ejaculatory mechanism by which the female prostate is emptied (and which has received inappropriately great attention), there also is con-

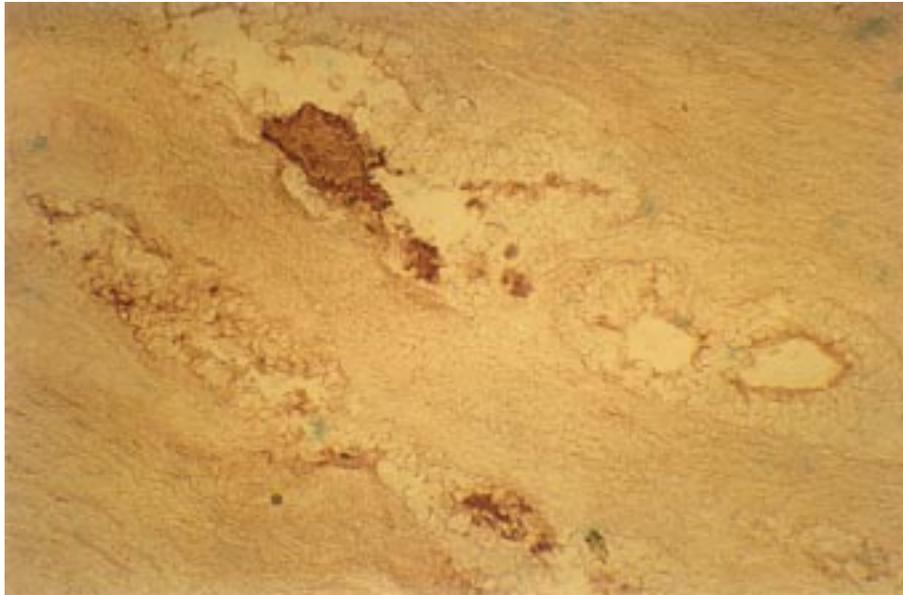


Fig.V/10 Prostate-specific acid phosphatase expression in the luminal part of cells bordering the prostatic duct, in a prostatic intraductal gland, and mainly in prostatic fluid in the duct. Female, 38-year-old. Two-step indirect immunoperoxidase technique and PSAP antibodies, x 180

tinual release of small amounts of female prostatic secretion into the urethra, as evidenced by spots on underwear showing acid phosphatase positivity. This mode of secretion of the female prostate is fully comparable with the continual spontaneous secretion by the male prostate (Mann 1974).

The most typical components of the male prostatic fluid include acid phosphatase, citric acid, zinc, and spermine (Spring-Mills and Hafez 1980). Similarly as in the male prostatic fluid, acid phosphatase can also be identified biochemically and histochemically (Adiego et al. 1981; Sensabaugh and Kahane 1982; Belcer et al. 1984; Zaviačič et al. 1984a; 1987b; 1988d; Stifter 1988) and fructose biochemically (Zaviačič et al. 1988a) in the female prostatic secretion, including that *in situ* in the female prostatic ducts and glands (Fig.V/10) and female ejaculate (Fig.V/5), representing a substantial portion of the latter. Additional components which would correspond to the known male prostatic components are being looked for. So, crystals were found on scanning electron microscopy (Zaviačič et al. 1984a) which could resemble spermine crystals by their appearance (three-sided bodies)(unpublished observation). Apparently, the female prostatic tissue should also be analyzed for the presence of zinc; the male prostate contains this metal which has for long been considered a typical prostatic parameter in vertebrates (Bertrand and Vladesco 1921). However, fundamental differences

were observed by histochemical and atomic absorption spectrophotometry methods in the distribution of zinc within the various zones of the male prostate (Györkey et al. 1967). Should spermine and zinc be demonstrated to be present in the female prostate, further markers will have to be excluded from the methodological armamentarium of forensic medicine used to provide evidence for rape, since they would lose their forensic relevance (after acid phosphatase, maybe also spermine and zinc). It seems premature to speak about the role of zinc in the female prostate. If however the presence of zinc is convincingly demonstrated, it may not be ruled out to play an important role in reproductive physiology in women similarly as is the case in men (Byar 1974). An inverse relationship between zinc concentration and pathology of the prostate is known in males. So, zinc is reduced to about one third of the normal level in malignant conditions of the prostate (Bush et al. 1974; Muntzig et al. 1974). So far, zinc levels have not been monitored in female prostate cancer or normal female prostatic tissue.

There are substantial changes brought about by DNA analyses with respect to providing evidence for rape where the suspect's sperm contains no spermatozoa or if there is a technical failure to demonstrate them (Zaviačič and Ablin 1998a). Now, we are able to not only find out whether a biological piece of evidence originates from a man or a woman, but even to individually exactly identify the suspect individual. The value of the forensic medical expertise which, prior to the period of DNA analyses, would more or less determine the guilt or innocence of the accused now increasingly turns historical.

VI.

Neuroendocrine Function of the Female Prostate: Morphological Basis

Since its very beginnings, the recent studies of the female prostate have set out on the path of looking for the parameters of the male prostate which have been known and considered as typical of male prostatic tissue. On the one hand, this has to a certain degree limited the possibility of finding entirely new parameters of the female prostate which may be missing in the male prostate; on the other one, investigations of the female prostate have been moving on a realistic comparable level which has contributed to the implications of the female prostate being accepted easier since they are known to be identical and of similar importance as for the male prostate.

One of these areas have been studies of the female prostate focussing on the identification of neuroendocrine cells in the female prostatic tissue and on the evidence of polypeptides and hormones produced by the female prostate. Thus, this has concerned the basic concept of whether the female prostate can be seen as a female neuroendocrine organ – the neuroendocrine function of the male prostate has been well known and understood, including a broad range of polypeptides produced by the male prostatic neuroendocrine cells. Even if it were so, the neuroendocrine function can not be expected to be more important than the exocrine function of the female prostate. The preferential concept of the male prostate as a predominantly exocrine gland producing prostatic fluid, remains the primary and most important one, and this will likely be the case with the female prostate, even if the neuroendocrine function of the male prostate is much better understood than the same function in the female prostate.

Argyrophil and argentaffin neuroendocrine cells (endocrine-paracrine cells, APUD cells) have been described in the human male prostate and male prostatic urethra a long time ago (Pretl 1944; Azzopardi and Evans 1971; Kazzaz 1974; Police et al. 1979; Capella et al. 1981; Fetissof et al. 1983; Di Sant' Agnese and De Mesy Jensen 1984a, b). The existence of these cells in the female urethra has also been established since long (the whole female urethra corresponds to the pars prostatica of the male urethra) as shown by Koch and Engelhard (1959), Lendon et al. (1976), and Zaviačić (1986a, b). Numerous neuroendocrine argyrophil Grimelius-positive cells of the closed (Fig. VI/1)

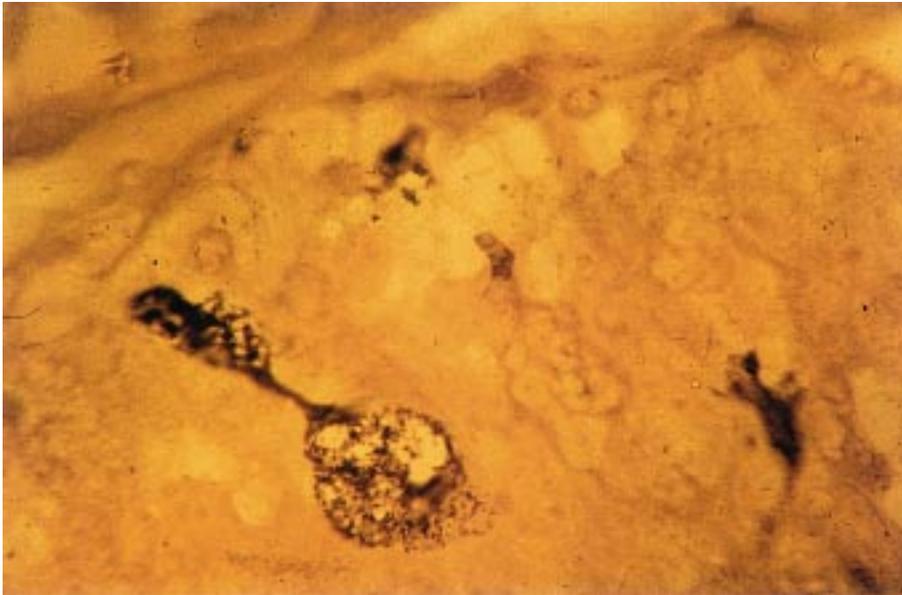


Fig.VI/1 Large oval argyrophil cell with a short thick process not reaching to the lumen of the female prostate duct (closed neuroendocrine cell type). Grimelius' argyrophil method, x 1,150

and open (Fig.VI/2) type were found in the female prostate ducts, argentaffin cells were rare (Zaviačič 1986a, b). Open and closed types of neuroendocrine cells were also found in a study concerned with human protein 1 (urine protein 1) using polyclonal antiurinary protein 1 antibody (Figs. VI/3, 4)(Zaviačič et al. 1997b). If there is a similar different induction of the production of the hormone polypeptide by open and closed types of neuroendocrine cells in the genitourinary area as established in the gastro-entero-pancreatic system (Fujita and Kobayashi 1973), then it may be assumed that there actually is a number of stimuli to act on the closed types of neuroendocrine cells in the female prostate and urethra, where these types predominate. Local, paracrine production of hormone polypeptides may be assumed for the closed types, which could be mediated by several cells in parallel, as they are frequent communications between them (processes). Neuroendocrine cells located among epithelial cells which line the duct without any contact with the cavital system lumen may react to a variety of mechanical stimuli, including the pressure of the corpus spongiosum in the urethra upon congestion and tumescence of the genitals during sexual response in the woman, changing muscular tension of the pelvic bottom during micturition and defecation. The open types are of the receptor-secretory cell nature, communicating by their projections with the lumen of the prostatic-urethral complex. These types could get stimulation directly from the lumen of the prostatic ducts, and could release the hormone polypep-



Fig,VI/2 Open argyrophil cell type in the female prostate duct. The cell spreads across the whole ductal wall, and its process reaches the surface of the ductal lumen. Argyrophil method according to Grimelius, x 1,150

tide into their lumen, as known for somatostatin in the gastrointestinal tract (Uvenas-Wallenstein 1980).

The hormone polypeptides produced by the male prostate have repeatedly been demonstrated immunohistochemically in real neuroendocrine cells. Many of these cells have been found to contain serotonin (Fetissof et al. 1983) and somatostatin or somatostatin-like polypeptides (Di Sant'Agnesse and De Mesy-Jensen 1984b). In addition, immunoreactivity for bombesin (gastrin-releasing peptide), thyroid stimulating hormone and calcitonin has been regularly found in a small population of male prostatic neuroendocrine cells, and the less frequent neuroendocrine products demonstrated include the alpha subunit of human chorionic gonadotropin, adrenocorticotrophic hormone, leu-enkephalin, beta-endorphin, and glucagon (Di Sant'Agnesse and De Mesy Jensen 1984a; Fetissof et al. 1987; Abrahamsson et al. 1989; Di Sant'Agnesse 1990).

As for the female prostate, production of serotonin in the female prostatic glands and ducts has only been reported by Wernert et al. (1992), and we have the same experience with this polypeptide in the female prostate (unpublished observation). According to our experience with the rich equipment of neuroendocrine cells and the identification of parts of nerve fibres, in particular in the female prostatic ducts using silver-staining methods (Zaviačič 1986a) and mainly Grimelius' (1968) and to a lesser extent

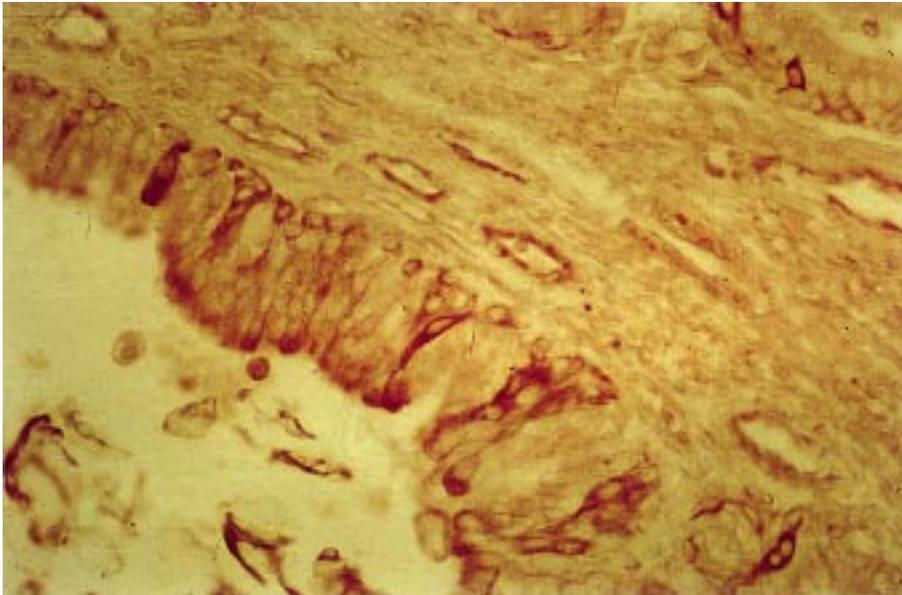


Fig.VI/3 Portion of a female prostate duct close to the meatus of the urethra with urinary protein 1 in the cytoplasm of triangle and barrel-shaped neuroendocrine cells located deep in the epithelial lining of the duct (closed neuroendocrine cell type) and in the membranes of the uroepithelium. Female, 19-year-old. Rabbit polyclonal antiurine protein 1 antibody, biotin-streptavidin-peroxidase technique, x 320

Sevier-Munger's method (1965), and their almost total absence when using argentaffin techniques (Masson-Hamperl's method as modified by Singh 1964), the rich presence of neuroendocrine cells expressing chromogranin A and human protein 1 (urine protein 1) and neuron-specific enolase (Zaviačič et al. 1997b), it is justified to see female prostatic ducts as an exclusive neuroendocrine part of the female prostate rather than a passive ductal portion which drains female prostatic secretion to the urethra. Because of the predominating equipment with neuroendocrine cells, prostatic ducts may also have a different pathology as compared to the remaining parts of the female prostate. Of the group of genitourinary neuropeptides, the greatest interest has been focused on vasoactive intestinal polypeptide (VIP) which has been demonstrated immunohistochemically in nerve fibres at several sites of the human female reproductive organs (Alm et al. 1980). The presence of nerve fibres or their parts, which can easily be visualized by argyrophilia, may suggest the presence of this polypeptide in the female prostatic ducts. Based on a certain analogy with the male reproductive organs (Larsen et al. 1981), this polypeptide might be assumed to participate in the regulation of the blood flow in the corpus spongiosum of the female urethra, in development of excitation with congestion and tumescence of the genitals during the first

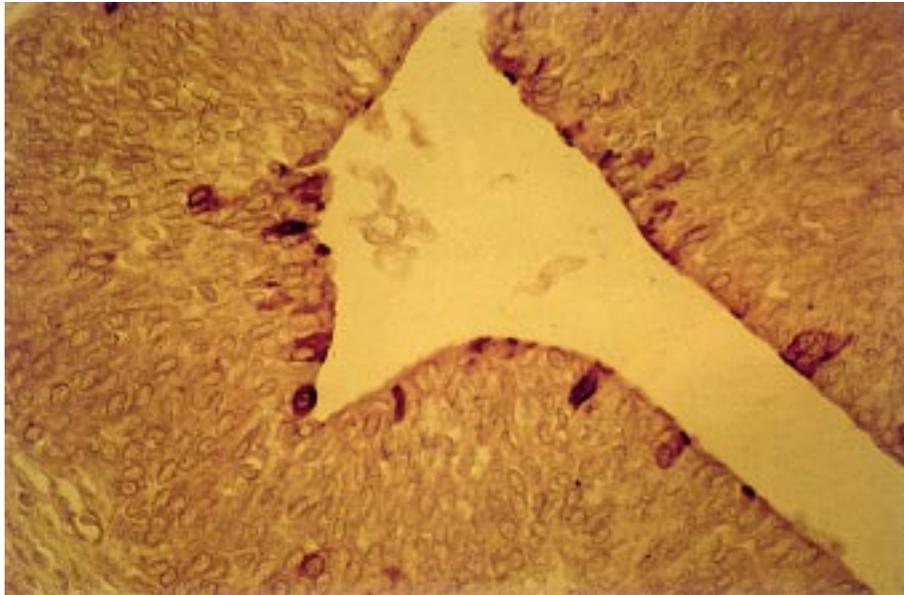


Fig.VI/4 A female prostate duct showing urinary protein 1 immunoreactivity in individual neuroendocrine cells, mostly located luminally and communicating with the ductal lumen (open neuroendocrine cell types) and in the membranes of the pseudostratified columnar epithelium of the duct lining. Female, 19-year-old. Rabbit polyclonal antiurine protein 1 antibody, biotin-streptavidin-peroxidase technique, x 100

phase of the EPOR model (Masters 1960). However, VIP may also directly regulate the secretion by female prostatic cells as VIP has been shown to be involved in the local control of the secretory process at other sites (Lindkaer et al. 1978). Also, the existence of the „urethro-prostatic-vaginal body“ which represents one interconnected and mutually communicating system, supports similar considerations. In addition to Huffman's (1948) three-dimensional demonstrations of the urethra-female prostate complex, histochemical (Zaviačič 1987a) and other works (Heath 1984) have also made a contribution to the acceptance of the common body concept. Probably, we have to account for overlapping of prostatic and urethral parameters and for the involvement of the anterior vaginal wall and/or of the erectile tissues of the female genital. These interconnections may also be influenced by broader physiological, pathophysiological and pathomorphological characteristics of this area.

The spectrum of neuroendocrine polypeptides produced, at least those typical of the prostate and other genitourinary structures in the male, is worth of being investigated with respect to the female prostate as another female neuroendocrine organ. When it comes to the investigation of the female prostate as a neuroendocrine organ, we are still in the early stages, and new knowledge in this respect is to be expected.

Note: Nonspecific binding of proteins was inhibited by incubating the tissue in a blocking reagent (protein block serum-free; DACO, CA, USA) for 5 min, and endogenous peroxidase or pseudoperoxidase activity was quenched by incubating the tissue in 3% hydrogen peroxide in water for 5 min prior to the application of the primary antibody (as recommended by DACO).
Controls were incubated without primary antibodies.

VII.

The Female Prostate and Female Ejaculation: Sexologic Implications

The biological phenomenon of female ejaculation has always been an attractive component of traditional sex cultures, particularly of those of ancient India, Japan, as well as other territories in Asia and Africa. Stifter (1988) presented a historically well founded overview on the position of the female ejaculation phenomenon in individual sex cultures, documented by copies of original texts and works of art. This specific manifestation of female erotism was mentioned already in the ancient Indian text Ananga-Rang (Ananga means erotism and Rang means colors of different shades of human sexuality). It was published in the 16th century, 200 years later than the much better known Kamasutra, which besides erotic passages on human sexuality deals also with social and cultural aspects of life in the given period of time. Ananga-Rang presents a detailed female genital anatomy with representations of the erotically especially sensitive area of the vagina (saspana nadi), whose (penocoital) stimulation leads to the production of great amount of „love juice“ in the female. The erotically highly sensitive site of the vagina indicated in Ananga-Rang is topically identical with the vaginal erogenic zone described by Graefenberg (1950). Designated G-spot, it was introduced into human sexology by Perry and Whipple (1981). The role and significance of the G-spot in the contemporary sexual life of the woman was analyzed by Whipple (1994). Thus the concept of female ejaculation and the role of the G-spot in modern western human sexology was mentioned already in Ananga-Rang in the 16th century (Samak 1997). The female ejaculation phenomenon of the ancient sex cultures has always been a component of the sexual image of the woman and has remained an attractive phenomenon of female sexuality, although in the western knowledge of sexuality its evaluation has involved problems and discussions (Winton 1989).

The long-lasting controversy and doubt whether there is an association between the female prostate and the ejaculation phenomenon (Whipple and Komisaruk 1991; 1992) and thus whether the female prostate contributes to the female ejaculate by its prostatic component appears to be definitely settled. The majority of authors no longer question the fact that during their sexual response or/and orgasm women emit a certain fluid

that differs from vaginal lubrication (Graefenberg 1950; Sevely and Bennett 1978; Belzer 1981; Addiego et al. 1981; Perry and Whipple 1981; Bohlen 1982; Sensabaugh and Kahane 1982; Ladas et al. 1982; Fischer 1983; Belzer et al. 1984; Bullough et al. 1984; Zaviačič et al. 1984a; 1987a; Zaviačič 1985b; 1987a; Stifter 1988; Zaviačič and Whipple 1993) and that the female prostate is a substantial source of the fluid of female ejaculation (urethral expulsions) (Sevely and Bennett 1978; Zaviačič 1985b; Zaviačič et al. 1988a, b, c; Zaviačič and Whipple 1993; Zaviačič and Ablin 1998a, b, c).

Graefenberg (1950) described induction of orgasm in women by penocoital or digital stimulation of a specifically sensitive area on the anterior wall of the vagina accompanied by release of a milky opalescent fluid from the urethra. The mode of release as well as the resemblance of the urethral fluid to the male ejaculate has resulted in the phenomenon being designated female ejaculation.

Based on our experience with the results of digital stimulation of the G-spot under laboratory conditions, we described three types of responses to this kind of stimulation (Zaviačič et al. 1988b). They differed as to the duration of stimulation, the response of subjects to digital massage of the G-spot and the culmination accompanied by urethral expulsion of fluid.

The subjects of the group with „relatively-hard-to-induce-expulsion“ were characterized by great personal involvement in the stimulation and considerable demands on vaginal digital friction concerning both the procedural technique and duration. We present one case to illustrate the type. The subject was a married 29-year-old nullipara. Her pattern of sexual stimulation was limited to the vagina. The clitoris had never been involved in her self-stimulation or in heterosexual petting activity of her husband. She had experienced urethral expulsions of fluid during her premarital sexual activity. She developed urethral expulsions immediately before or simultaneously with orgasm during long-lasting sexual intercourse. For this purpose she preferred the face-to-face position, with her hips (not waist) placed on a support and elevated and her lower limbs raised. She could induce urethral expulsions by masturbation, using a dildo (artificial membrum) or with her fingers manipulating the anterior wall of the vagina. In order to induce urethral expulsions in laboratory conditions, massage of the G-spot had to be applied for at least 15 minutes. On using a vibrator, we achieved only a slight, 1- to 2-minute reduction of the time needed for evoking urethral expulsions. Within 10 to 30 seconds from the onset of stimulation, marked lubrication of the vagina was observed. During the following 10 minutes, the subject developed distinct hyperapnea and erythema of the face appeared. There was pronounced tumescence of the external genitals with intensive red coloration of the labia minora pudendi and protrusion of the uterus towards the introitus of the vagina. On intensive and long-lasting regular friction of the G-spot, she developed orgasm with rhythmic 8 to 10 contractions of the deep circumvaginal muscles, digitally confirmed by the doctor who was performing the stimulation. Perineal as well as carpedal spasms were observed frequently. At the peak of orgasm, apnea was recorded. Simultaneously with orgasmic contractions, the urinary meatus opened and a whitish opalescent fluid was ejected in one or two portions into the test vessel. The urethral expulsions were followed by manifestations of the resolution phase.

The subjects of the group with „easily-induced-expulsion“ were minimally involved in the stimulatory technique itself. Release of fluid from the urethra occurred after a very short time (maximally one and a half minute) of G-spot stimulation. Neither during stimulation nor on ejaculation was any other visible manifestation of sexual arousal observed in these subjects. The prototype of this response pattern was a 37-year-old multipara, in whom over 160 stimulations resulted in ejaculation. We analyzed the female ejaculation phenomenon and the urethral fluid obtained from this woman repeatedly in several papers (Zaviačič et al. 1984a, b, c). The subject preferred clitoral (mostly direct) stimulation for achieving orgasm. She achieved orgasm during intercourse, yet invariably only on accompanying digital stimulation of the clitoris. She described her orgasm as having a vehement course during which she experienced repeated contractions of the vulva (regularly 8 to 12 rhythmic contractions) with spasms of the perineum and rectum. Before volunteering for the program, she had not experienced ejaculation. Now she is able to induce urethral expulsions on concentrated stimulation of the G-spot by a dildo or digitally by herself or her husband. Within 30-50 seconds of digital massage of the G-spot, which was far less intensive than that applied in subjects of the previous group, distinct tumescence of the G-spot was observed. Frequently, within one minute of onset of the massage, anteroposterior reduction of the vagina was observed. The doctor stimulating the G-spot felt under his/her fingers the uterus protruding forward into the ostium of the vagina. At the moment of descent of the uterus, the urinary meatus opened and under slight pressure a whitish opalescent fluid flowed out in one stream. Besides the descent of the uterus, no other perceptible manifestation of female sexual response, seen typically in subjects of the previous group, was observed. Although subjects of this group reported the sensation experienced at ejaculation as agreeable, they strictly differentiated it from the sensations accompanying orgasm achieved by stimulation of the clitoris. These subjects stressed repeatedly that ejaculation does not represent the climax of their sexual response.

Between these two extreme groups of basically different response patterns there are subjects of the „intermediate group“ whose response during stimulation and expulsion resembled the „easily-induced-expulsion group“ yet was not identical with it. Compared to subjects of the „relatively-hard-to-induce-expulsion group“, the required stimulation was far less intensive and lasted for about five minutes.

In cooperation with the 2nd University Hospital of Gynecology and Obstetrics, we examined more than 200 women and these investigations are continuing. According to history data of Slovak women, they experience relatively frequently (40-50 %) ejaculation at coital activity (mostly in positio obversa, with the penis stimulating the anterior wall of the vagina). These findings are in keeping with data reported by Bullough et al. (1984). The corresponding data appear to be of interest also in light of the fact that in the USA this phenomenon received great publicity in the media in the early 80s, which might have biased the results concerning its frequency. Thus e.g. the well-known American sexologist Professor Beverly Whipple, co-author with Ladas and Perry of the book „The G Spot and Other Recent Discoveries About Human Sexuality“, is the author of over 200 radio and TV programs on human sexuality, including the phenomenon of female ejaculation (Whipple 1998). Data on the occurrence rate of ejaculation

in the female population cover a considerable range from 10 % (Perry and Whipple 1981), to 19 % (Kratochvíl 1993;1994) up to respective 40 % and 54 % (Bullough et al. 1984; Darling et al. 1990), which are close to our findings. Later on, Whipple and Komisaruk (1991) reported ejaculation experience in as many as 69 % of women. Cabello (1997) has suggested that most women ejaculate, sometimes with retrograde direction towards the bladder, as occurs in retrograde ejaculation in some men. Stifter (1988) voiced a similar opinion, convinced that the ejaculation capacity is a generally present sexological phenomenon given to every woman. In some cases, the woman may not be aware of her ejaculation, particularly when the amount of the emitted fluid is small. In many women however, the ejaculation phenomenon (urethral expulsions) is so characteristic, mostly associated with orgasm, that it can not be overlooked. These women usually prefer and even try to achieve orgasm associated with fluid expulsions since this type affords a subjectively higher degree of satisfaction than orgasm without ejaculation (Zaviačič 1994). It is however important to inform women on this normal manifestation of female sexuality to avoid their frustration and that of their partners on incorrectly interpreting this phenomenon and considering it to be orgasmic micturition (urinating sex).

The usual masturbation activity or petting stimulation of the clitoris-labial complex results in ejaculation less frequently than does stimulation of the vagina. Vibrators are nowadays commercially available which are specially shaped to stimulate the G-spot on the anterior wall of the vagina. At masturbation or petting activities with the partner, they can relatively simply induce orgasm with ejaculation. Even women with complete spinal cord injury as high as T-7 do experience vaginal orgasm as a result of using vaginal or cervical self-stimulators (Whipple et al. 1996a, b; Komisaruk et al. 1997; Whipple and Komisaruk 1998). When the clitoris-labial complex is stimulated, ejaculation occurs at inadequately long extension of the plateau phase, at repeated difficulties in achieving orgasm, after long sexual abstinence, or at oral-genital contact (at cunnilingus or lambit of the vulva). Some women induce expulsions by suprapubic massage of the cervix of the urinary bladder through pressure or friction with fingers in the spatium praevesicale Retzii. Such a patient volunteered to cooperate in a clinical study aimed at demonstration of fructose in the female ejaculate (Zaviačič et al. 1988a). We found that different ways of stimulation inducing female ejaculation (vaginal and clitoral) can affect the amount of PSA in female ejaculate. On massaging the urethra through the anterior vaginal wall (G-spot?), using a maneuver not unlike that of transrectal friction of the prostate in the male for obtaining male prostatic secretion, PSA can reach exceptionally high values of 7.0 up to 33.0 ng/mL of female ejaculate (Zaviačič et al. 1999). As early as the beginning of this century, in Freud's era of psychoanalysis, some female patients with nocturnal orgasm reported ejaculation episodes, called female pollution (Heyn 1924). They were considered outlet manifestations of female sexual abstinence, similarly as seen in the male under comparable circumstances. They occur during dreams with erotic content (wet dreams). Later on, attention was given to such episodes also in psychiatric patients (Winokur et al. 1959).

Not even to date, however, has the female prostatic fluid been isolated in pure form and it has been investigated only as part of the female ejaculate. While in males it is

known that approximately 0.5 – 1.5 mL (i.e. 15 – 30 %) of the seminal fluid or ejaculate originates from the male prostate (Spring-Mills and Hafez 1980), corresponding data on the amount of female prostatic fluid in the female ejaculate are not available. In any case, compared to the male, the functional capacity of the female prostate must be expected to be considerably smaller. Probably, it will reflect the different size of the gland and the amount of prostatic tissue in the male and female (Zaviačič 1987a; Zaviačič et al. 1998a), and that despite the fact that the qualitative parameters of the gland are fully comparable in the two genders even at ultrastructural level (Zaviačič et al. 1998d).

The procedure used most frequently for obtaining the fluid of female urethral expulsions (female ejaculate) is the digital stimulation technique (Graefenberg 1950; Zaviačič et al. 1988a, b, c). Controlled use of this technique allows to determine objectively the amount of female ejaculate released from the urethra. The data reported do cover a certain range. Nevertheless, if we do not consider the data in historical literature concerning the years between 1688 and 1927 as given by Stifter (1988) in measures little understandable for the contemporary reader, the data on the amount of fluid reported since the early 80s are practically comparable, although some relate to one stimulation while others are the result of repeated stimulation. Belzer (1981) reported 10 mL, Ladas et al. (1982) 0.5 mL, Goldberg et al. (1983) 3-15 mL, Bullough et al. (1984) 12 mL, Heath (1984) 30-50 mL, Alzate and Hoch (1986) 2 mL, Zaviačič (1987a) and Zaviačič et al. (1984c) 1-5 mL after single stimulation and 16 mL after fivefold stimulation.

Studies from the early 80s have already indicated that the fluid of urethral expulsions, the female ejaculate, contains components different from urine (Addiego et al. 1981; Sensabaugh and Kahane 1982; Belzer et al. 1984; Zaviačič et al. 1984a; 1988a,b). Addiego et al. (1981) and Belzer et al. (1984) found the female ejaculate to have significantly higher levels of prostatic acid phosphatase and significantly lower levels of urea and creatinine than urine specimens from the same women. The significance of this finding for the field of sexuality is that it has helped many women who thought they were urinating during sex to have the knowledge that the fluid they expel may be different from urine and a normal phenomenon that occurs during sexual response (Bullough et al. 1984; Heath 1984; Whipple and Komisaruk 1991; Zaviačič et al. 1993b). In the past recommendation to women who experienced this expulsion of fluid was to hold back from achieving orgasm or to undergo surgery for urinary stress incontinence. The author of this Monograph is confident that awareness of the existence of female ejaculation will help women and their partners feel more comfortable with this normal phenomenon and certainly avoid surgery designed to eliminate it. Goldberg et al. (1983) and Alzate (1985) failed to find differences in the chemical analysis of female urethral ejaculate and urine.

Studies searching to determine in female ejaculate components typical of male prostatic fluid were apparently more prospective. Following biochemical (Sensabaugh and Kahane 1982) and histochemical (Zaviačič et al. 1987b) determination of lysosomal and prostatic acid phosphatase in female ejaculate, the presence of a further component of male ejaculate, fructose, was established (Zaviačič et al. 1988a). Immunohistochemical studies identifying PSA in female prostatic tissue proved to be particu-

larly important (Mallon 1983; Tepper et al. 1984; Pollen and Dreilinger 1984; Zaviačič et al. 1994). PSA in male seminal plasma was long referred to as gamma seminoprotein (Hara et al. 1971) and/or as p30 (Sensabaugh 1978).

The presence of fructose in the female urethral ejaculate (Zaviačič et al. 1988a), once confirmed also by other authors, may be considered also with respect to the important role of this sugar in the physiology of human reproduction. Macroenzymatic histochemical findings of acid phosphatase on parts of lingerie which were in constant contact with the female genitals are indicative of the existence of continual secretion of the female prostate (Zaviačič et al. 1988d), as has long been known concerning the male prostate (Mann 1974). Contrary to the male, the ejaculatory mechanism of the female prostate (urethral expulsions) is not directly related to reproduction, it is rather an attractive phenomenon of the woman's sexuality. On the other hand, continual secretion of the female prostate, with the secretion containing fructose and other prostatic components flowing under gravitation in small amounts from the urethra to the vagina, may be of importance for reproduction. It is this amount of fructose produced by the female that may provide a permanent basal low level of this sugar in the vaginal environment. After coital ejaculation of the male, the level of this sugar is substantially increased in the vagina by the amount of fructose derived from the seminal vesicles of the male. Since fructose represents the main energy source for the motility of sperms, the woman herself may with her own fructose affect to some extent this parameter important for the reproduction process. It appears to be biologically conceivable that due to the particular significance of this parameter for natural selection of the highest-quality sperm for successful fertilization of the egg, the process would be warranted also by the female. This apparently calls for greater attention to be paid to the analysis of continual (spontaneous) secretion of the female prostate, which may importantly come into play in reproduction biology.

In our studies, female ejaculate samples were always obtained, after complete micturition of the proband, by the female herself or with the help of her partner. Perry and Whipple (1981) first termed the special erotically sensitive area on the anterior vaginal wall which was to be stimulated to induce urethral expulsions the G-spot, after the obstetrician and gynecologist Ernst Graefenberg (1881-1957). Graefenberg (1950) described this zone of erogenous feeling and the expulsion of fluid that occurs simultaneously with orgasm. Perry and Whipple (1981) identified the hypogastric plexus and the pelvic nerve as the sensory pathways in sexual response of women when there is vaginal stimulation. This is different from clitoral stimulation, when the major sensory pathway is via the pudendal nerve, as identified by Masters and Johnson (1966).

Despite the fact that the G-spot can easily be identified in gynecologico-sexual investigation on digital vaginal examination, at autopsy digital identification of the G-spot on the anterior wall of the vagina is rather problematic. Contrary to *in vivo* conditions, when identification is facilitated by the tumescence of the spot on friction, this characteristic phenomenon is conceivably absent on post mortem tissue. Clinical experience of the examiner with identification of the spot in female patients has proved useful in finding the relevant area also post mortem. We generally succeeded in the procedure and were usually able to mark the supposed area of the G-spot on the ante-

rior wall of the vagina in order to perform detailed histological examination after its fixation. Although the knowledgeable doctor can clinically identify the G-spot without problems, its anatomical substance remains unclear. We detected collagen and elastic fibers in the given area, often in plexiform arrangement with muscle fibers, rich in blood vessels and nerve fibers. On comparing the equipment of different parts of the anterior vaginal wall, the area of the G-spot and the distal areas of the vagina exhibited greater richness in these elements than did the proximal parts. In some cases these differences were pronounced, in others they were but minimal. Nevertheless, the anterior wall of the vagina appears to be better equipped with the given structures than the posterior wall of the vagina. We failed in our expectation to detect in the G-spot specific morphological structures that would be absent in other parts of the anterior vaginal wall. We are rather inclined to agree with the opinion that the G-spot is part of the Halban fascia, considered by some authors to be analogous with the corpus spongiosum penis (Minh 1981), playing an important role in sexual physiology as a source of deep sensations during intercourse (Minh et al. 1979). The role of the Halban fascia in supporting the bladder is well known and must be carefully preserved in all operations by the vaginal route (Minh et al. 1979). Our finding of the richer presence of nerve fibers in samples from the anterior wall compared to the posterior wall of the vagina is in keeping with results of the study on the innervation of the human vaginal mucosa using as neuronal marker the protein gene product 9.5 (Hilliges et al. 1995). Lenck and Vanneuville (1992) voiced the opinion that the G-spot was identical with the urethral sphincter. They reached this conclusion by correlating clinical (sexological), ultrasonographic, and anatomical findings. Generalizing, they situated vaginal and clitoral sensitivity in the same entity of the urethro-clitorido-vulval complex (Lenck and Vanneuville 1992). O'Connell et al. (1998) presented new aspects on human female urethral and genital anatomy. They showed that the female urethra, distal vaginal wall and erectile tissue are packed into the perineum caudally (superficially) to the pubic arch. The perineal urethra is embedded in the anterior vaginal wall and is surrounded by erectile tissue in all directions, except posteriorly where it relates to the vaginal wall.

These studies have broadened our attention beyond the so far studied areas of the female urethra, female prostate, and the anterior wall of the vagina, which form one functional-morphological complex (Heath 1984; Zaviačič 1987a), so as to involve also their connections with further, especially erectile structures of the female genitals (clitoris), focusing thus on an even greater complex.

VIII.

Prostate-specific Antigen: Immunohistochemical Localization in Female Prostate Tissue, Serological Parameters, and Implications of this Prostate Marker in the Woman and Man

At present, prostate-specific antigen (PSA) is generally accepted as the most useful biological marker of male prostate carcinoma, and has become the mainstay of the prostate carcinoma screening and staging, in monitoring response to therapy, and in predicting the outcome. In spite of this optimism, the role of PSA as a sole criterion in screening and staging of male prostate cancer remains controversial. First, the principal concerns are inherently related to the fact that PSA, although specific of the prostatic tissue, is not tumor specific; prostatic cancer is heterogenous, with subpopulations of cells that vary as to their synthesis and possible secretion of PSA. A second concern is whether screening will detect what is generally thought to be latent or clinically indolent cancers, present in approximately 30% of males aged over 50, and whether morbidity and mortality associated with the treatment of these tumors will exceed those of the disease itself (Ablyn 1996; 1997). Just to present the complete picture, a further concern is the cost-related clinical utility of screening (Coley et al. 1997).

From the viewpoint of staging, wide variations in PSA levels exist in many patients with either localized or advanced metastatic disease (Brawer and Lange 1989; Scardino 1989). Therefore, except within broad ranges, PSA serum levels but poorly predict tumor stage on an individual basis.

In terms of the use of PSA for the screening for early detection of prostatic carcinoma in males, a major limitation has been false positive elevations produced by benign prostate hyperplasia. In addition, prostatitis (Robles et al. 1988) and prostatic ischemia and/or infarction (Glenski et al. 1992) can be associated with elevated levels of the antigen.

Stamey et al. (1989) demonstrated that the gland weight in the male is the most important non-cancer variable in increases in PSA levels. It has been proposed on this basis (Littrup 1991a, b; Lee et al. 1992) that what has been said in the introduction holds true despite some indications in recent reviews on PSA (Ablin 1996; 1997) which prompt us to be more cautious. In his recent papers, Ablin states that „PSA is far from being the perfect „tumour“ marker as show elevations of PSA in other irregularities of the prostate, notably in benign prostatic hyperplasia, and increasing frequency and number of non-prostatic tissues, including those in women expressing PSA have implications for future immunoassays for PSA and strategies for immunotherapy using PSA-based monoclonal antibodies or vaccines, as well as for the molecular basis for its anomalous expressions and physiological functions.“ (Ablin 1996; 1997).

Measurement of gland volumes by transrectal ultrasound (Miyashita et al. 1984) may help detect PSA level increases due to cancer or benign prostate hyperplasia. Investigations of the distribution of PSA levels in a large population of healthy men suggested the importance of age and prostatic volume. Dalkin et al. (1993) and Oesterling et al. (1993a,b) independently found that serum PSA levels correlate directly with patient's age, in association with the increase in prostatic volume with advancing age.

Immunohistochemical evidence of prostate-specific antigen (PSA) as presently the most reliable prostatic marker, plays a crucial role in the identification of normal and pathologically altered tissue in the male (Nadji et al. 1981; Epstein and Eggleston 1984; Purnell et al. 1984; Stein et al. 1984; Svanholm 1986; Jöbsis 1990; Keillor and Aterman 1993). Immunohistochemical staining for PSA is weaker in poorly differentiated primary tumours and in metastases, and may even be absent in the latter. Given that tissue PSA has been shown to be age-dependent, to correlate with androgen levels (Goldfarb et al. 1986), and that male prostate cancer is heterogeneous in its responsiveness to antiandrogen therapy, one must be cautious when interpreting the relevance of weaker staining in PSA. Recent studies by Pretlow et al. (1991) in which the heterogeneity in PSA expression observed immunohistochemically in prostate cancer and benign prostate hyperplasia tissues were confirmed by quantification of PSA in extracts prepared from the same tissues as examined immunohistochemically. In accordance with earlier comparative studies of the PSA diversity in normal, benign and malignant prostatic tissue (Ablin 1972) PSA was found to be expressed at a significantly lower level in malignant than in benign prostatic hyperplasia. Hamdy et al. (1992) reported very interesting results which supported cell-type specificity of antibodies to PSA. Using flow cytofluorography, these authors detected circulating PSA-positive cells in the peripheral blood of male patients with metastatic prostate carcinoma. The presence of PSA-positive cells showed a higher degree of sensitivity and specificity in predicting a positive bone scan indicative of the presence of bone metastases than did serum PSA levels (Hamdy et al. 1992).

Immunohistochemical demonstration of PSA also appears to be of equal importance with respect to the identification of normal (Pollen and Dreilinger 1984; Tepper et al. 1984; Wernert et al. 1992; Zaviačič et al. 1994) and pathologically altered (cancerous) prostatic tissue in the female (Svanholm et al. 1987; Wernert 1991; Zaviačič et al. 1993a; Sloboda et al. 1998 and references therein).

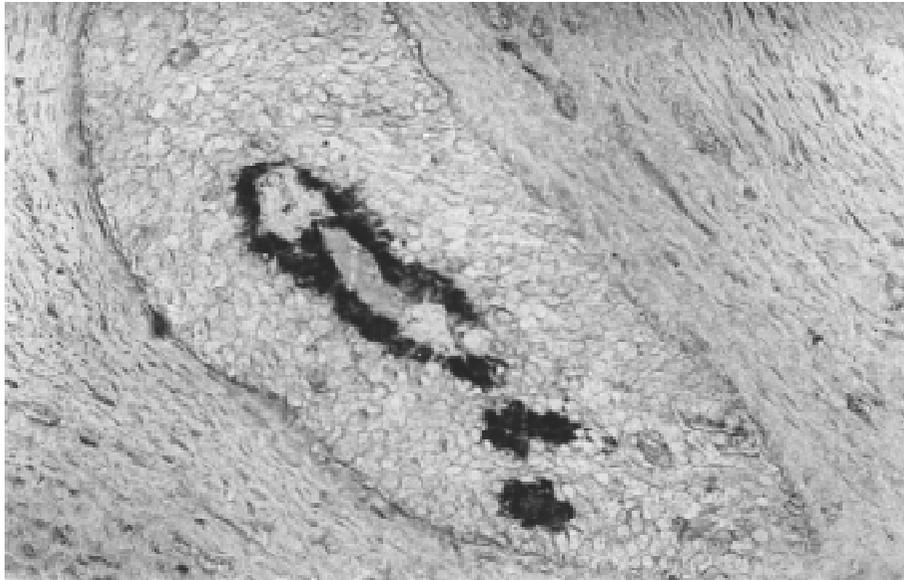


Fig.VIII/1 Distinct expression of PSA in the apical parts of cells of two intraductal prostatic glands and in apical parts and on the surface of cells of the pseudostratified columnar epithelium lining the lumen of a female prostate duct, and in membranes of these cells. Female, 41-year-old, peroxidase-antiperoxidase (PAP) technique, x 170

Immunohistochemical determination of PSA by peroxidase-antiperoxidase (PAP) technique and by the method of biotin-streptavidin-alkaline phosphatase (BSAP) or by the biotin-streptavidin-peroxidase (BSP) method yielded concordant expression of the examined marker in the highly specialized apically superficial layer of male and female secretory (luminal) cells of the prostatic glands and membranes of secretory and basal cells and membranes of columnar cells of the female prostate ducts lining (Figs. VIII/1,2,3,4,5)(Zaviačić et al. 1994; Zaviačić 1997), which is in agreement with PSA expression reported by other authors. We may agree with Pappoti et al. (1989) who claim that, in a majority of tissues, immunohistochemical determination of PSA is more efficient when rabbit polyclonal antibodies rather than mouse monoclonal antibodies are used. Similar differences could also be observed in immunohistochemical determination of PSA in female prostatic tissue. Only some glandular cells reacted with monoclonal antibodies, the reaction being less massive than that with polyclonal antibodies (Zaviačić and Ablin 1998c). A comparison of hetero (polyclonal) antisera and monoclonal antibody raised against malignant prostatic tissue showed that monoclonal antibody was less sensitive (Schevchuk et al. 1983). In a routine immunohistochemical demonstration of PSA and PSAP monoclonal antibodies appear less useful than polyclonal antibodies in the diagnosis of prostatic carcinoma (Gallee et al. 1986).

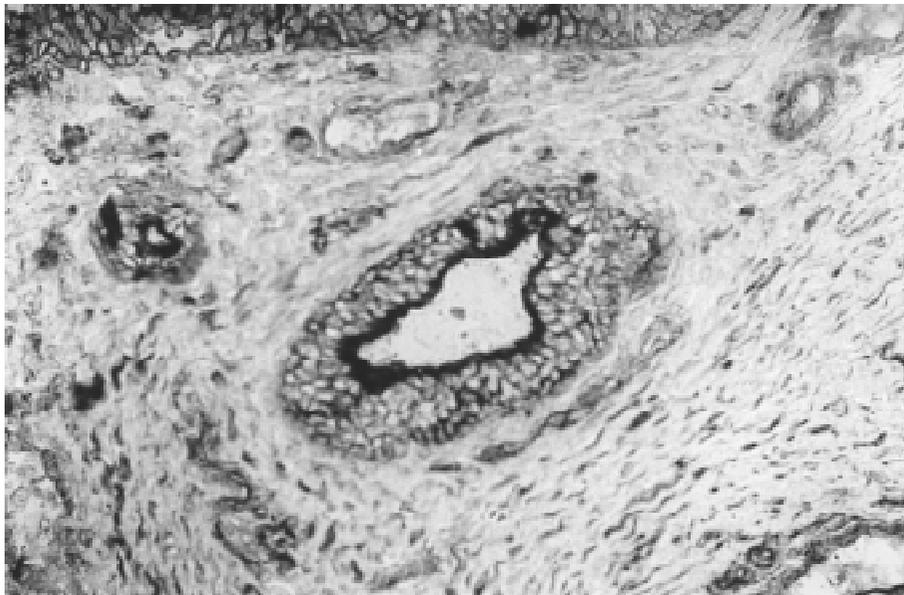


Fig. VIII/2 Marked PSA expression in the apical part and on the surface of cells lining the lumen of a small female prostate duct, and in membranes of columnar cells lining the duct. A small female prostatic gland expressing PSA. Female, 27-year-old, biotin-streptavidin-alkaline phosphatase (BSAP) method, x 170

In addition to secretory cells, PSA is expressed in membranes and on the surface of cells of the pseudostratified columnar epithelium of the lining of the ducts of the female (Figs. VIII/1,2) and male prostate. This unique layer of cells of the urogenital system is distinctly formed and abundantly equipped with glycosamine glycans, glycoproteins and enzymic proteins. Besides numerous enzymes (Zaviačić 1984a,b; 1985a,b) and the presence of urinary protein 1 as shown very recently (Zaviačić et al. 1997 a), distinct immunological properties could be observed between male and female prostate given by the presence of an antigen specific for the prostate – PSA. The findings of immunohistochemical studies focusing on PSA (Pollen and Dreilinger 1984; Tepper et al. 1984; Wernert et al. 1992; Zaviačić et al. 1993a; 1994; Zaviačić 1997; Sloboda et al. 1998 and references therein) have broadened our understanding and enhanced the biological value of PSA since this prostate marker has been found relevant not only in studies of the male but equally so of the female prostate.

For males, the reference range is about 1 – 2 ng/mL and values above 3 – 4 ng/mL are indicative of prostate cancer, benign prostatic hyperplasia or prostatitis (Borchert et al. 1997). A short update on the female prostate (Zaviačić and Ablin 1998a, b, c) has strongly suggested the possibility that, similarly as in the male, the prostate (Skene's gland) is a regular source of PSA in the serum and/or urine of the female as well. The

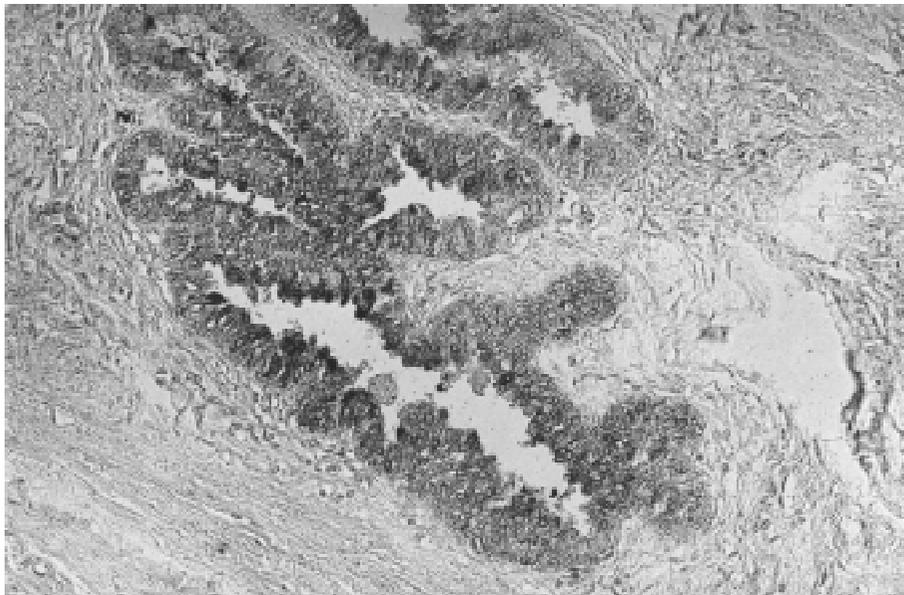


Fig.VIII/3 Moderate to strong PSA positivity in groups of normal female prostate (Skene's) glands. Female, 19-year-old, biotin-streptavidin-peroxidase (BSP) technique, x 180

contribution of the female prostate to PSA formation and its quantities in urine has been confirmed by the results reported by Cabello (1997) who could demonstrate significant differences in urinary PSA levels in the same women between samples drawn prior to and after orgasm. The increased post-orgasmic urinary PSA levels can be explained by the emptying of the female prostate due to orgasm-induced contractions of muscles surrounding the female urethra when the prostate contents with prostatic components including PSA are pressed into the urethra, thus getting to the urine.

A healthy female with a normal prostate typically shows a broad range of serum PSA values from effectively unappreciable amounts to the highest reported ones of 0.9 ng/mL (Borchert et al. 1997). The latter value is very close to the normal reference range for the male. Serological and/or urinary parameters of PSA in females should no longer be considered surprising since they are very well in line with the nonvestigial concept of the female prostate (Zaviačič et al. 1985b; Zaviačič 1987a; Zaviačič and Whipple 1993; Zaviačič and Ablin 1998a, b, c) whose structure and function have been well established and its pathology broadly studied. These parameters are very similar to those of the male prostate (Zaviačič 1987a; Zaviačič and Ablin 1998a, b). Increased serum PSA values may be the result of pathological changes of the female prostate itself, e.g. in carcinoma of the prostate in the female when levels as high as 5.9 ng/mL can be encountered (Dodson et al. 1994); or the increase may present a summation of

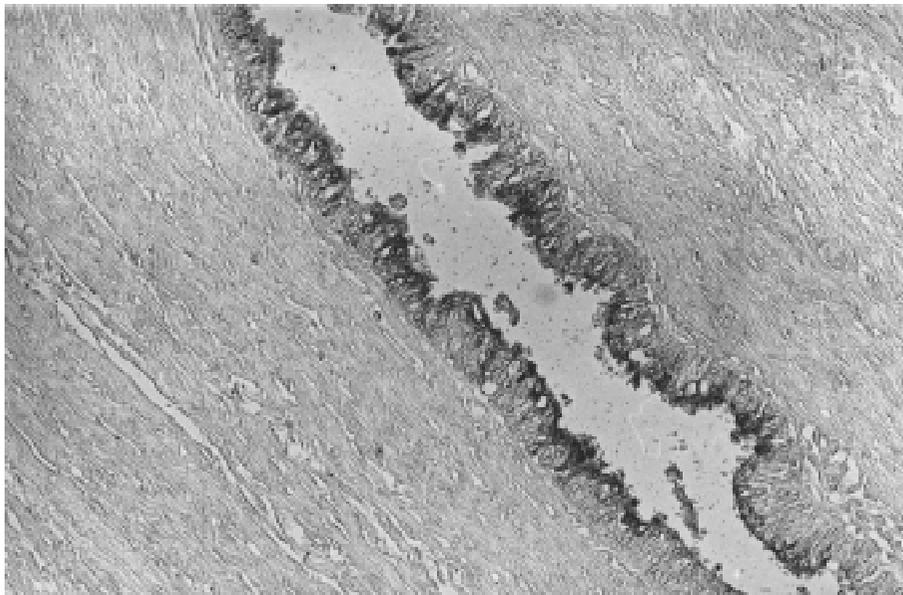


Fig.VIII/4 PSA expression in the apical part, on the surface and on membranes of columnar cells lining the lumen of a narrow duct of the female prostate. Female, 19-year-old, biotin-streptavidin-peroxidase (BSP) technique, x 180

values derived from PSA production of the normal and pathological female prostate (Skene's gland)(Zaviačić and Ablin 1998a, b, c) and PSA of possibly non-prostatic tissue origin, e.g. in female breast cancer (Diamandis et al. 1994; Yu et al. 1994; 1996; Borchert et al. 1997). In female patients with breast fibroadenoma, serum PSA values are very high compared with female breast cancer, and may amount up to 55.1 ng/mL (Borchert et al. 1997). According to our results with immunohistochemical determination (Zaviačić et al. 1998b, c), normal female breast epithelial tissue produces no PSA.

One should be aware of the fact that every serum and/or urine PSA determination in the female inevitably comprises PSA produced by the female prostate (Skene's gland).

Novel, more sensitive serological methods introduced into clinical practice, e.g. IMMULITE-r immunochemiluminescent third-generation assay (Diagnostic Products Corp., Los Angeles, CA) or further modern tests may enhance our knowledge of further parameters which characterize female PSA.

Reading the rapidly increasing numbers of papers concerned with the PSA marker in a broad range of relationships, it must however be inferred that only a minor part of authors know the names of the actual discoverers of this prostate marker. The majority of publications supply the reader with incorrect and misleading information (Diamandis and Yu 1995), including the most recent Cover Legend which appeared in *Cancer Research* (Weinhouse 1998).

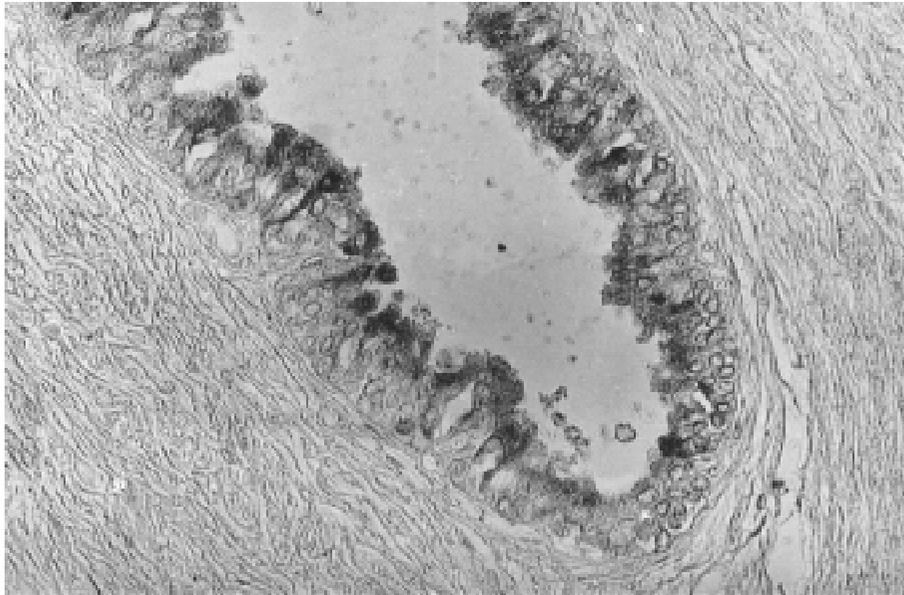


Fig.VIII/5 Marked PSA expression in the columnar epithelium lining a female prostate duct. Female, 19-year-old, biotin-streptavidin-peroxidase (BSP) technique, x 360

It has to be noted that the tissue specific antigens of the human prostate, now known as PSA, were first identified by Richard J.Ablin and his coworkers (W.A. Soanes, P.Bronson, E.Witebsky); they have a justified priority claim as they published their results in two renowned journals (Ablin et al. *J.Immunol.* 1970a; Ablin et al. *J. Reprod.Fertil.* 1970b), nine years before the paper by Wang et al. (1979). Nevertheless, the discovery of PSA is often attributed to the latter authors (M.C.Wang, L.A.Valenzuela, G.P.Murphy, T.M.Chu). Such misleading information („Dr.Chu’s work in collaboration with Ming C.Wang, eventually resulted in the discovery and purification of PSA from the prostate“, Wang et al. *Invest. Urol.* 1979) also appeared in the April issue of *Journal of Cancer Research* (Weinhouse 1998). Even before our reference, the first identification of PSA by the team of Richard J.Ablin has been pointed out by the late Dr.William H.Cooper from Emory University School of Medicine (Cooper 1993) and by the group of Dr.Joseph E.Oesterling [(J.M.Monda, M.J.Bary, J.E.Oesterling) (Monda et al. 1994)]. Although some of the authors incorrectly mentioned as PSA discoverers did publish some important partial findings concerning PSA, their work was essentially based on the groundbreaking studies of the Ablin team.

It seems safe to state that the situation concerning the priority claim with respect to PSA discovery may be best expressed as follows: „PSA was initially identified by R.J.Ablin, W.A.Soanes, P.Bronson, and E.Witebsky in 1970 (Ablin et al. 1970a, b),

and was purified and characterized by M.C.Wang, L.A.Valenzuela, G.P.Murphy and T.M.Chu in 1979 (Wang et al. 1979).“ Wang et al. (1979) characterized PSA as a monomer with molecular mass of 33-34 kDa. Seven years later, PSA was shown to be a 240-amino-acid single-chain glycoprotein (Watt et al. 1986). The primary gene structure and the amino acid sequence of PSA exhibit a high degree of similarity with those of other serine proteases of the kallikrein gene family. PSA participates in the liquefaction of the semen following ejaculation (Lilja 1985; Watt et al. 1986; Lilja et al. 1987). PSA has been shown to exist in multiple forms and, being a protease, it forms complexes with protease inhibitors in the serum (Stenman et al. 1991), mainly with alpha-1-antichymotrypsin (ACP). Stenman et al. (1991) and Lilja et al. (1991) believe that the major proportion of serum PSA is ACT-bound to form PSA-ACT complex.

In his Letter to the Editor which appeared as Commentary in the magazine *Oncology*, Ablin (1998) presented a good overview of the individual steps in the investigation of prostatic antigens which mouthed into the discovery of PSA. In his Letter, he responded to incorrect information presented by some authors of articles appearing in the same journal of *Oncology* [(Pannek and Partin 1997) according to Ablin 1998]] concerning the historical chronology of the PSA identification. The statements of these authors have been even more surprising in the view of the fact that Dr.Partin previously (1994) published a paper on the initial identification of PSA by Ablin’s group (Partin and Oesterling 1994).

IX.

Prostatic and Non-prostatic Sources of Prostate-specific Antigen

In the male, the main PSA producer are epithelial cells of the prostate (Partin and Oesterling 1994; Zaviačič et al. 1994; Ablin 1996; 1997 and references therein; Zaviačič 1997). Nevertheless, this prostate marker was immunohistochemically detected not only in the normal male prostate and male periurethral glands but also in the normal female prostate (Skene's gland) and in diseased male and female prostate tissues including cancer in both sexes (Frazer et al. 1992; Zaviačič et al. 1993a; Elgamal et al. 1994; Zaviačič et al. 1994; Ablin 1997; Breul et al. 1997; Zaviačič 1997; Sloboda et al. 1998 and references therein; Zaviačič and Ablin 1998a, b, c and references therein).

Some authors consider the breast to be the principal PSA producer in the female (Diamandis and Yu 1995; Yu et al. 1996; Diamandis 1998). In their opinion the main PSA producer in the female is not only diseased female breast tissue and fluids, especially benign breast disease and cancer, but also normal female breast tissue (Yu et al. 1996; Mannello et al. 1996; Diamandis 1998). So far, preliminary immunohistochemical data concerning PSA examination in the normal female and male breast tissue have been published in one short communication (Zaviačič et al. 1998b). The quantitative immunochemical data reported by the Diamandis' team (Yu et al. 1996; Diamandis 1998) as being typical of normal breast tissue do not represent values for normal female breast tissue since their „normal“ group of female patients consisted of 38 women with hyperplastic breasts, and tissue samples were obtained during breast reduction surgery. This type of female breast tissue is far from being normal breast tissue – even the authors of the original paper admit so (Yu et al. 1996).

In the male, there are no doubts on the primary role of the normal or pathologically altered prostate with respect to PSA production. More recent reports providing evidence for a similar nonvestigial role of the prostate in the female (Zaviačič et al. 1985b; Zaviačič 1987a; Zaviačič and Whipple 1993; Zaviačič and Ablin 1998a, b, c) are either not sufficiently known or have been ignored (Wernert et al. 1992; Borchert et al. 1997; Elgamal et al. 1997; Ignatoff 1997; Diamandis 1998).

In our recent works (Zaviačič et al. 1998b, c), we could verify, using immunohistochemical methods on necroptic and bioptic material, whether and to what extent normal and pathologically altered male and female tissues participate in the PSA production. Considering the fact that in healthy women, serum PSA levels range from non-detectable to high, reaching up to 0.9 ng/mL, a value approaching that of the normal reference range for males (1-2 ng/mL, according to Borchert et al. 1997), it appears justified to address the issue of which organ or tissue in the healthy and diseased female is actually responsible for the production of this prostate marker.

Using immunohistochemical methods PSA was examined in tissues taken during many biopsies and autopsies (a total of 115 cases). The bioptic material of the female and male breasts involved 39 cases of benign breast disease (35 women and 4 men). The majority of the cases concerned fibroadenomas and cysts of the female breast; in the male patients, they concerned gynecomastia. In 18 women, breast cancer was diagnosed. Our material did not include any case of male breast cancer.

Normal breast tissue was obtained at autopsy of 52 deceased (23 women and 29 men). Histological examination of normal female breast tissue revealed only age-dependent involutionary postmenopausal atrophic changes, typical of female subjects aged over 50 years, and resting female breast tissue in younger female individuals. The normal male breast only contains ducts and no lactiferous glands (Zaviačič et al. 1998c).

The female urethra with prostate tissue was obtained from 37 cases at autopsy, and treated as published elsewhere (Zaviačič 1984a,b). The whole male prostate was obtained at autopsy from 33 individuals, and PSA was immunohistochemically determined in the peripheral part of the prostate.

Tissue samples from the axilla and the perineum containing apocrine sweat glands were taken from 42 necropsies (16 females and 26 males) for PSA determination (Zaviačič et al. 1998c).

PSA was determined in six gastrobiptic samples obtained from patients with different diseases of the stomach, including two cases of signet-ring cell carcinoma of the stomach (two males aged 69 and 53 years).

PSA expression was demonstrated in samples from 52 normal and 57 pathologically changed female and male breasts (Zaviačič et al. 1998c). The 57 breast tissues examined included 39 benign (22 cases of dysplasia of the female breast, 4 cases of gynecomastia in the male, 6 fibroadenomas, and 7 cases of inflammatory breast diseases) and 18 malignant diseases (13 cases of ductal and 5 cases of lobular carcinoma).

PSA expression could not be observed in any epithelial structures of the normal male and female breast (Zaviačič et al. 1998b, c).

PSA positivity could be identified in 17 out of 39 cases of benign breast diseases in both sexes (44%).

Out of the 18 cases of female breast cancer examined, 7 cases of ductal carcinoma were PSA positive (38%), and 6 cases were negative. All lobular carcinomas examined were PSA negative.

The data on PSA expression in normal necroptic prostatic tissue in both sexes (37 female and 33 male prostates) were grouped according to the age of the individuals;

also, results of immunohistochemical examination of PSA in 42 samples of normal axillary and perineal tissue have been published (Zaviačič et al. 1998c).

All the samples of the normal male and female prostate tissue showed moderate to high PSA expression in the glands and ducts (Zaviačič et al. 1998c).

Extraprostatic tissues of the axilla and the perineum showed weak PSA positivity in the apocrine sweat glands.

Moreover, PSA could be immunohistochemically detected, sometimes at the detection limit, in membranes of adipocytes of the female and male breast fat tissue (Fig. IX/1), in small vessel endothelium and some blood cells, perineal glands, and in basal membranes of various genito-urinary and gastrointestinal organs (Zaviačič et al. 1998c). Examination of gastrobiopsies yielded characteristic findings of PSA expression in parietal cells of the fundal gastric mucosa. Unlike the signet-ring cell variant of ductal female breast carcinoma whose cells displayed intense PSA positivity (Fig. IX/2), the mucus accumulating cells of the signet-ring cell carcinoma of the stomach exhibited PAS (periodic acid-Schiff) positivity but no PSA expression.

In keeping with the findings of Papotti et al. (1989), the best results of PSA determination were obtained with rabbit polyclonal antibodies. The polyclonal antibody reacts with several epitopes, whereas the monoclonal antibody only recognizes a single one (Ferenčik 1993). PSA expression was intensified by monoclonal antibody antigen revitalisation in microwave oven; the procedure however had a negative effect on the structure of the preparation and interfered with the expression assay.

The results of our immunohistochemical studies provided a clear-cut answer as to the role of the normal female and male breast tissue in the production of PSA. In contradiction to the conclusion arrived at by the Diamandis' group (Yu et al. 1996; Howarth et al. 1997; Diamandis 1998) and in agreement with our preliminary study (Zaviačič et al. 1998b) we could confirm that normal female breast epithelium does not produce PSA (Zaviačič et al. 1998c). The discrepancy between the results of the quantitative immunochemical determination obtained by the above authors and our findings may be explained by the fact that despite the higher sensitivity of quantitative immunochemical methods compared to immunohistochemical methods, the former are used with heterogeneous homogenates which, in the given case, contain adipose tissue and small vessels in addition to female breast glands; adipose tissue and small vessels have been reported to show positivity on immunohistochemical examination. This may account for the discrepancies between our results obtained using the immunohistochemical method and those of the Diamandis' group, which made them erroneously conclude that normal female breast tissue produces PSA. Moreover, as already mentioned, their results were obtained in material from hyperplastic female breasts rather than from normal tissue. Our immunohistochemical results apply to normal resting and postmenopausal atrophic female breast tissue representing age-dependent physiological variations of the normal female breast (Ahmed 1992). Our immunohistochemical findings lead to the conclusion that the normal female breast cannot be a major PSA producer and can, by no means, explain the PSA levels observed in normal healthy women.

No PSA expression could be detected in the samples of the 29 normal male breasts examined by us (Zaviačič et al. 1998c). Unlike female breast tissue, that of males only

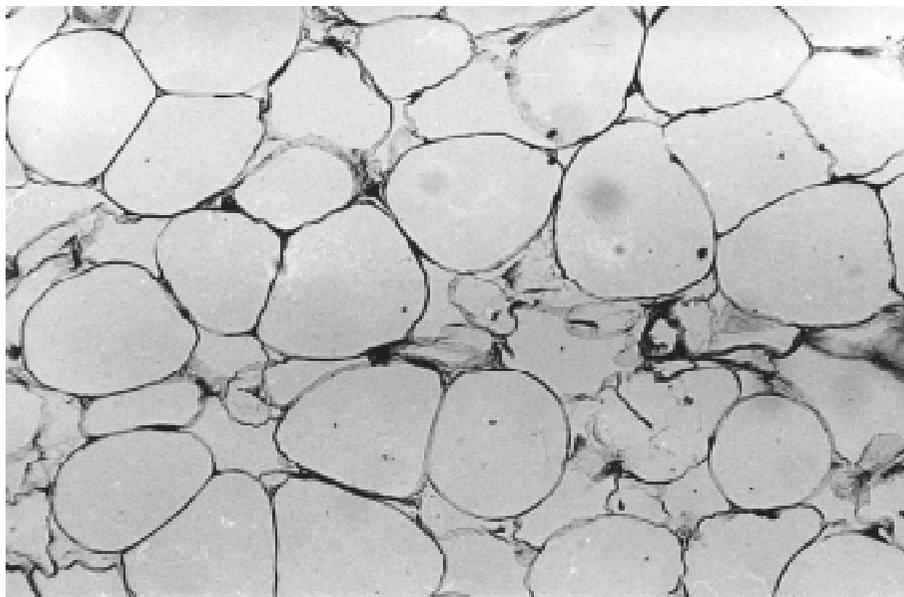


Fig. IX/1 PSA positivity in membranes of adipocytes of the male breast fat tissue. The same male (aged 45 years) with gynecomastia as shown in Fig. IX/4, x 90

contains scattered ducts lined by epithelial and myoepithelial cells, but no lactiferous sinuses and no lobule formation (Ahmed 1992). Our results showed that the normal male breast, similarly as that of females, is not involved in PSA production.

Some authors have reported PSA expression in normal acinar pancreatic and salivary glands and some normal blood and bone marrow cells (Elgamal et al. 1997), endometrial tissue (Clements and Mukhtar 1994), axillary and perineal apocrine sweat glands (Papotti et al. 1989), breast tissue in women on oral contraceptives (Yu et al. 1995), and „normal“ (actually hyperplastic) breast tissue (Yu et al. 1996).

In our material, PSA expression, sometimes at the limit of detectability, was observed in apocrine (but not eccrine) axillary and perineal (and nipple?) sweat glands, perianal glands, in the endothelium of small vessels (no PSA expression was however observed in the aorta and the pulmonary artery), in membranes of adipocytes of the breast fat tissue (Fig.IX/1), the perineum and the axilla, and in the basal membranes of various genito-urinary and gastrointestinal organs. Interesting was the finding of PSA expression in parietal cells of the fundal gastric mucosa seen in bioptic samples (Zaviačić et al. 1998c). Also, parietal cells exhibit prostatic acid phosphatase (PSAP) activity, and this enzyme cross-reacts with many other tissues and cannot thus be considered as a specific prostate marker any more (Zaviačić et al. 1993a and references therein).

A simple conclusion can be drawn based on the finding of consistently high PSA expression in the structures of the female prostate glands and ducts (Fig.VIII/3, 4, 5) in

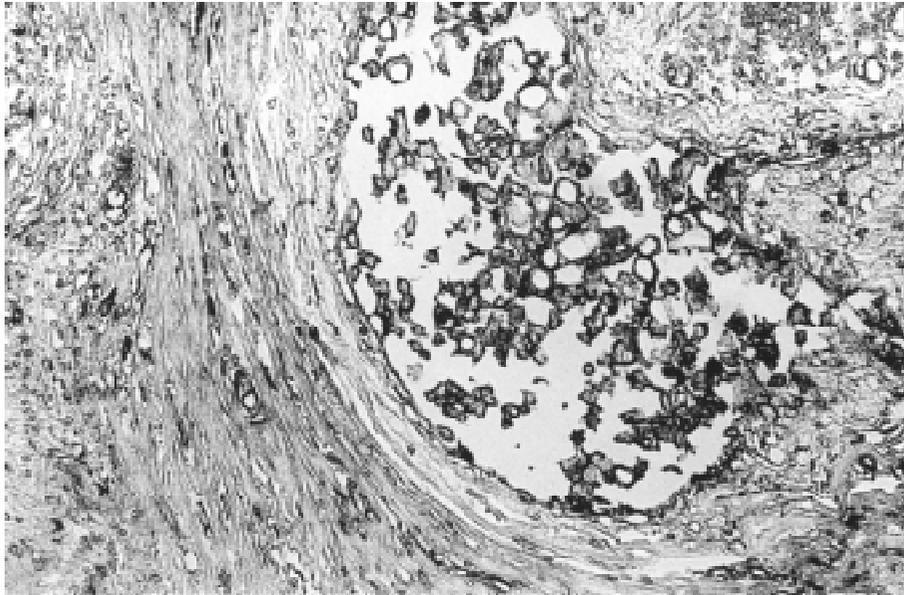


Fig. IX/2 Moderate PSA positivity in cells of the signet-ring cell variant of breast ductal carcinoma. Female, 78-year-old, x 90

37 autptic cases that, similarly as in the male, the prostate (Skene's glands) is a regular and major PSA producer also in the female. The variability of the female prostate (Zaviačič et al. 1983; 1985b; Zaviačič 1987a; Zaviačič and Whipple 1993; Zaviačič and Ablin 1998c; Zaviačič et al. 1998a) as well as its variable size and weight compared to the male prostate (the adult female prostate weighs slightly more than 5g, representing about 20 – 25% of the adult male prostate – Zaviačič et al. 1998a) may account for the broad variation in the serum and urine PSA values in healthy females ranging from undetectable levels to as high as 0.9 ng/mL (Borchert et al. 1997). This explanation of the female prostate role as the PSA producer is well in keeping with the current non-vestigial concept of the prostate in women as a genito-urinary organ with a structure, function and pathology comparable to those typical of the male prostate (Zaviačič et al. 1983; 1985b; Zaviačič 1987a; Zaviačič and Whipple 1993; Zaviačič et al. 1994; Zaviačič and Ablin 1998a,b,c and references therein). This role in the female, with the female prostate PSA production being comparable to that by the male prostate, offers the simplest explanation for the origin of PSA in females. PSA immunoreactivity has however been identified in a number of extraprostatic tissues and secretions in males and females. Immunoreactivity has been reported in a variety of neoplastic and benign tumorous tissues including apocrine sweat gland carcinomas and apocrine breast carcinomas (Papotti et al. 1989; Allanen et al. 1996), salivary gland and salivary duct carcinoma (Van Krieken 1993), colon cancer (Wilbur et al. 1987),

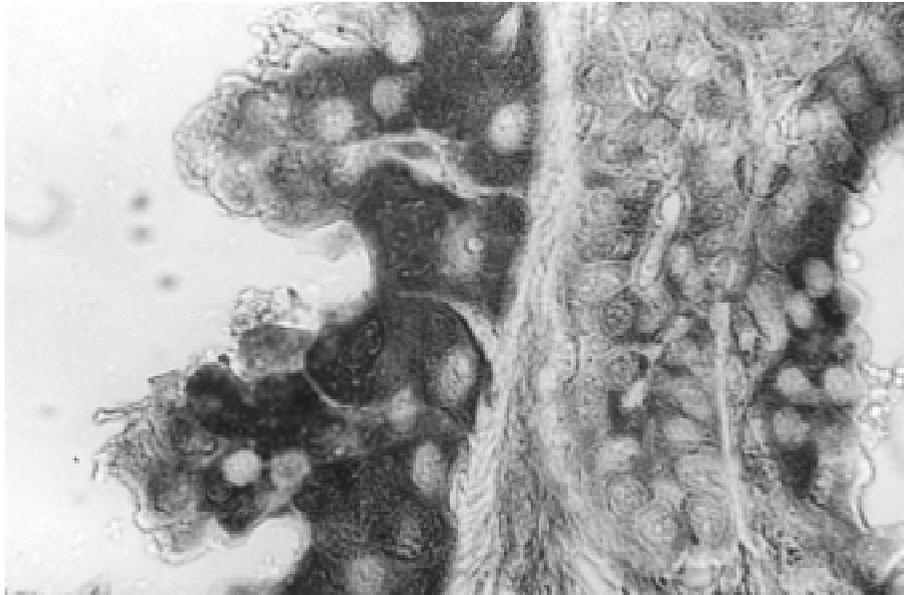


Fig.IX/3 Moderate PSA positivity in the biopsy of female breast apocrine metaplasia in benign breast disease. Female, 51-year-old, x 360

pancreatic acinar cell carcinoma (Kuopio et al. 1995), biliary tract carcinomas (Wilbur et al. 1987), urinary bladder carcinomas (Grignon et al. 1991), mature cystic teratomas of the ovary (McLachlin and Srigley 1992), male and female breast tumours (Diamandis et al. 1994; Yu et al. 1994; 1996; Monne et al. 1994); no PSA was however found in male breast cancer (Dawson 1992).

Our materials which consisted of pathologically changed female and male tissues effectively without exception derived from biopsies and autopsies taken routinely, and thus represented a random collection of samples. Unlike normal tissue of the female and male breast whose epithelial structures did not express PSA (Zaviačič et al. 1998b, c), apocrine metaplasia in benign female breast disease (Fig.IX/3) and male gynecomastia (Fig.IX/4) exhibited distinct PSA positivity (Zaviačič et al. 1998c).

Our immunohistochemical findings in tissues from benign female and male breast diseases are in conformity with the immunochemical data reported by the Diamandis' group who referred the highest PSA production for these tissues compared to carcinoma and „normal“ breast tissue (Yu et al. 1996; Diamandis 1998). PSA was expressed in 17 out of 39 cases of benign breast disease (35 women and 4 men) in our series (Zaviačič et al. 1998c).

Also, PSA expression was observed in tissue from female breast cancer, especially in differentiated types of ductal carcinoma. In undifferentiated types, PSA expression was declining (Fig.IX/5) or missing at all, and no PSA expression could be detected in tissue

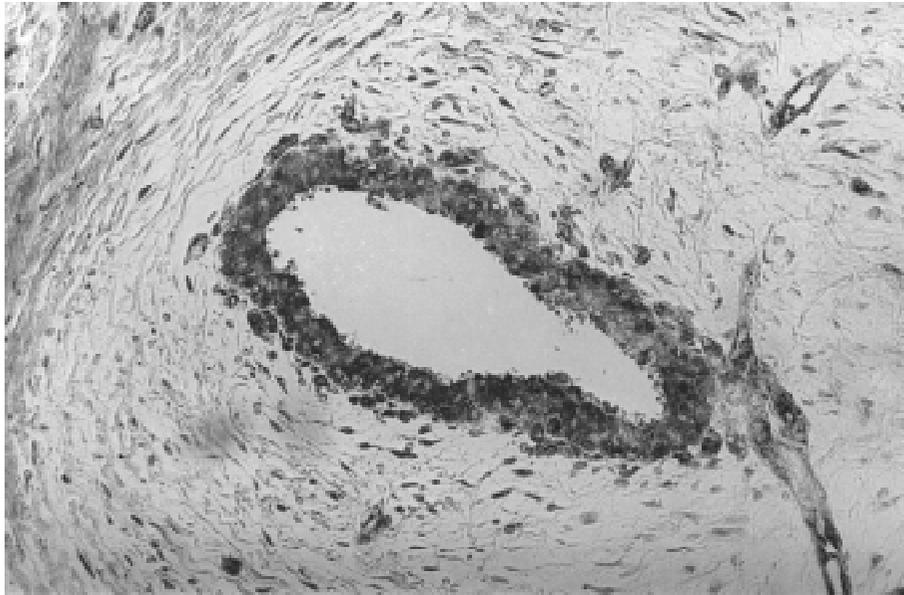


Fig. IX/4 Moderate PSA positivity in an autopsy case of male breast apocrine metaplasia in gynecomastia. Male, 45-year-old, x 90

from lobular carcinoma of the breast. The signet-ring cell variant of ductal female breast carcinoma displayed high PSA expression (Fig.IX/2). This may be a specific feature of the cancerous breast tissue since, in two cases of signet-ring cell carcinoma with different localization (gastric mucosa), the cancer cells were characterized by periodic acid-Schiff (PAS) positivity of mucus accumulating cells; yet, in contrast to cells of this type of cancer in the female breast, they did not express PSA (Zaviačič et al. 1998c). Only 7 out of the total of 18 cases of cancer of the female breast in our study displayed PSA positivity, and 11 were negative (Table 1 in Zaviačič et al. 1998c). Based on our material, we were unable to address conclusively the issue concerning the relationship between PSA production and the equipment with steroid hormone receptors of normal and pathologically altered female breast and other tissues (Yu et al. 1994; Bodey et al. 1997; Borchert et al. 1997; Diamandis 1998). Further studies are needed to confirm or reject the hypothesis on PSA being exclusively produced in structures equipped with steroid hormone receptors, as promoted by Diamandis (1998). In contrast to our immunohistochemical study where a majority of cancerous female breasts produced no PSA (PSA negativity was found in 11 out of a total of 18 cases of breast cancer), in a paper published in the March 1999 issue of British Journal of Cancer, Majumdar and Diamandis (1999) reported about 70% of breast cancer tissues to produce PSA. They claim that mutations associated with the androgen response elements have been shown previously to result in an 80% decrease in PSA gene expression (Majumdar and Diamandis 1999).

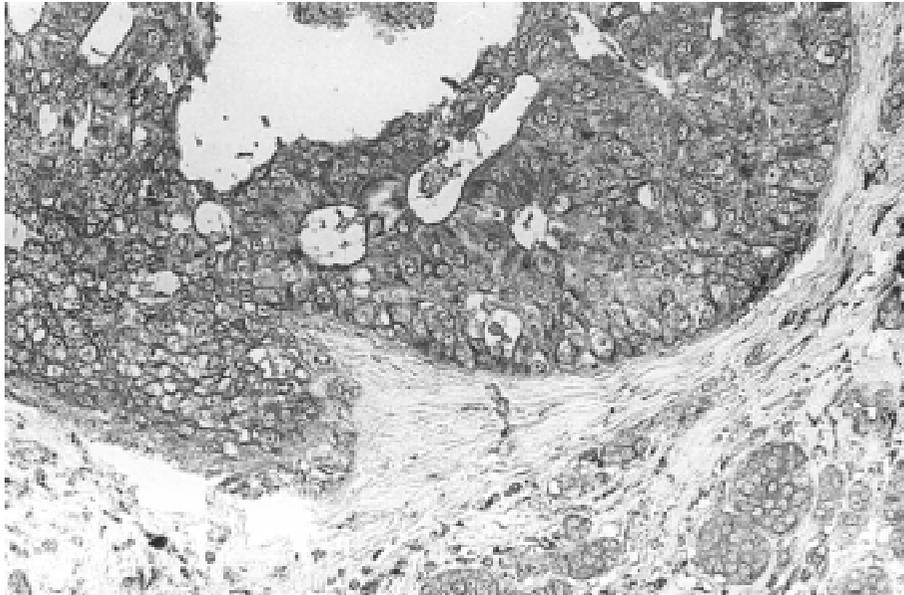


Fig.IX/5 Very weak PSA positivity in the biopsy tissue from infiltrating ductal carcinoma of the breast (G-2). Female, 32-year-old, x 90

Ablin (1996; 1997) and Zaviačič and Ablin (1998a, b, c) consider the expression of PSA in male and female non-prostatic cancerous tissues, e.g. in the female breast, as apparently anomalous, being a manifestation of the neoplastic transformation process.

Immunohistochemically detectable expression of PSA in the normal (Pollen and Dreilinger 1984; Tepper et al. 1984; Zaviačič et al. 1994) and cancerous female prostate tissue (Zaviačič et al. 1993a; Sloboda et al. 1998 and references therein) allows to identify female prostate tissue and, to the pathologist, it provides the means to differentiate between true female prostatic carcinoma and other adenocarcinomas of the female urethra which frequently occur in relation to urethral diverticulum, the latter being PSA negative (Tanabe et al. 1982; Oliva and Young 1996; Amin and Young 1997) and are not assumed to be of prostatic origin in the female, rather, their mesonephric origin has been suggested (Dodson et al. 1995; Sloboda et al. 1998).

Convincing clinical evidence is accumulating on PSA production by the female prostate. Sexological studies have demonstrated differences in pre- and post-orgasmic urine PSA levels (due to the release into the urine of the urethral contents including PSA by contractions of muscles surrounding the urethra during the orgasm)(Cabello 1997); moreover, the study of Dodson et al. (1994) who observed preoperatively an increased serum PSA level in a female patient with carcinoma of the prostate (female urethra) which promptly decreased after excision of the tumour has been frequently referred to. Neither us nor the authors of the report (Dodson et al. 1994) have ever

questioned the prostatic origin of this marker in the female or considered extraprostatic production of PSA by female breast tissue.

The rather weak and variable expression of PSA by some normal extraprostatic tissues (membranes of adipocytes, apocrine sweat glands, parietal cells, endothelium, etc.) does certainly not qualify these structures as major PSA sources in the healthy male or female.

The principal source of PSA is the prostate in both sexes. There are however distinct quantitative differences in the production of PSA between the male and the female prostate, probably reflecting the lesser efficiency of the female organ.

Pathologically altered male and female breast, especially in benign breast diseases (Figs.IX/3,4) produces higher PSA levels compared to both normal and cancerous breast tissue. In the latter as well as in other pathologically altered tissues of male and female patients, known to produce PSA, the total amounts of this prostate marker (PSA) represent the summation of regular prostatic and anomalous diseased extraprostatic tissue production (Zavlačič et al. 1998c).

X Pathology of the Female Prostate with Special Reference to Carci- noma, Benign Prostate Hyperplasia and Other „Prostatic“ Diseases in Female Patients

Permanent awareness and position of a given organ in the hierarchy of organs in the human body is established not only by understanding its physiology and pathophysiology but also and particularly by insight into its pathology. As our knowledge on the pathology of the organ broadens, we attempt to understand the essential mechanisms involved in the development of the diseases affecting the organ and search for ways how to treat them. These general statements do fully apply to the problem area of the female prostate. In the majority of women, the prostate is considered to be an organ devoid of problems. This simplistic, traditionally repeated approach is absolutely unsubstantiated. Objective data from pathologists, urologists and gynecological urologists documenting the actual incidence of female prostatic diseases on the basis of adequately large material are not available as yet. The pathology of the female prostate has so far been dealt with mostly in case reports. The situation would change rapidly if autopsy of the female urethra along with the prostatic tissue became a routine part of the post mortem examination, and that also in forensic cases, and if gynecologists, urologists, and gynecological urologists (urogynecologists) approached the diseases as actual diseases of the female prostate rather than of the urethra. Many clinically valuable data could be obtained from patients by routine use of the already existing questionnaires, adequately adapted for establishing relevant findings, which are commonly used to record and document symptoms and complaints of patients in urological and andrological departments. The obtained data might not only promote early diagnosis of cancer, benign hyperplasia and prostatitis in female patients but they could also

Immunohistochemical examination of PSA and PSAP in cases of adenocarcinoma of the female urethra-female prostate (Skene's gland)

Author	N cases	PSA	PSAP
Svanholm et al. 1987	1	+	+
Spencer et al. 1990	1	+	+
Mostofi and Sesterhenn cited by Wernert 1991	3	+	+
Kamoto et al. 1993	1	-	-
Zaviačič et al. 1993	1	+	+
Dodson et al. 1994	1	+	+
Dodson et al. 1995	12	-	0
Ebisuno et al. 1995	1	+	+
Miyai and Ebisuno 1995	1	+	+
Zaviačič et al. 1995*	1	+	+
Oliva and Young 1996	5	+	+
	13	-	-

+ Positive expression of PSA or PSAP in cancerous cells

- Lack of expression of prostate markers in cancerous cells

0 No data on PSAP

* This case report appeared in the form of abstract (Congress of ESP, 1995) and as a full publication (Sloboda, Zaviačič et al. 1998)

** Serum level of PSA was increased preoperatively and promptly decreased after surgical excision of the tumor

Fig. X/1 Cases of adenocarcinoma of the female prostate (female urethra) with results of PSA and PSAP immunohistochemical examination. Data from the Table in Sloboda et al. (1998) – modified.

become an important basis for studying the actual incidence of diseases of the prostate in the female population. The present chapter, virtually based on case reports and analysis of small series, focuses on carcinoma, benign hyperplasia and inflammation of the female prostate, diseases which represent also the most important diagnostic and therapeutic entities of the diseased prostate in the male.

Carcinoma of the female prostate

Tumors of Skene's paraurethral glands, the female prostate, are very rare when compared with their incidence in the male prostate. Primary urethral carcinomas are of the less frequently occurring carcinomas of the female reproductive system, with a reported incidence of 0.16 to 0.70 or 0.95 % (Egloff 1972). They are mostly squamous or urothelial in nature (Levine 1980; Kamat et al. 1981; Groben et al. 1985). Approxi-

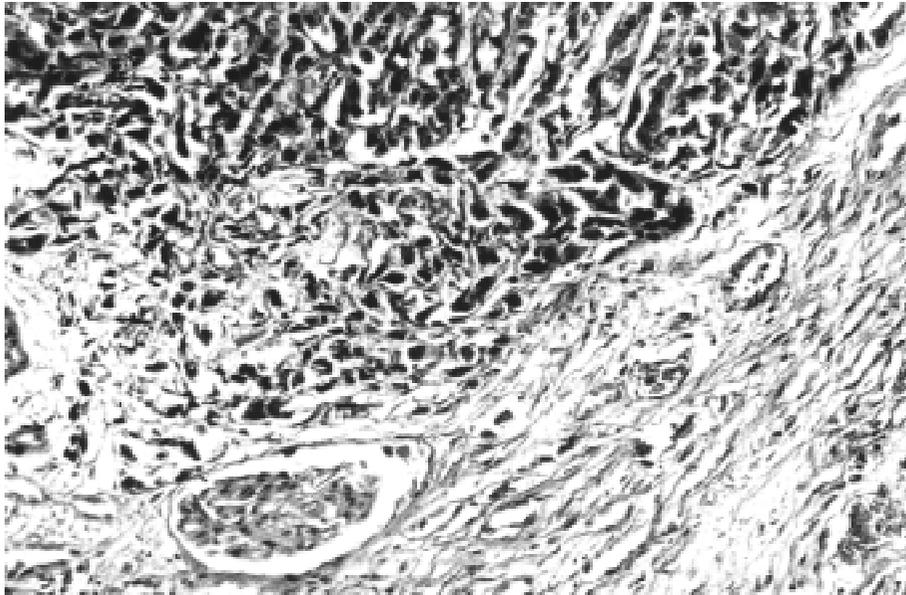


Fig. X/2 Solid parts of renal cell carcinoma of the left kidney. On the margin renal tissue with glomerulus. HE, x 175.

mately 10 % of malignant tumors of the female urethra were reported to be adenocarcinomas derived from paraurethral ducts and glands (Huffman 1951; Schnitzer 1964; De Haan 1965; Adler 1968; Roberts and Melicow 1977).

The morphological similarity between adenocarcinoma of the female urethra and male prostatic carcinoma has been known for many decades (Huffman 1951). Female urethral adenocarcinoma is generally assumed to arise from the female prostate – Skene's paraurethral ducts and glands (Huffman 1951; Zaviačič et al. 1993a). In cases of urethral adenocarcinomas, immunohistochemical examinations of prostatic markers were rare till the 90s. In their paper published in *Pathology Research and Practice*, Sloboda et al. (1998) however, presented a table with 15 cases of adenocarcinoma of the female prostate (female urethra), with immunohistochemical staining for PSA and PSAP, supporting the diagnosis of female prostate carcinoma (Fig. X/1). This paper has provided the first published results of electron microscopic examination of formalin-fixed cancerous tissue showing the ultrastructure of female prostate carcinoma, which was comparable to that of male prostate carcinoma.

The results of Svanholm et al. (1987), Spencer et al. (1990), Mostofi and Sesterhenn (cited by Wernert 1991), Zaviačič et al. (1993a), Dodson et al. (1994), Ebisuno et al. (1995), Miyai and Ebisuno (1995), Oliva and Young (1996), Sloboda et al. (1998), and Sesterhenn et al. (1998) concerning PSA and PSAP positivity provided crucial contribution to the diagnosis of female prostate carcinoma. Immunohistochemical expres-

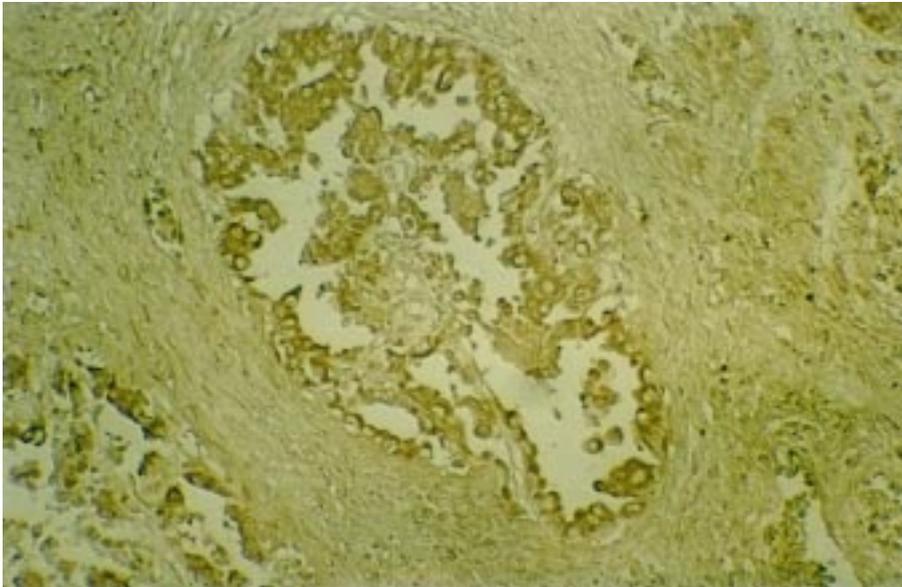


Fig. X/3 Tumor cells of adenocarcinoma of the female prostate (tumor of the „anterior wall of the vagina“) with distinct expression of PSA. Immunoperoxidase (PAP) technique, x 175.

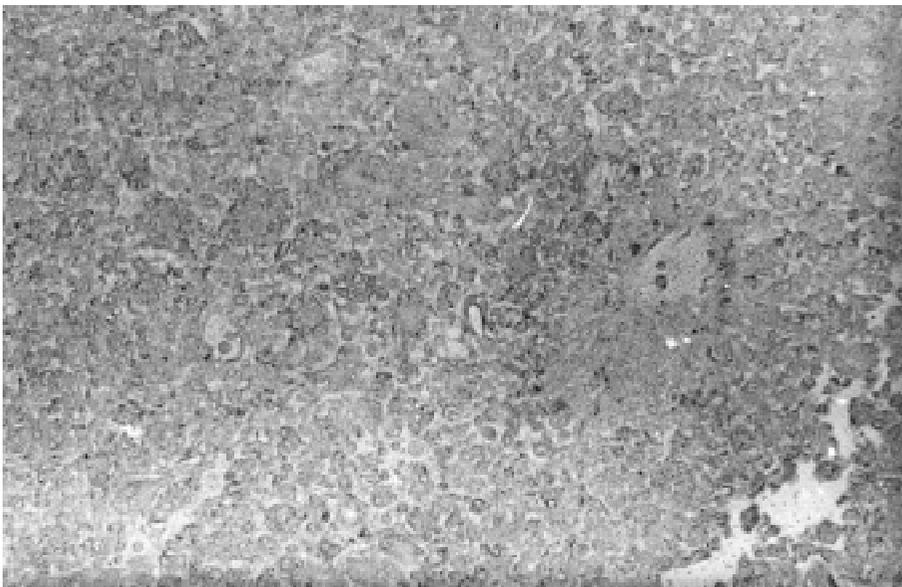


Fig. X/4 Metastasis of renal cell carcinoma in the liver. Tumorous cells show negative cytoplasmic staining for PSA. Immunoperoxidase (PAP) technique, x 175.

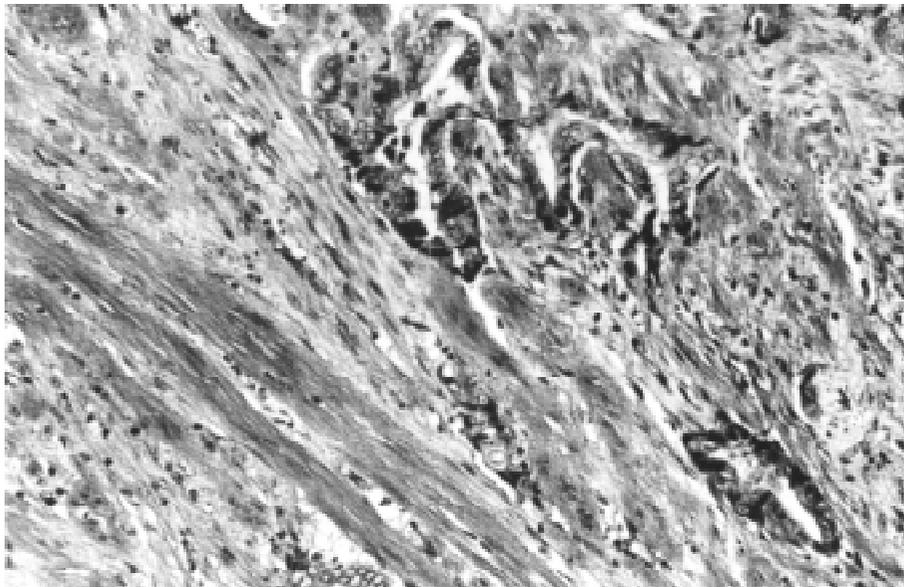


Fig. X/5 Well differentiated glands of adenocarcinoma of the female prostate. HE, x 180.

sion of the prostatic marker PSAP in cancerous tissue of the female prostate is not identical with the diagnostic and interpretative value of PSA. Unlike the high PSA specificity (although this marker is far from being a perfect „tumor“ marker – Ablin 1996; 1997), PSAP cross-reacts with many other tissues (Zaviačič et al. 1993a), such as pancreatic islet cells, gastric parietal cells, liver cells, renal tubular epithelium, epithelial cells of seminal vesicles and breast carcinomas, as well as some carcinoids and adenocarcinomas of the urinary bladder. This makes PSA immunohistochemical staining the approach of choice both for normal and cancerous prostatic tissue of the male and for normal and cancerous prostatic tissue of the female (Zaviačič et al. 1993a).

For the pathologist, positive immunohistochemical staining of tumor cells will apparently become an important indicator for distinguishing between „true prostatic“ adenocarcinomas and other adenocarcinomas of the female urethra (Sloboda et al. 1998). The latter are PSA negative and occur frequently in relation to the urethral diverticulum (Oliva and Young 1996; Amin and Young 1997). They are not assumed to be of prostatic origin (originating from the female prostate), rather their mesonephric origin has been suggested, and one would agree with Dodson et al. (1995) that female urethral adenocarcinomas may have more than one tissue origin. The evident prostatic origin of adenocarcinomas of the female urethra characterized by PSA expression in tumor cells is supported by the finding of preoperatively increased serum PSA level in a female patient with tumor of the urethra which promptly decreased after removal of the tumor (Dodson et al. 1994). This highly important observation has also provided

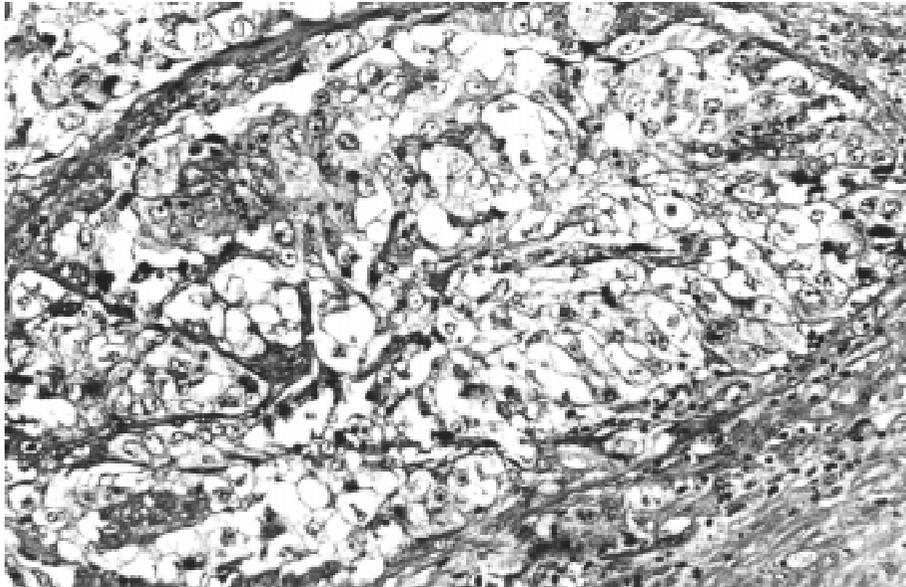


Fig. X/6 Carcinoma of the female prostate with cribriform multiple gland-like and solid cancerous tissue composed of clear vacuolated cells. Thin fibrous tissue strips between neoplastic cells. HE, x 180.

clinical evidence corroborating the non-vestigial concept of the female prostate as a genitourinary organ which evidently exerts its function, and that differently under normal and under pathological conditions. The logical message of the given serological findings is that serum PSA examination should become a regular constituent of preoperative and postoperative monitoring of female patients with prostatic (urethral) tumors.

One of the cases listed in the table given by Sloboda et al. (1998) is our patient whose case report was published in *Virchows Arch A Pathol Anat* six years ago (Zavlačič et al. 1993a). We reported on adenocarcinoma of the female prostate (paraurethral Skene's glands) in a 70-year-old woman. On gynecological examination a flat tumor (1.2 cm in diameter) was observed on the anterior wall of the vagina in the suburethral region, approximately 1.5 cm behind the vaginal orifice. A biopsy specimen taken from the tumor was sent for histological examination. In the meantime the patient died of cardiorespiratory failure. Autopsy revealed renal cell carcinoma of the left kidney (Fig.X/2) with metastases in the lung, liver, lymph nodes and ribs. On the anterior wall of the vagina, at the site where the gynecologist had diagnosed the tumor, the mucous membrane was protruding over an area of about 1 cm. Vertical section showed tumor tissue to be below the vaginal mucosa and to spread diffusely into the depth of the urethrovaginal septum, towards the urethra. Both biopsy and autopsy of the tumor in

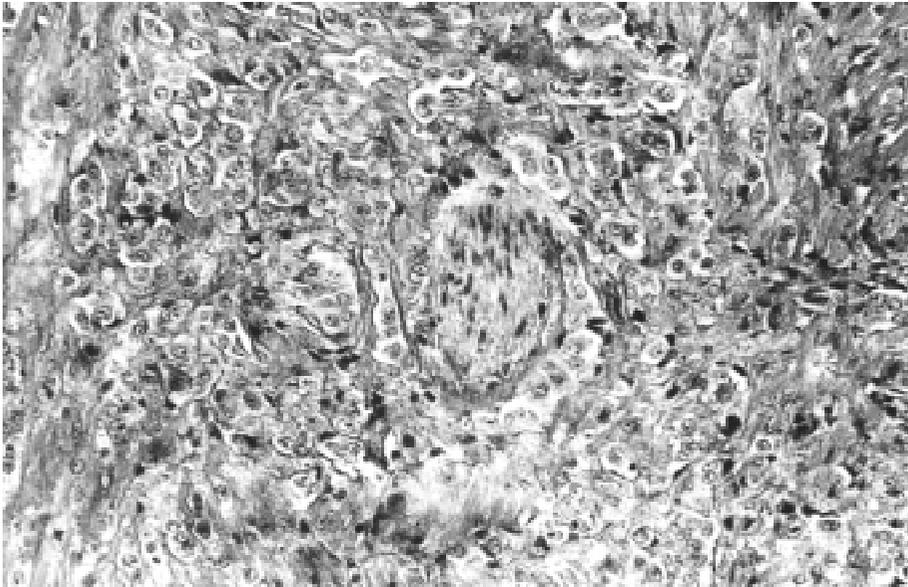


Fig. X/7 Undifferentiated parts of female prostate carcinoma infiltrating perineural space. HE, x 180.

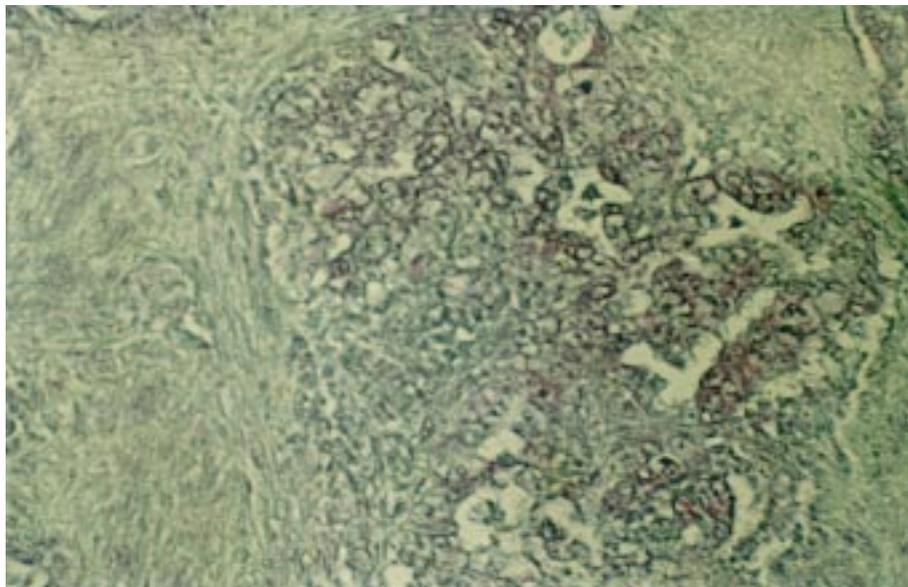


Fig. X/8 Positive staining for PSA in clear neoplastic cells forming cribriform multiple gland-like lumina of adenocarcinoma. Avidin-biotin-alkaline phosphatase complex, x 180.

the anterior vaginal wall showed adenocarcinomatous structure with cribriform multiple gland-like lumina. Immunohistochemical examination of PSA and PSAP showed strong cytoplasmic positivity in cells of the tumor in the vagina (Fig.X/3), while staining of prostatic markers (PSA, PSAP) was negative in the renal tumor and in the metastases (Fig.X/4). Classification of the tumor as non-metastasizing adenocarcinoma of the female prostate (Skene's paraurethral glands and ducts) was made on the basis of the microscopic appearance of the tumor of the anterior vaginal wall and the results of immunohistochemical examination of prostatic markers, particularly PSA..

The case reported by Svanholm et al. (1987) was also a non-metastasizing carcinoma of Skene's glands (female prostate) with coincidence of ovarian carcinoma. Spencer's case (Spencer et al. 1990), on the other hand, concerned urethral adenocarcinoma (female prostate carcinoma) with PSA and PSAP positivity not only in cancerous cells but also in regional metastases.

Our second case of carcinoma of the female prostate diagnosed in our Department was recently published in Pathology Research and Practice (Sloboda et al. 1998). We reported on a 46-year-old woman, mother of two children, with stress incontinence over the last year and complaint of urethritis. She was examined at the Urology Department of the Hospital in Karlskrona, Sweden. A paraurethral tumor was found and urethral diverticulum was suspected. We received a surgical specimen of the tumor from Karlskrona and examined it histologically and electron microscopically in our Department in Bratislava, Slovakia. Histologically, a part of the tumor tissue consisted of well and less well differentiated structures of adenocarcinoma (Fig. X/5). The predominant part of the tumor was composed of clear vacuolated cells with large nuclei, forming glands, glandular cribriform and solid cancerous tissue (Fig.X/6). Anaplastic areas of the carcinoma infiltrating perineural spaces were also seen (Fig.X/7). Examination of prostatic markers demonstrated PSA (as well as PSAP) positivity in all cancerous cells in well-differentiated and cribriform clear cell glandular structures of the adenocarcinoma (Fig.X/8) and in anaplastic cells of solid tumor areas. Electron microscopic examination allowed for the first time to demonstrate the subtle cellular architecture of tumor cells of female prostate carcinoma. In the female, similarly as in the male, prostate carcinoma probably originates from secretory (luminal) cells of the prostate glands. In this case, diagnosis of adenocarcinoma of the female prostate (Skene's paraurethral ducts and glands) was based on the histological and ultrastructural pattern resembling male prostate carcinoma, on the results of immunohistochemical positivity of prostatic markers – mainly PSA – in cancerous cells, and on the results of aspiration cytology of an inguinal lymph node.

Benign hyperplasia of the female prostate

According to Folsom and O'Brien (1943), John Caulk (1921) was the first to suggest resection for bladder neck obstruction in the female. Folsom and O'Brien (1943) reported that from the early 30s publications appeared repeatedly supporting the exist-

ence of benign prostate hyperplasia in the female (Nesbit 1933; Fite 1934; Van Houtum 1939 – cited in Folsom and O'Brien 1943). Folsom and O'Brien published a paper in JAMA entitled „The Female Obstructing Prostate“, stating that the disorder referred to as female prostatism is a clinical entity occurring in women much more frequently than recognized and treated properly. Physicians often fail to ask the proper questions to get an accurate and revealing history. Folsom and O'Brien believed that many women had some type of prostatism. In the male, the term prostatism has been replaced by the term lower urinary tract symptoms (LUTS), the disorder being practically the same. Clinically, besides bladder irritation, these female patients present with some degree of difficulty in voiding up to complete retention. Three out of 15 cases with female obstructing prostate develop complete retention. The majority of reported cases showed fibromuscular hypertrophy with fibrous hyperplasia, although true adenomatous enlargement of the female prostate also occurred in these female patients resulting in complete obstruction and complete retention of urine in the bladder (Folsom and O'Brien 1943). In some cases, autopsy showed bilateral hydronephrosis and hydroureter with trabeculated bladder wall, bladder stones and a prostatic bar. In these cases, the complications found in women were typical of benign male prostate hyperplasia. With the exception of the contribution of Nesbit (1943), the discussion to the lecture of Folsom and O'Brien, published in the same issue of JAMA immediately following their paper, was carried on strictly along the line that „... the female does not have a prostate“ (Ockerblad 1943; Kretschmer 1943; O'Conor 1943). Interestingly enough, many clinicians remembered the unequivocally negative interpretation of the existence of the female prostate as presented in the discussion on the obstructing prostate rather than the very text of the paper by Folsom and O'Brien (1943) with the brilliantly presented non-vestigial concept. It is to be emphasized that the published discussion to their paper provided further generations of physicians sufficient reasons to accept the vestigial concept of the female prostate under Skene's name as an organ insignificant and unnecessary in the woman's life. It can not be excluded that similarly as carcinoma of the female prostate used to be considered adenocarcinoma of the urethra, so also cases of benign hyperplasia of the female prostate may have been reported under a different name. Sharma et al. (1988) published two case reports of bladder outflow obstruction due to fibromatous (fibroma) and glandular hyperplasia of female prostatic tissue. The paper appeared under the descriptive title: „Benign Periurethral Mass Lesions: The Female Prostate“.

Recent findings have provided convincing support to the belief of Folsom and O'Brien and of several clinicians who accepted the existence of the female prostate and considered its pathology to be comparable with that of the male prostate, including the existence of benign female prostate hyperplasia and/or prostatism (LUTS). Further continual research has to be carried out on large pathological material to verify the notion of Folsom and O'Brien (1943) that it is obstruction of the enlarged female prostate in the posterior part of the female urethra that causes retention of urine in the bladder. The relatively low occurrence rate of the so-called posterior type of the female prostate found only in about 10 % of women (Zaviačič 1987a; Zaviačič et al. 1998a), as concluded on the basis of detailed examination of the urethra in 150 autopsies, fails

to be in agreement with earlier published data reviewed by Deter et al. (1946). I quote from his paper: "The closer the bladder sections were taken, the greater the number of (prostatic) glands". In keeping with the findings of Huffman (1948), our data concerning distribution of female prostatic tissue predominantly in the distal (anterior) urethra rather than in the posterior urethra, might conceivably account for the relatively lower incidence of benign prostatic hyperplasia in women compared to the high incidence of this disorder in men. In spite of our, probably largest series of autopsies of the female urethra (150 cases), we failed to see in our material (Zaviačič 1987a; Zaviačič and Whipple 1993; Zaviačič and Ablin 1998a; Zaviačič et al. 1998a) such characteristic pictures of fibromuscular and adenomatous hyperplasia of the female prostate as reported and distinctly documented in pictures by Folsom and O'Brien (1943). On the other hand, in their abstract Sesterhenn et al. (1998) reported not only on the normal prostate and on prostatic carcinoma but also on prostatic hyperplasia in female patients. It appears to be necessary to detect and study the combined incidence of prostatitis and benign female prostate hyperplasia, a combination frequently seen in the male, and to attempt to define clinically and pathologically which actual diseases and conditions are involved in LUTS in the female.

Female prostatitis (Female Urethral Syndrome?)

The urethral syndrome in women is described as lower urinary tract symptoms with a plethora of subjective complaints of retropubic pressure, dyspareunia, urinary frequency and dysuria, yet associated with a lack of objective findings (Bashi 1988; Gittes and Nakamura 1996). The symptoms resemble lower urinary tract infection but there are no abnormal midstream urinalysis findings, no positive bacterial culture (Obrink 1979), and no obvious findings on pelvic examination (Gallagher et al. 1965; Messing 1986). The urethral syndrome remains a diagnosis per exclusion. More serious causes of urinary frequency, dysuria and suprapubic pressure must be considered and excluded. Only a combination of careful history, physical examination, inspection of urine, urine culture, urine cytology and cystourethroscopy with biopsy can establish the diagnosis (Bodner 1988). According to Jackson (1976), the pathological changes of the tissues clinically manifested as urethral syndrome, produce signs which are radiologically recognizable. Excretory urography findings correlate closely with cystographic findings. Transabdominal ultrasonographic measurement of mucose thickness around the bladder neck and internal examination for tenderness at the anterior wall of the vagina are thought to be useful approaches to diagnosis and follow-up of urethral syndrome (Sagaya et al. 1992).

Many factors have been suggested as causative of this syndrome, including non-specific infection, urethral obstruction and spasm, senile atrophy, psychosomatic and traumatic factors, muscular abnormality of the pelvic floor, spasm of the external sphincter (Cardon et al. 1979; Kaplan et al. 1980; Stamm et al. 1981; Schmidt and Tanagho 1981; Schmidt 1985; Bashi 1988; Bernstein et al. 1992). Splatt and Weedon (1981)

found in biopsies of tissue obtained on Richardson urethroplasty and in autopsy cases of females with urethral syndrome a significant increase in fibrous tissue in the urethrovaginal septum, accompanied by loss of smooth muscle fibers and local clumping of elastic tissue.

The variety of treatments practiced over the years reflect the many „causative“ factors of this syndrome. They cover the full spectrum from aggressive surgical excision of periurethral tissue (Richardson 1969), internal urethral cutting procedure and forceful overdilatation of the urethra (Rieser 1968; Evans 1971; Bergman et al. 1989) to the use of anxiolytic and tricyclic antidepressant drugs. Although all treatments were judged ineffective and it has been suggested that treatment be supportive and „harmless“, aggressive management continues to be widely practiced even to date.

This survey clearly shows that despite intensive research, the problem of female urethral syndrome remains still an open question, both as to diagnosis and treatment. It is however surprising that in searching the structure whose damage is the cause of the broad clinical symptomatology in women with urethral syndrome, the female prostate was not considered for a long period of time, and that despite the fact that similar symptoms in man would suggest prostatitis and would lead to microscopic examination of prostatic secretion for the presence of inflammatory cells (Drach et al. 1978). It was only in 1996 that Gittes and Nakamura called attention to the fact that the female urethral syndrome concerns prostatitis, namely inflammation of the female prostate with a broad range of clinical manifestations accompanying the syndrome.

Experts in urinary infection attempted to detect the offending organism, Chlamydia species, and found antibiotic therapy empirically effective (Stamm et al. 1980; 1981). Yet before Gittes and Nakamura (1996) none of the investigators related the diagnosis of the infection anatomically to the tissue of the female prostate (Skene's paraurethral ducts and glands). On examining the female prostate, Gittes and Nakamura (1996) recommend careful pinpoint palpation of the soft tissue of the anterior wall of the vagina on each side of the urethra (similarly to the examination mode described by Huffman already in 1951). Upward fingertip pressure against the pubic bone laterally to the urethra elicits localized tenderness when the paraurethral glands are infected. The examination has certain parallels with digital rectal examination that localizes limited prostate gland tenderness in the male (Gittes and Nakamura 1996). Provided that Chlamydia species have invaded the female prostatic gland, antibiotic treatment with tetracycline or erythromycin usually eliminates the symptoms (Stamm et al. 1980). Russi (1996) recommended administration of doxycycline. Objective vaginal re-examination during follow-up usually confirms the decrease or absence of tenderness in the limited area of the anterior vaginal wall. Nevertheless, relapses of female prostatitis (recently termed also „recurrent cystitis“ – Moore 1975) may occur months or years later. Relapses reflect the easy spread of infection through the rich, mutually communicating system of prostatic glands, including intraepithelial glands (Huffman 1948; Zaviačič et al. 1998a) and ducts of the female prostate, with the urethra and anterior wall of the vagina. These anatomical structures are parts of the urethro-prostatic-vaginal entity (Zaviačič et al. 1998a). The existence of this common genitourinary entity may explain the easy spread of infection and relapses of prostatitis (Skeneitis) in the

female. The anatomical continuity between the female urethra and the urinary bladder predisposes the spread of inflammatory diseases of the female urethra, and the female prostate embedded in it, to the urinary bladder with manifestations of cystitis, or possibly also a simultaneous inflammatory response of all these structures (urethro/prostato/cystitis). The rich mutual communication in the cavities of the system of the female urethra and prostate provides exceptionally good conditions for long-term survival of uropathogens in these areas, possibly accounting not only for relapses of female prostatitis but also potential recurrent episodes of urinary tract infections (UTI) appearing as acute cystitis. Acute cystitis is the commonest form of UTI, whose incidence in young women in the USA was reported to be 0.5-0.7 episodes per person per year (Hooton et al. 1996). About 25 % of women with acute cystitis develop frequently recurring infections (Foxman 1990). Stapleton (1999) was concerned with factors predisposing to recurrent UTI. Unfortunately, in her contribution there is no information on the female prostate and/or female prostatitis and UTI. We believe (Ablin and Zaviačič 1999 – Commentary, *Lancet*) that the contributory role of the female prostate to recurrent UTI is much more important than the majority of factors related to recurrent UTI as given by Stapleton (1999).

The paper by Gittes and Nakamura (1996) has considerable implications for clinical practice. The authors state that female prostatitis has actually to be treated as an inflammatory disease of the prostate (here the commonly given designation as Skene's paraurethral glands and ducts appears to be useless and counterproductive) and not as a disease of the urethra, as done so far. It is certainly time to stop performing forceful overdilatations of the urethra (Bergman et al. 1989) and administering anxiolytic and tricyclic antidepressant drugs to patients suffering from female prostatitis, an ailment affecting a great number of the female population in the USA as stated by Karram (1990), who reported more than 5 million visits of female patients with this problem in the office per year. Inflammation of the female prostate can be successfully treated by taking advantage of all the available possibilities of conservative therapy which have proved effective in treating inflammation of the prostate in the male.

Once physicians become aware of the fact that prostatitis as well as other diseases of the female prostate, such as benign hyperplasia and carcinoma, have to be treated as female prostatic and not other diseases, they will be equipped with therapeutic strategies and patterns verified and successfully used for years in the treatment of the same diseases in the male. New perspectives open up also for large pharmaceutical companies which have so far produced drugs for the treatment of the male prostate and have thus saturated the needs of one half of the population. They should broaden their production and sale of „prostatic“ drugs to satisfy also the needs of the female population suffering from diseases of the prostate.

It appears to be precocious to pronounce any conclusions on the incidence and prevalence of these female urological diseases of the prostate, especially on female benign prostate hyperplasia, prostatitis, or the combination of both diseases in one female patient. As mentioned in the introduction to this chapter, urologists and gynecological urologists, on taking the patient's history, have to ask targeted questions concerning the frequency of micturition and the degree of difficulty in voiding the

urinary bladder. This could be done also by questionnaires as are used in male patients with benign prostate hyperplasia, after appropriate modification of the questions presented. A further key requirement should be invariable rather than exceptional examination of the urethra at autopsy. Pathologists could thus help establish the as yet missing objective data on the actual incidence of diseases of the prostate in the female population.

Nevertheless, there are certainly some diseases of the urogenital tract that are and will remain characteristic of one gender while absent or rare in the other one.

Thus e.g. a situation which would result in paraphimosis or phimosis in the male is practically unknown in the female, presumably due to the substantially larger space between the prepuce and the glans clitoridis than between the prepuce and the glans penis in the male. An exception might present an enormous hypertrophy of the glans clitoridis with a short hood (prepuce), which at autoerotic stimulation of the clitoris or at petting activities may occasionally after an initially pleasant feeling induce one of traction and even discomfort in the region of the vulva (unpublished observation). Phimosis and particularly paraphimosis are relatively frequently occurring disorders in boys and men causing discomfort. Yet especially paraphimosis may present a serious complication requiring urgent surgical intervention. The difference between the genders is reflected also by the fact that the prepuce may become one of the causes of dyspareunia in the male but in the female it has not been mentioned among the causes of dyspareunia (Wabrek and Wabrek 1975). Priapism, on the other hand, does not affect males only. Painful priapism of the clitoris was described which resulted from retrograde neoplastic embolization of the corpora cavernosa of the clitoris by cervical carcinoma, and required surgical intervention (Lozano and Castañeda 1981).

Concomitant infection of the ducts and glands of the female prostate invariably accompanies acute gonorrhoeal urethritis and may persist as an undiscovered source of reinfection during the later stages of the disease (Huffman 1951). Female prostate secretion may contribute also to the development of vaginal flow. If the female prostate exhibits the immunopermissiveness observed in the male prostate (Ablin 1991), it may also serve as a site for viral latency and origin of infection in women with the human immunodeficiency virus (Zaviačič and Ablin 1998a). The ducts of the female prostate (paraurethral ducts) may at times harbor *Trichomonas vaginalis*. In recurrent or intractable vaginal trichomoniasis the female prostate ducts play a role in persistent reinfestations of the vagina (Huffman 1951).

In other diseases of the female prostate (Skene's glands), its involvement in acute and chronic inflammation of the urethra has been repeatedly emphasized. Huffman (1951) states: „The paraurethral ducts and glands (female prostate gland) are of clinical significance not only because they are foci for acute and chronic inflammation of the female urethra but also because of the diverse roles which they play in other lesions of the urethra and the urethrovaginal tissues. Suburethral abscesses develop in obstructed and infected retention cysts of the paraurethral (prostatic) ducts. These cysts and abscesses are important factors in the etiology of acquired urethral diverticula. Urethrovaginal fistulas may follow rupture of paraurethral (prostatic) duct abscesses into the vagina and urethra or severance of the channel of a prostatic (paraurethral)

duct during surgical procedures on the anterior vaginal wall“. Skene’s duct cysts, and mainly those larger than 2 cm, induce clinical symptoms including obstruction, dyspareunia and dysuria. Superposed infection may cause significant discomfort as well. Treatment usually consists of antibiotic management (Raz 1996).

After John W. Huffman (1951) apparently nobody did focus in so concentrated a form on the clinical significance of the female prostate. Relevant information is scattered in urological and gynecological journals, mostly as case reports. Although our knowledge has substantially broadened, particularly on carcinoma of the female prostate, concerning its other diseases Huffman’s findings are to be accepted even more than 40 years after their publication. One of the reasons may lie in the circumstance that interest in the female prostate and its diseases has appeared only in the last 10 – 15 years, following a relatively long period when this female organ was more or less ignored. We can only hope that a gynecologist or urologist, a new „Huffman“, will turn up who would study this female organ with the same enthusiasm as did his/her predecessor half a century ago. The publication by Gittes and Nakamura (1996) initiated an unexpectedly great response (Russi 1996; Peterson 1996; Zaviačič and Ablin 1998b), demonstrating that interest in the female prostate is much more intensive than it used to be, and that also among clinicians. However, despite the caution voiced by some doctors who long ago considered urethral dilatation alone unsatisfactory for treatment (Richardson and Stonington 1969), the attitude of some urologists to therapeutic dilatation of the urethra is still positive. In Comments to Gittes and Nakamura (1996) Peterson (1996) wrote: „A caliber of 38F in adults is necessary, and mild, temporary urethral bleeding is a favorable prognostic sign. Benefit is reflected in the patients who voluntarily return after varying intervals for retreatment when symptoms recur. The second dilatation is seldom as uncomfortable as the first“ (Peterson 1996).

The present boom of interest in the female prostate especially in clinicians might be promoted also by their insight that if we persist in doubting the existence of the female prostate as a functional organ we will hardly be able to explain without a great deal of speculation the origin of PSA in serum and urine of the healthy female (up to 0.9 ng/mL in female serum, Borchert et al. 1997). Contrary to the data of Diamandis et al. (1994), Yu et al. (1996), and Diamandis (1998), our immunohistochemical examinations of normal epithelial tissue of the female breast, as well of the male breast, failed to demonstrate PSA expression (Zaviačič et al. 1998b,c). Like in the male so in the female, the main producer of PSA is the prostate, whose secretory capacity determines the concentration of this prostatic marker in serum and urine (Zaviačič and Ablin 1998a, b, c). Even in cases of abnormal PSA production by hyperplastic or cancerous tissue of the female breast (Borchert et al. 1997) and of some other organs (Zaviačič et al. 1998c), the production of the female prostate does participate in the total serum and urinary PSA concentration, reflecting the sum of prostatic and extraprostatic PSA production (Zaviačič and Ablin 1998a; Zaviačič et al. 1998c).

Concluding this chapter on the pathology of the female prostate it can be stated that several findings on the diseased female prostate published in the past appear to emerge in new associations and relationships unknown before. This may be accounted for especially by advances in laboratory medicine marked by the introduction of highly sen-

sitive methods in immunochemical and immunohistochemical demonstration of prostatic markers. These approaches have not only broadened the diagnostic possibilities and made them more accurate in detecting diseases of the female prostate but have also provided means to monitor their course and assess the efficacy of the therapy applied. We are only in the initial phase, and further advances can be achieved by efficient support of clinical research into the problem of the female prostate. In this Monograph, we direct attention to some topical issues of the clinical problem area of the female prostate.

XI.

Reasons for Rejecting the Term Skene's Paraurethral Ducts and Glands in Designating the Prostate in the Human Female (Terminological Note)

The term *female prostate* was commonly used in the past and occurred frequently also in the first decades of our century, as seen in titles of papers given in the References of this Monograph. Later on, the term appeared mostly only in sexologically oriented literature (Sevely and Bennett 1978; Addiego et al. 1981; Belzer 1981; Perry and Whipple 1981; Ladas et al. 1982; Bohlen 1982; Mallon 1983; Belzer et al. 1984; Bullough et al. 1984; Heath 1984; Zaviačić 1987a), although there were also some sexologists who voiced arguments against its use (Alzate and Hoch 1986; 1988; Alzate 1990). The term *female prostate* has been commonly used in veterinary literature in describing prostatic tissue of females of different animal species (Shehata 1972; 1975; 1980; Ichihara 1976; Gross and Didio 1987). Papers published in sexologic or sexologically orientated journals have considerably contributed to the use of the term *female prostate* at a time when other medical journals stubbornly kept to the official terminology and refused to use any other designation than the official one of „Skene's paraurethral ducts and glands“.

In the 80s, and particularly in the later years of the decade, we witnessed the appearance of papers on the female prostate or female prostatic tissue using these terms also in journals of other than sexologic orientation (Longo 1982; Pollen and Dreilinger 1984; Tepper et al. 1984; Zaviačić 1984a, b; 1985a, b; 1986a, b; 1987b; Zaviačić et al. 1983; 1985b, c, 1987a, b; 1988d; 1989). Looking back at the last 15 years, I feel obliged to mention particularly the name of Professor R. Wegmann, Editor-in-Chief, who as early as in 1984, without any argument, accepted for publication in his journal *Molecular and Cellular Biology* our pioneer work on the enzymatic equipment of the female prostate (Zaviačić 1984a, b) with the term “*adult human female prostate*“ ap-

pearing in the title of the paper. In the majority of other journals (with the exception of the Histochemical Journal, Editor Prof. P. J. Stoward), even later on, we had to explain and defend the term again and again in our correspondence with the editors.

At present, the use of the term *Skene's paraurethral ducts and glands* for the female prostate fails to reflect the results published from the beginning of the 80s to date in the field of research into the problem of the female prostate. In his conclusions on the female prostate, the American gynecologist Alexander Skene was incorrectly concerned only with two paraurethral ducts, which however defies the actual state, as repeatedly described by several authors (Huffman 1948; 1951; Zaviačič et al. 1983; Zaviačič 1987a; Wernert et al. 1992; Zaviačič and Whipple 1993). Although Skene studied the female prostate 200 years after de Graaf, his contribution to the understanding of the structure and function of the female prostate does hardly justify the use of his name as eponym. Should however an eponym be used, it would only be appropriate to designate the female prostate by the name of de Graaf who was the first to refer to it by this term. The fact that after more than 300 years we have returned to the designation used by de Graaf is causally fully substantiated by convincing evidence.

Particularly important in this respect were the results of Mallon (1983), Pollen and Dreilinger (1984), Tepper et al. (1984), Zaviačič et al (1994) and Zaviačič (1995; 1997), showing expression of (male) prostate specific antigen (male PSA) in structures of Skene's paraurethral glands and ducts, namely demonstrating similar antigenicity between the male prostate gland and Skene's gland. Equally corroborating proved the results of histochemical studies on the enzyme equipment of the female prostate (Zaviačič 1984a, b), unknown before the early 80s. The enzyme equipment of the male and female prostate was found to be comparable (Zaviačič 1985a), including both immunohistochemical (Pollen and Dreilinger 1984) and histochemical (Zaviačič et al. 1984b) demonstration of prostatic and lysosomal acid phosphatase. It was the expression of PSA in Skene's glands and ducts and the finding of characteristic „prostatic“ and lysosomal acid phosphatase in Skene's glands, i.e. evidence of their exocrine function and equipment for neuroendocrine function, along with the increasing number of publications on diseases of the female prostate formerly considered to be characteristic diseases of the male prostate, and last but not least awareness of implications of the exocrine function of the female prostate in gynecologic urology, forensic medicine, sexology and chronobiology that provided conclusive evidence that the tissue concerned was actually prostatic tissue in the female, thus substantiating and justifying the preference of the term *female prostate* over that of *Skene's glands and ducts* (Zaviačič 1987a).

It appears to be illogical to use the term *prostate* for the tissue in the male and a different term (*Skene's glands and ducts or paraurethral glands and ducts*) for the same tissue in the female. The use of the term *Skene's paraurethral glands and ducts* wrongly implies that some other structure rather than the prostate is involved, promoting the vestigial notion concerning this female organ. In light of the new information and knowledge on this genitourinary organ, we advocate the renaissance of the term *female prostate*, its strict use in the same meaning as applies to this organ in the male, and inclusion of the term in *Nomina Anatomica*. The term *prostata feminina* does not

appear in the Fifth Edition of *Nomina Anatomica* published in 1983, or in any of the previous editions issued in 1955, 1961, 1963, 1966, 1968, 1977 (Allan et al. 1983). Neither did, for that matter, the Sixth Edition of *Nomina Anatomica* along with the *Nomina Histologica* and *Nomina Embryologica* (Third Edition) from 1989 give the term *prostata feminina*. Since the time of the Paris Anatomical Terminology (Parisiensia *Nomina Anatomica* 1955), the *Nomina Anatomica* have avoided the use of the eponym and Skene's name has not appeared in relation to the female prostate. The organ is given under the anatomico-histological term *paraurethral ducts and glands*. In clinical practice, with its relatively liberal approach to terminology and ready acceptance of synonyms and eponyms, the designation of the female prostate under Skene's name has persisted. Gynecologists and urologists appear to be rather conservative in this respect. Skene did not detect the female prostate and there is thus no reason to use his name considering the meaning of the Greek word eponymos, i.e. giving a name to somebody or something. Eponyms are usually conferred in honor of a person closely related to the given phenomenon, mostly by having detected or discovered it. The problem would however not be eliminated if we just avoided Skene's name and used instead the term *paraurethral glands and ducts*, while the objectively justified term *female prostate* would be missing in *Nomina Anatomica*. Nor do we see a solution in using the term *prostate* for the prostate gland in the male and *female prostate* for that in the female, although this might be regarded as a compromise. The optimal, most exact mode reflecting the actual situation appears to be the use of the terms the *male prostate* and the *female prostate*, separately for each gender, as we have repeatedly recommended (Zavaičič 1987a; Zavaičič and Whipple 1993; Zavaičič and Ablin 1998a, b, c).

The situation is probably not unlike that applying to the term *mamma masculina* and *glandula mammaria – mamma feminina*, both to be found in *Nomina Anatomica*, in spite of differences in the size of these structures in the male and female, which in some cases are certainly greater than between the male and female prostate. Moreover, the male breast consists only of scattered ducts lined by epithelial and myoepithelial cells, embedded in fibrofatty connective tissue, lactiferous sinuses are absent and there is no lobule formation (Ahmed 1992). And yet, not even with respect to missing structures in the male breast compared to the female breast, and considering the exceptionally rare pathology of this male gland confined to gynecomastia and carcinoma, affecting the male at a much later age than the female (Ahmed 1992), none of the differences has been considered so significant as to justify exclusion of the term *mamma masculina* from *Nomina Anatomica*. Even the greatest sceptic has to admit that the number of corresponding parameters between the female and male prostate is incomparably higher than between the female and male breast. Nevertheless, the term *the female prostate* does not occur in *Nomina Anatomica*, while the term *the male breast (mamma masculina)* is listed along with the term *the female breast (mamma feminina)* in the Fifth and Sixth Edition of *Nomina Anatomica* issued in the respective years of 1983 and 1989.

Summarizing the knowledge on the female prostate, including recently published information, it is to be stated that in the female the notion of the prostate as an insignificant, afunctional, vestigial Skene's gland (Skene's paraurethral glands and ducts in

the female) has completely lost its substantiation. It can however hardly be expected that so controversial a problem as that of the female prostate has been for over 300 years would be simply and unequivocally solved for each and every person involved in this field of interest. The recent more than 15 years of intensive research into the function and pathology of the female prostate, building on the high-quality morphological studies of the 40s and 50s, have clearly justified the inclusion of this small organ functioning as the female prostate into *Nomina Anatomica* under the term it deserves. In light of the copious discussions mentioned in this monograph and published in our papers, the equivalent position of the female prostate with other female genitourinary organs and particularly with the male prostate should by now be accepted. This would apply not only to urologists, gynecologists and pathologists, but practically to all physicians and doctors, even those not closely involved in the given problem area. The attitude of physicians can clearly influence also the level of information reaching the lay population who still consider the female prostate as a „mystery female organ“ (Zaviačič and Ablin 1998c).

Summary

Comparably to the majority of organs in the male and in the female, the parameters of the female prostate (size, weight, and apparently also functional capacity) are smaller than those of the male prostate.

While the male prostate surrounds the urethra, the female prostate lies in the wall of the female urethra. This is the basic macroscopic difference between the male and female prostate glands. The thickness of the wall and the length of the female urethra thus limit the size of the prostate, which for these reasons is smaller than the prostate in the male. Nevertheless, despite the smaller space available for the female prostate, it possesses all the structural components characteristic of the male prostate.

The mean weight of the prostate of the adult female is 5.2 g and its size is 3.3 cm (length) x 1.9 cm (width) x 1.0 cm (height). If we consider the meatal type, the most frequent type of the female prostate occurring in approximately 70 % of adult women and presenting the greatest amount of prostatic tissue in the distal half of the female urethra, then the weight of the female prostate would vary within the range of 2.6 to 5.2 g and represent roughly one tenth to one fifth or one quarter of the mean weight (23.7 g) of the adult male prostate.

The female prostate possesses histologically the same structures as the prostate of the male, i.e. glands, ducts, and smooth musculature. The ducts are more numerous than the glands and they exceed in number also the ducts in the male prostate. The smooth musculature (musculofibrous tissue) are also more abundant in the female compared to the male prostate. The prostatic (paraurethral) ducts do not open into the vulva on the sides of the meatus of the female urethra, they rather penetrate into the lumen of the urethra along its whole length, and it is through the urethra and not through separate openings that the female prostate discharges its contents.

Similarly as the prostate in the male, the female prostate has at least two main functions: exocrine – production of female prostatic fluid – and neuroendocrine function. The exocrine function of the female prostate is reflected by its particular structure, including the presence of secretory and basal cells with their characteristic ultrastructural appearance. Tall cylindrical secretory (luminal) cells are the predominant type both in the female and male prostatic glands. Apical cytoplasm contains abundant

secretory elements (secretory vacuoles and granules), rough endoplasmic reticulum, developed Golgi complexes and numerous mitochondria. These organelles characterize the active secretory configuration of female prostatic secretory cells with apocrine (apical blebs) and merocrine (secretory vacuoles and granules) type of secretion.

Basal (reserve) cells were seen to be located between the secretory cells and the basement membrane. Their ground cytoplasm is dense with rough endoplasmic reticulum and mitochondria, without secretory elements. Their nuclei, unlike those of secretory cells, possess more peripheral condensed chromatin, dense dispersed chromatin, and sporadic nucleoli.

Besides the two basic types of mature prostatic cells there are also intermediary cells, located between the basal and secretory cells or in their close vicinity. Their cytoplasm exhibits numerous profiles of rough endoplasmic reticulum and free ribosomes. Secretory granules are practically absent (type 1 intermediary cells), so that they resemble basal (reserve) cells. In some of them, however, similarly as in secretory cells, secretory elements do appear (type 2 intermediary cells). The finding of intermediary cells supports the assumed function of basal (reserve) cells in the renewal of cells in the female prostate glands, comparably to the role played by intermediary cells in the male prostate. Ultrastructural analysis of the normal female prostate performed by transmission electron microscopy confirmed that, similarly as in the postpubertal male, the prostatic glands in the adult female display morphologically mature secretory and basal cells.

Like in the male also in the female prostate, especially in its luminally located secretory cells, lysosomal and prostatic (specific) acid phosphatase was determined histochemically using Gomori's, azo-coupling and Serano's methods. Histochemical demonstration of E-600 sensitive esterase and glucose-6-phosphatase with further enzymes indicates secretory activity of female prostatic cells. These enzymes involved in proteosynthesis participate in the production of female prostatic fluid. Concerning the spectrum of the enzymes determined, the enzyme equipment of the male and female prostate is comparable. Differences were however observed in the activity of some prostatic enzymes (naphthyl esterase, glucose-6-phosphatase, some dehydrogenases) in women of childbearing age compared to women after menopause, potentially indicative of a varying functional capacity of the prostate in the course of woman's life.

Prostate-specific antigen (PSA) is currently the most frequently used marker for identification of normal and pathologically altered prostatic tissue in the female. Immunohistochemically, PSA is expressed in the highly specialized apically-superficial layer of female secretory cells of the prostate as well as in uroepithelial cells at other sites of the female urogenital tract. In clinical practice, PSA is a valuable marker in diagnosis and monitoring of diseases of the female prostate, particularly carcinoma. Besides other evidence, the non-vestigial concept of the female prostate is at present based on the demonstration of similar antigenicity between the male prostate and Skene's paraurethral glands, as evidenced by PSA and prostate-specific acid phosphatase (PSAP) positivity. Expression of the highly specific male prostate antigen in Skene's glands justifies by itself the use of the term *prostate* in the female. It defies logical consideration to refer to prostatic tissue in the male as *prostate* and to the same tissue in the female as *Skene's paraurethral glands and ducts*.

Considering the immunohistochemical absence of PSA expression in normal breast epithelial structures and the minimal and variable PSA expression in some normal extraprostatic tissues (membranes of adipocytes, apocrine sweat glands, small vessel endothelium, gastric parietal cells), it is evident that in the female, similarly as in the male, the prostate is the principal source of PSA. With respect to pathological breast tissue, and/or other pathological tissues known to produce PSA, the total amount of PSA in serum and urine is the summation of the production by the normal prostatic and the anomalous extraprostatic pathological tissue in the male and female patient.

For neuroendocrine production, the female prostate is richly equipped with neuroendocrine cells, especially in the lining of prostatic ducts. These cells display immunohistochemical positivity for neuron specific enolase, chromogranin A, and urinary protein 1. Using silver staining, these cells were found to be positive by the Grimelius and less by the Sevier and Munger method, and exceptionally also by the Masson and Hamperl argentaffin method. The majority of these cells are in contact with the lumen of the female prostate ducts and represent the open type of neuroendocrine cells. In the male, the range of hormonal polypeptides produced by neuroendocrine cells of the prostate is well known. In the female, however, immunohistochemically only the production of serotonin by female prostatic neuroendocrine cells has so far been established. To date we are but at the beginning in the study of the female prostate as a further neuroendocrine organ, a constituent part of the diffuse neuroendocrine system of the woman.

Our insight into the exocrine function of the female prostate in producing female prostatic fluid is much more developed than our knowledge on its neuroendocrine function. It is true that pure female prostatic fluid has not yet been isolated and it has been studied only as a component of the female ejaculate, whose substantial component it actually is. Nevertheless, important features of the biological phenomenon of female ejaculation and of the fluid of urethral expulsions (female ejaculate) have been gradually revealed, which appear to have implications for a variety of medical disciplines.

Morphologically, the female ejaculate was found to be produced by cellular, mucinous, and urinary components. The cellular component of the female ejaculate is formed by squamous cells of the vaginal type, originating mainly from the lining of the female urethra and large prostatic (paraurethral) ducts. The qualitative rhythm of uroepithelial squamous cells (cellular component of the female ejaculate) during the menstrual cycle allows to use the cellular component for hormonal urocytology in those cases where vaginal smears can not be obtained. On biochemical analysis, the fluid of urethral expulsions (female ejaculate) was found to have a significantly higher concentration of components arising from the female prostate, namely prostatic acid phosphatase and especially prostate-specific antigen, and a significantly lower concentration of urea and creatinine than urine specimens taken from the same women.

Chronobiological analysis of female ejaculate during the menstrual cycle exhibited a quantitative circatrigintan rhythm (30 ± 5 days) of cellular component volume of the female ejaculate (female urethral expulsion fluid) with acrophase during the secretory phase of the menstrual cycle. At that time reduction in the height of the urethral epithe-

lium appears, weakening the closing sphincter mechanism of the urethra. During the secretory phase of the menstrual cycle conditions develop which facilitate the occurrence of urinary incontinence, in contrast to the first half of the cycle when fewer cells are released into the ejaculate, the epithelium remains in situ, and the closing sphincter mechanism of the urethra can operate effectively.

Forensic aspects of the female ejaculate, containing female prostatic fluid, and the female ejaculation phenomenon as such concern two issues: critique of the significance of the acid phosphatase test in evidence of rape in women and the possibility to study modes of secretory mechanisms of the female prostate. In providing expert evidence of rape in women, the acid phosphatase test was found to be without forensic significance in identifying sperm spots which contain no spermatozoa, since the same acid phosphatase positivity was established in *in vitro* formed spots of female ejaculate and in *in vivo* originated spots on used female lingerie. Thus positively reacting spots may originate from the woman herself, without male participation. At present, in the time of forensic DNA analysis, macroenzyme histochemical findings are of historical rather than forensic importance in providing evidence of rape in women.

On the other hand, macroenzyme histochemical findings of acid phosphatase on those parts of used underwear which are in constant contact with the female genitals are indicative of the existence of continual secretion of the female prostate. The hypothesis has been put forward that the continual type of female prostate secretion (with fructose in the female prostatic fluid) may come into play in the human reproductive process as far as motility of spermatozoa is concerned. Thus both the male and the female appear to affect the concentration of fructose in the vaginal environment. The basal amount of fructose in the vagina is represented by female fructose, which at continual secretion of the female prostate flows under gravitational forces from the urethra into the vagina. At coital ejaculation of the male into the vagina, this basal level is considerably increased by fructose from the seminal vesicles. Sperm motility could thus be affected also by the female, though certainly to a far lesser degree than by fructose which is of male origin. Since this parameter is of particular importance for successful fertilization of the egg by the highest-quality sperm, it is conceivable that female mechanisms may also be involved in securing the desirable result. Similarly as in the male, initiation of female prostate secretion precedes the onset of puberty.

The ejaculation mechanism, the biological phenomenon of urethral expulsions in the female, which contrary to the male is not directly involved in reproduction yet remains an attractive phenomenon of female sexuality, is a further mode of evacuation of the prostate in the female. It is most frequently induced by stimulation of the erotically sensitive spot on the anterior wall of the vagina, the so-called G-spot. Stimulation of the clitoris or suprapubic massage of the urinary bladder neck are relatively rare modes of inducing urethral expulsions. Asphyxia accompanying strangulation, suffocation and hanging, typical phenomena in the experience of forensic doctors at autopsy, were also found to trigger urethral expulsions (female ejaculation). Knowledge that the female ejaculation phenomenon may potentially play a role also in the motivation of life threatening eroticizing paraphilic behavior – sexual asphyxiophilia

(Koczwarism) in women could improve diagnosis of these lethal cases often mistaken for suicide rather than fatal accidents that they actually are.

Study of the pathology of the female prostate has remained underresearched due to the long-lasting lack of interest in this female organ shown by urologists, gynecologists, gynecological urologists as well as pathologists. When critically evaluating our present knowledge on the pathology of the female prostate, we have to admit that compared to the clinical studies of Huffman published fifty years ago, considerable advancement has been made only in the problem of female prostate carcinoma. Immunohistochemical expression of PSA and PSAP in tumor cells and in metastases has been used to advantage in diagnosing female prostate carcinoma and serum PSA determination has proved beneficial in monitoring the disease. For the pathologist, positive immunohistochemical PSA staining will apparently become an important indicator in distinguishing between „true prostatic“ adenocarcinomas and other, yet PSA negative adenocarcinomas of the female urethra, occurring frequently in relation to urethral diverticulum. The latter are not assumed to originate from the female prostate, but have been suggested to be rather of mesonephric origin. As far as other diseases of the female prostate are concerned, such as benign prostate hyperplasia, prostatitis (female urethral syndrome), and prostatism, our knowledge is based mainly on case reports while a conceptual description of these diseases is still lacking. Neither pathologists nor gynecological urologists have provided reliable data on the incidence of diseases of the female prostate. As a consequence, unlike the male prostate, the female prostate is largely considered not to be affected by „prostatic“ diseases and this false traditional view may bias some authors to believe in the vestigial concept of the female prostate. Mapping of the actual incidence of prostatic diseases in the woman and insight into functions of the non-vestigial female prostate may open completely new clinical possibilities in the therapy of this organ. Diseases of the female prostate have been mostly incorrectly diagnosed as diseases of the female urethra and also treated as such. Thus e.g. dilatation of the urethra and tranquilizers were used in urethral syndrome (female prostatitis). Dilatation of the urethra has been applied also in other forms of urethral obstruction in female patients with retention syndrome, which may be caused by some other female prostatic disease as well (benign hyperplasia of the female prostate?). All other potential pathological changes frequently occurring in this region have however to be excluded. In treating the pathologically altered female prostate, urologists have not even tried to use the broad possibilities of highly effective and verified conservative treatment and the successful therapeutic strategies applied in the same diseases of the prostate in men. These remarks are intended to stimulate the interest of clinicians into problems of the female prostate and to further develop their insight acquired in relation to female PSA determined by means of sophisticated highly sensitive laboratory methods (IMMULITE – immunochemiluminescent third generation assay).

Compared to its male counterpart, the female prostate does not only have a similar structure, expression of prostate markers, enzyme equipment, the same exocrine and possibly neuroendocrine function but it may also be the site of origin of similar serious „prostatic“ diseases, such as prostatitis, prostatism, benign prostate hyperplasia and

carcinoma. Expression of the antigen specific for the male prostate, PSA, in female Skene's paraurethral glands and ducts, along with structural and functional parameters as well as diseases similar to those of the male prostate have provided convincing evidence on the existence of a functional prostate in women. All this seems to fully justify the definitive preference of the term "*prostate*" over that of "*Skene's paraurethral glands and ducts*". The use of Skene's eponym and/or the term *paraurethral glands and ducts* in referring to the female prostate incorrectly implies that some other structure rather than the prostate is involved and promotes the vestigial notion of this female organ.

The fluid of female urethral expulsions (female ejaculate) contains female prostatic components, mainly PSA and PSAP, and also fructose, which clearly confirms, particularly with respect to the first two parameters, participation of the prostate in the production of female ejaculate. The female ejaculate (fluid of female urethral expulsion) exhibits properties important for specific issues in urology, gynecological urology, chronobiology, sexology, forensic sexology, forensic medicine and reproductive medicine. Insight into the female ejaculation phenomenon may lead to resolution of several problems concerning issues of female urinary incontinence, secretory modes of the female prostate, evidence of rape in women, exfoliative hormonal urocytology, as well as the quality of female sexual life, presenting female ejaculation as a normal and often attractive phenomenon of the woman's sexuality.

Súhrn

Podobne ako pri väčšine orgánov muža a ženy, je aj ženská prostata orgánom, ktorého parametre (veľkosť, hmotnosť a zrejme aj funkčná výkonnosť) sú menšie v porovnaní s prostatou muža.

Zatiaľ čo prostata muža obklopuje uretru, prostata ženy je uložená v stene ženskej močovej rúry. Toto je základný makroskopický rozdiel medzi prostatovými žľazami muža a ženy. Hrúbka steny a dĺžka ženskej uretry tak obmedzujú veľkosť ženskej prostaty, ktorá je z uvedených dôvodov menšia ako mužská prostata. Napriek menšiemu priestoru, ktorý má ženská prostata k dispozícii, tvoria ju všetky štruktúrne komponenty charakteristické pre mužskú prostatu.

Priemerná hmotnosť prostaty dospelaj ženy je 5,2 g a jej veľkosť 3,3 cm (dĺžka) x 1,9 cm (šírka) x 1 cm (výška). Ak považujeme „meatálny typ“ za najčastejší typ ženskej prostaty vyskytujúci sa približne u 70 % dospelých žien, s najväčším množstvom prostatového tkaniva v distálnej polovici ženskej uretry, potom hmotnosť ženskej prostaty kolíše od 2,6 g do 5,2 g a predstavuje zhruba 1/5 až 1/4 respektíve 1/10 priemernej hmotnosti prostaty (23,7 g) dospelého muža.

Ženská prostata má histologicky tie isté časti ako prostata muža, t.j. žľazy, vývody a hladkú svalovinu. Vývody sú početnejšie ako žľazy a prevyšujú tiež počet vývodov mužskej prostaty. Hladkej svaloviny (svalovofibrózneho tkaniva) je viac v ženskej prostate v porovnaní s prostatou muža. Prostatové (parauretrové) vývody nevyúsťujú do vulvy po stranách vchodu (meatu) ženskej uretry, ale vnikajú do lumenu uretry v celom jej priebehu. Tak cez močovú rúru a nie cez osobitné vývody ženská prostata uvoľňuje svoj obsah.

Ženská prostata má rovnako ako prostata muža najmenej dve funkcie: exokrinnú – produkciu ženskej prostatovej tekutiny a neuroendokrinnú funkciu.

Exokrinná funkcia ženskej prostaty je obrazom jej osobitnej štruktúry s prítomnosťou sekrečných a bazálnych buniek charakteristického ultraštruktúrneho vzhľadu.

Vysoké cylindrové sekrečné (luminálne) bunky sú najčastejšími bunkami ženských prostatových žliaz, rovnako ako je tomu v žľazách mužskej prostaty. Apikálna cytoplazma obsahuje početné sekrečné elementy (sekrečné vakuoly a granuly), drsné endoplazmové retikulum, vyvinutý Golgiho komplex a početné mitochondrie. Tieto orga-

nely charakterizujú aktívnu sekrečnú konfiguráciu ženských prostatových sekrečných buniek s apokrinným (apikálne mechúriky) a merokrinným (sekrečné vakuoly a granuly) typom sekrécie.

Medzi sekrečnými bunkami a bazálnou membránou sú uložené bazálne (rezervné) bunky. Ich základná cytoplazma je denzná s drsným endoplazmovým retikulom a mitochondriami, ale bez sekrečných elementov. Jadrá týchto buniek na rozdiel od jadier sekrečných buniek majú viac periférneho kondenzovaného chromatinu, denzný disperzný chromatin a zriedkavé jadierka.

Okrem dvoch základných typov prostatových buniek sa našli tiež prechodné bunky, uložené medzi bazálnymi a sekrečnými bunkami alebo v ich tesnej blízkosti. Ich cytoplazma obsahovala početné profily drsného endoplazmového retikula a voľné ribozómy. Sekrečné vakuoly a granuly v nich väčšinou chýbali (1. typ prechodných buniek), tým sa podobali na bazálne bunky. V niektorých však, rovnako ako v sekrečných bunkách, sa tieto sekrečné elementy postupne objavovali (2. typ prechodných buniek). Nález prechodných buniek podporuje úlohu bazálnych (rezervných) buniek pri obnove buniek žľazy ženskej prostaty. Rovnakú úlohu majú prechodné bunky v mužskej prostate. Ultraštruktúrna analýza normálnej ženskej prostaty transmisným elektrónovým mikroskopom ukazuje, rovnako ako u muža po puberte, že prostatové žľazy dospelaj ženy tvoria morfológicky zrelé sekrečné a bazálne bunky.

Rovnako ako u muža, aj v žľazách ženskej prostaty, osobitne v luminálne lokalizovaných sekrečných bunkách, sa histochemicky dokázala lyzozómová a prostatová (špecifická) kyslá fosfatáza a to pomocou metód podľa Gomoriho, Seranu a azokopulačných techník. Histochemický dôkaz E-600 senzitivity esterázy, glukóza-6-fosfatázy a ďalších enzýmov poukazuje na sekrečnú aktivitu buniek ženskej prostaty. Tieto enzýmy sa zúčastňujú na proteosyntéze pri produkcii ženskej prostatovej tekutiny. Čo sa týka spektra dokazovaných enzýmov, enzýmové vybavenie mužskej a ženskej prostaty je porovnateľné. Pozorovali sa však rozdiely v aktivitách niektorých enzýmov (naftyl esterázy, glukóza-6-fosfatázy, niektorých dehydrogenáz) v prostate žien fertillného veku a žien po menopauze, čo by mohlo poukazovať na rozdielnú funkčnú kapacitu prostaty počas života ženy.

Prostatový špecifický antigén (PSA) je v súčasnosti najčastejšie využívaným markerom na identifikáciu normálneho a patologicky zmeneného prostatového tkaniva ženy. Imunohistochemicky je PSA lokalizovaný vo vysoko špecializovanej apikálno-povrchovej vrstve ženských prostatových sekrečných buniek ako aj uroepitelových buniek na iných miestach ženského močovopohlavného systému. V klinickej praxi je PSA významným markerom uľahčujúcim diagnostiku a monitorovanie ochorení ženskej prostaty, najmä karcinómu. Súčasná nevestigiálna koncepcia prostaty u ženy sa okrem iných dôkazov zakladá na demonštrácii rovnakých antigénových epitopov medzi mužskou prostatou a Skeneovými parauretrovými žľazami, čo dokazuje najmä prítomnosť PSA a prostatovej špecifickej kyslej fosfatázy (PSAP). Expresia vysoko špecifického antigénu mužskej prostaty v Skeneových žľazách a vývodoch oprávňuje sama osebe použitie termínu „ženská prostata“. Javí sa nelogickým hovoriť o prostatovom tkanive muža ako o prostate a o tom istom tkanive ženy ako o Skeneových parauretrálnych žľazách a vývodoch.

Ak nebereme do úvahy chýbanie expresie PSA v normálnych epitelových štruktúrach prsníka ženy a muža pri imunohistochemickom vyšetrení a jeho minimálnu a varujúcu expresiu v niektorých normálnych extraprostatových tkanivách (v membránach tukových buniek, apokrinných potných žľazách, endotele malých ciev, žalúdočných parietálnych bunkách), je zrejmé, že u ženy rovnako ako u muža je prostata hlavným zdrojom PSA. V patologicky zmenených tkanivách prsníka a v ďalších patologických tkanivách, o ktorých je známe, že tvoria PSA, je celkové množstvo PSA v sére a v moči súčtom normálnej prostatovej a anomálnej extraprostatovej produkcie patologicky zmenenými tkanivami muža a ženy.

Pre neuroendokrinnú funkciu má ženská prostata bohaté vybavenie neuroendokrinnými bunkami, nachádzajúcimi sa osobitne vo výstelke prostatových vývodov. Tieto bunky vykazujú imunohistochemickú pozitívitu neurónovej špecifickej enolázy, chromogranínu A a močového proteínu 1. Pri striebreniach sú tieto bunky pozitívne pri Grimeliusovej, menej Sevierovej a Mungerovej metóde a výnimočne aj pri Massonovej a Hamperlovej argentafinnej metóde. Väčšina týchto buniek komunikuje s lumenom vývodov ženskej prostaty a predstavuje otvorený typ neuroendokrinných buniek. Spektrum hormónových polypeptidov produkovaných neuroendokrinnými bunkami mužskej prostaty je andrológom už dobre známe. Na rozdiel od toho bola doteraz imunohistochemicky dokázaná v ženských prostatových bunkách len produkcia serotonínu. Musíme konštatovať, že pri štúdiu ženskej prostaty, ako ďalšieho neuroendokrinného orgánu, ktorý je súčasťou difúzneho neuroendokrinného systému ženy, sme len na začiatku.

Naše znalosti o exokrinnej funkcii ženskej prostaty pri produkcii ženskej prostatovej tekutiny sú podstatne konkrétnejšie v porovnaní so znalosťami o jej neuroendokrinnnej funkcii. Napriek tomu, že sa doteraz nepodarilo izolovať čistú ženskú prostatovú tekutinu, ktorá bola doteraz študovaná len ako súčasť ženského ejakulátu, ktorého podstatnou časťou skutočne aj je, postupne sa objavili dôležité implikácie biologického fenoménu ženskej ejakulácie a tekutiny uretrových expulzií (ženského ejakulátu) v najrôznejších medicínskych disciplínach.

Ukázalo sa, že ženský ejakulát morfológicky tvorí bunková, mucinózna a močová zložka. Bunkový komponent ženského ejakulátu tvoria dlaždicové bunky vaginálneho typu, ktoré pochádzajú hlavne z výstelky ženskej močovej rúry a veľkých prostatových (parauretrových) vývodov. Kvalitatívny rytmus uroepitelových dlaždicových buniek (bunkový komponent ženského ejakulátu) počas menštruačného cyklu ponúka možnosť využiť ho na hormónovú urocytológiu v tých prípadoch, kde nie je možné získať stery zo sliznice pošvy. Pri biochemickej analýze tekutiny uretrových expulzií (ženského ejakulátu) boli signifikantne vyššie hladiny zložiek pochádzajúcich zo ženskej prostaty, prostatová kyslá fosfatáza a najmä prostatový špecifický antigén, so signifikantne nižšími hodnotami močoviny a kreatinínu v porovnaní s hodnotami vo vzorkách moču od tých istých žien.

Chronobiologická analýza ženského ejakulátu počas menštruačného cyklu ukazuje kvantitatívny cirkatrigintánny rytmus (30 ± 5 dní) objemu bunkovej zložky ženského ejakulátu (tekutiny ženských uretrových expulzií) s akrofázou počas sekrečnej fázy menštruačného cyklu. V tomto čase dochádza k zníženiu výšky epitelovej výstelky

uretry, čo vedie k oslabeniu uzáverového sfinkterového mechanizmu uretry. Počas sekrečnej fázy menštruačného cyklu sa vytvárajú u ženy podmienky uľahčujúce výskyt inkontinencie moču, na rozdiel od prvej polovice cyklu, kedy sa oveľa menej buniek uvoľňuje do ejakulátu, epitélie zostávajú *in situ* a sfinkterový uzáverový mechanizmus uretry môže efektívnejšie fungovať.

Forenzno medicínske aspekty ženského ejakulátu, (ktorý obsahuje ženskú prostatovú tekutinu) a ženského ejakulačného fenoménu sa týkajú dvoch otázok: kritiky významu kyslej fosfatázy ako testu pri dôkaze znásilnenia ženy a možnosti študovať spôsoby sekrečných mechanizmov ženskej prostaty. Pre vypracovanie znaleckého posudku pri znásilnení ženy sa ukázalo, že test na kyslú fosfatázu pri identifikácii škvŕn zo spermy, ktorá neobsahuje spermatozoá, nemá forezný význam, pretože rovnakú pozitívitu kyslej fosfatázy vykazujú *in vitro* vytvorené škvŕny zo ženského ejakulátu a *in vivo* vzniknuté škvŕny na používanej ženskej bielizni. Pozitívne reagujúce škvŕny môžu tak pochádzať od samotnej ženy, bez účasti muža. V súčasnej dobe forezných DNA analýz používaných pri dokazovaní znásilnenia ženy majú demonštrované makroenzýmovohistochemické nálezy viac historický ako justičný význam.

Pravda, makroenzýmovohistochemické nálezy kyslej fosfatázy na používanej ženskej bielizni na tých miestach, ktoré sú v trvalom kontakte s ženskými genitáliami poukazujú na existenciu kontinuálnej sekrecie ženskej prostaty. Je postavená hypotéza, že kontinuálny typ sekrecie ženskej prostaty (s fruktózou v ženskej prostatovej tekutine) môže hrať určitú úlohu v reprodukčnom procese človeka z hľadiska ovplyvnenia pohyblivosti spermií. Zdá sa, že muž a žena by mohli spoločne vplyvať na hladinu fruktózy v prostredí vagíny. Základné (bazálne) množstvo fruktózy vo vaginálnom prostredí reprezentujúce ženskú fruktózu pri kontinuálnej sekrécii ženskej prostaty, keď jej sekret v malých množstvách steká gravitáciou z uretry do vagíny, by sa po koitálnej ejakulácii muža do vagíny podstatne zvyšovalo o fruktózu pochádzajúcu z jeho seminálnych vezikúl. Tak by aj žena mohla ovplyvňovať, aj keď ďaleko menšou mierou ako muž, svojou fruktózou pohyblivosť spermií. Vzhľadom na to, že tento parameter má osobitý význam pre úspešnosť oplodnenia vajíčka biologicky najkvalitnejšou spermiou, je skutočne možné, aby bol tento proces pre svoju dôležitosť istený aj druhým (ženským) pohlavím. Začiatok sekrecie ženskej prostaty, rovnako ako u muža, predbieha začiatok puberty.

Ejakulačný mechanizmus (biologický fenomén ženskej ejakulácie, uretrové expulzie ženy), ktorý nemá na rozdiel od muža bezprostredný význam pre reprodukciu, ale bol a zostal atraktívnym fenoménom ženskej sexuality, je ďalším spôsobom, ako sa vyprazdňuje prostata ženy. Je vyvolaný najčastejšie stimuláciou eroticky citlivého miesta na prednej stene vagíny (tzv. G spotu). Menej často sa vyvolávajú expulzie stimuláciou klitorisu, alebo suprapubickou masážou krčka močového mechúra. Ukázalo sa, že dôležitú úlohu pri vyprovokovaní uretrových expulzií (ejakulácie ženy) môže mať asfyxia aká sprevádza škrtenie, dusenie a obesenie, teda typických fenoménov s ktorými sa bežne stretáva súdny lekár pri súdnej pitve. Poukázalo sa aj na možnú úlohu ženského ejakulačného fenoménu v motivácii život ohrozujúceho erotizujúceho parafilného správania sa – sexuálnej asfyxiófilie (Koczwarizmu) u ženy a na možnosť zlepšenia diagnózy takýchto úmrtí, ktoré bývajú často chybné považované za samovraždy a nie za smrteľné nehody, akými v skutočnosti aj sú.

Štúdium patológie ženskej prostaty zostáva nedostatočne spracovanou problematikou v dôsledku dlho pretrvávajúceho nezáujmu urológov, gynekológov, gynekologických urológov, ale aj patológov o tento ženský orgán. Ak kriticky zhodnotíme naše doterajšie vedomosti o patológii ženskej prostaty, musíme priznať, že v porovnaní s klinickou prácou Huffmana, publikovanou pred päťdesiatimi rokmi, došlo k významnému rozšíreniu našich znalostí len v prípade karcinómu ženskej prostaty. Pre diagnózu karcinómu ženskej prostaty sa s úspechom využíva imunohistochemická pozitivita PSA a PSAP v nádorových bunkách a v metastázach tohto karcinómu, ale aj stanovenie PSA v sére pacientiek pre jeho monitorovanie počas ochorenia. Pre patológov imunohistochemická pozitivita PSA a PSAP v nádorových bunkách je dôležitým indikátorom na odlíšenie „pravých prostatových“ adenokarcinómov od iných adenokarcinómov ženskej uretry, ktoré často vznikajú z divertikulov uretry a sú PSA negatívne. O týchto sa predpokladá, že nepochádzajú zo ženskej prostaty, ale majú mezonefroidný pôvod. V prípade iných ochorení ženskej prostaty, benígnej prostatovej hyperplázie, prostatitídy (ženského uretrového syndrómu) a prostatizmu nebola problematika týchto ochorení zatiaľ spracovaná koncepčne a opiera sa skôr len o kazuistiky. Doteraz nemáme k dispozícii údaje patológov a gynekologických urológov o skutočnej incidencii ochorení prostaty u ženy, čo vyvoláva dojem, že ženská prostata na rozdiel od prostaty muža „prostatovými“ ochoreniami netrpí, a tak sa to aj traduje, čo opäť podporuje vestigiálne chápanie tohto malého, fungujúceho ženského orgánu niektorými odborníkmi. So zmapovaním incidencie prostatových ochorení ženy a osvojením si súčasnej nevestigijálnej koncepcie fungujúcej ženskej prostaty sa otvárajú celkom nové klinické možnosti pri liečbe ochorení ženskej prostaty. Ochorenia ženskej prostaty sa doteraz nesprávne diagnostikujú väčšinou ako ochorenia ženskej uretry a takto sa aj liečia, napríklad pri uretrovom syndróme (ženskej prostatitíde) dilatáciou ženskej uretry a trankvilizérmami. Dilatácia uretry sa používa aj pri iných formách obštrukcie uretry u žien s retenčným syndrómom, ktorého príčinou by mohlo byť aj iné ženské prostatové ochorenie (benígna hyperplázia ženskej prostaty ?), pravda, s dôsledným vylúčením všetkých iných možných patologických zmien často sa vyskytujúcich v tejto oblasti. Urológovia doteraz pri liečbe patologicky zmenenej ženskej prostaty vôbec nevyužívajú a ani sa nepokúsili využiť široké možnosti overenej vysoko efektívnej konzervatívnej liečby a osvedčené terapeutické stratégie, používané pri tých istých ochoreniach prostaty u muža. Tieto konštatovania môžu podnietiť ďalší záujem klinických lekárov o tento ženský orgán a ďalej iniciovať získavanie potrebných klinických poznatkov, ktorých impulzy sa už objavili v súvislosti so ženským PSA pri použití súčasných vysoko citlivých laboratórnych metód (IMMULITE- imunochemiluminiscenčná metóda tretej generácie).

Ženská prostata, v porovnaní s rovnakou žľazou muža, nemá len rovnakú štruktúru, expresiu prostatových markerov, enzýmové vybavenie, tú istú exokrinnú a možnú aj neuroendokrinnú funkciu, ale môže byť aj zdrojom rovnako závažných „prostatových“ ochorení, t.j. prostatitídy, prostatizmu, benígnej prostatovej hyperplázie a karcinómu. Expresia antigénu špecifického pre prostatu muža, t.j. PSA v ženských Skeneových parauretrových žľazách a vývodoch, štruktúrne a funkčné parametre a ochorenia rovnaké ako pri prostate muža, podávajú presvedčivé dôkazy o existencii funkčnej

prostaty u ženy a vedú k definitívnemu uprednostneniu termínu „prostata“ pred označením „Skeneove parauretrové vývody a žľazy“. Používanie Skeneovho eponyma, alebo termínu parauretrové žľazy a vývody na označenie prostaty ženy nesprávne naznačujú, že sú prítomné akési iné štruktúry ako prostata, čo napomáha vestigiálnemu postaveniu tohto ženského orgánu.

Tekutina ženských uretrových expulzií (ženského ejakulátu) obsahuje ženské prostatové komponenty, hlavne PSA a PSAP, prípadne aj fruktózu, čo najmä v prípade prvých dvoch parametrov potvrdzuje jasnú účasť ženskej prostaty pri tvorbe ženského ejakulátu. Ženský ejakulát (tekutina uretrových expulzií) vykazuje parametre dôležité pre špeciálne otázky urológie a gynekologickej urológie, chronobiológie, sexuológie, forenznej sexuológie, súdneho lekárstva a reprodukčnej medicíny. Týkajú sa problematiky inkontinencie moču u ženy, sekrečných mechanizmov ženskej prostaty, dokazovania znásilnenia ženy, exfoliatívnej hormónovej urocytológie a kvality sexuálneho života ženy s vysvetlením ženskej ejakulácie ako normálneho (a často atraktívneho) fenoménu jej sexuálneho života.

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