Andrology
Preface to the 3rd Edition

The decade that has passed since publication of the second edition of this textbook has not only witnessed a tremendous increase in knowledge within the field of andrology, but also seen the field itself achieve a newfound status within the medical profession. Knowledge and status have been of mutual benefit to the field and the growing critical mass of diagnostic and therapeutic possibilities have caused andrology to be recognized as a medical subspecialty in some countries such as Germany, Poland, and Estonia. The European Academy of Andrology (EAA) served as a pacemaker for this development and continues to strive for establishment of andrology as a clinical field. Well-designed curricula and qualifying examinations have contributed to the official recognition of andrology as a specialty. This recognition of the field helps patients with andrological problems to find the specialist they seek.

This textbook summarizes the current state of knowledge in the field of andrology. It is a source of knowledge to all those who are or want to become andrologists. In addition, as andrology is clearly an interdisciplinary field, this book may serve as a compendium and source of reference for all those physicians and biologists active in neighboring areas, who want to obtain an overview of andrology and who require information on special problems. The extensive references are timely and up to date.

The majority of authors of the previous two and the current third edition of this book are coworkers or collaborators of the Institute of Reproductive Medicine of the University of Münster, which was renamed the Centre for Reproductive Medicine and Andrology of the University in 2008. The “Münster School of Andrology” provides the common basis of the work rooted in over 30 years of scientific and practical experience.

The editors are indebted to the authors for their input in creating this third edition. We also thank the Springer team, especially Dörthe Mennecke-Bühler and Claus-Dieter Bachem for producing this attractive volume. Maria Schalkowski (Münster) deserves special mention for her untiring efforts to make this book become a reality.

Eberhard Nieschlag
Herrman M. Behre
Susan Nieschlag
Münster and Halle
October 2009
Andrology, as the science of male reproductive function and dysfunction, has experienced exceptional progress in recent years. Especially clinical applications of molecular biology and molecular genetics to male infertility and hypogonadism, the “invention” of intracytoplasmatic sperm injection (ICSI) as a treatment of male infertility and the introduction of effective oral medication for erectile dysfunction can be considered major breakthroughs. The magnitude of these developments, along with many others, prompted this second edition of Andrology: Male Reproductive Health and Dysfunction.

As in the first edition, the textbook follows the principles of evidence-based medicine and provides a firm scientific basis for clinical andrology. As before, we consider andrology as part of the comprehensive field of reproductive medicine, but we are convinced that it can coexist alongside gynecology only when it qualifies as a scientific and clinical field in its own right. For this reason this textbook seeks to strengthen andrology as a field, along with acting as a source of information.

All chapters have been thoroughly revised and extended; some were completely rewritten. Among the new features: the diagnostic sections reflect the newest WHO guidelines on semen analysis (1999); the sections on testicular biopsy were enlarged by a contribution from Professor A.F. Holstein (Hamburg); the pathophysiological basis of numerous disease entities is explained by insights newly gained from molecular biology and molecular genetics; ICSI treatment and its genetic ramifications are thoroughly discussed; other therapeutic methods, especially the treatment of varicocele, have been brought up to date. Without disregarding the art of exact diagnosis, medical treatment of erectile dysfuntion is covered in detail. Because of increasing interest, the chapters on male contraception and male senescence have been expanded. As in the earlier edition, a chapter on the ethical aspects of reproductive medicine completes the picture. The layout of the first edition, with typographical features designed for the reader’s orientation, has been maintained and is supplemented with color illustrations and figures, contributing to a lively presentation.

In order to provide a uniform work, we selected authors who are either past or current colleagues at the Institute of Reproductive Medicine at the University of Münster or who work at collaborating centers. The interest shared by the authors contributed to a uniform presentation of andrology and prompted reviewers of the first edition to speak of a “Münster School of Andrology.” The editors are grateful to all contributors for their excellent cooperation. As before, Susan Nieschlag, M.A., as editorial assistant, contributed a high degree of professionalism and tireless effort to this second edition. The word-processing skills of Angelika Schick, Barbara Bahnes, and Maria Schalkowski, secretaries at the Institute, deserve special mention. Particular
thanks go to Dr. Trevor Cooper and Dr. Andrea Wagenfeld for their punctilious and professional review of all manuscripts. Finally, we are grateful to Dr. Udo Lindner, Dr. Annette Zimpelmann, and Axel Treiber of Springer-Verlag for their enthusiastic support of the present volume. They encouraged our input, which was rewarded by speedy production of the volume.

Many suggestions for the second edition were provided by reviewers and readers, and we gratefully incorporated their ideas. This dialogue was particularly helpful and we would like to repeat our earlier request for critical suggestions. We hope that the reader will again use this volume to his own advantage and to that of his patients.

Eberhard Nieschlag
Hermann M. Behre
Münster, February 2000
The present volume sets forth the basic principles and the clinical practice of andrology as the science of male reproductive health and dysfunction.

This book is to be viewed against the background of the development of reproductive medicine and andrology at our center in Munster, Germany. Following the establishment of the Clinical Research Group for Reproductive Medicine by the Max Planck Society in 1980, which was succeeded by the Institute of Reproductive Medicine at the Westphalian Wilhelms University in Munster in 1989, a center of andrological research and patient care developed, based on close cooperation between basic scientists and physicians. This close cooperation between basic research and clinical practice aims to apply scientific methods to explore the reproductive functions of the male and to harness them for mankind, both in positive and negative terms. The combination of research and patient care necessitates close contact between university clinics and institutes, in particular, the Women’s Hospital, Department of Urology, Institute of Human Genetics, Institute for Clinical Radiology, Institute for Medical Microbiology, and Institute for Medical Psychology. In addition, the Institute of Reproductive Medicine participates in the network of the WHO Collaborating Centers (since 1987) and the Training Centers for Clinical Andrology of the European Academy of Andrology (since 1994).

Over the course of time we have accumulated experience in patient care and have developed clinical principles, which have been published in numerous articles, reviews, and book chapters. We consider the time ripe to present our experience and view of andrology in a textbook.

In order to present a unified volume we chose our authors either from past or present coworkers of the Institute of Reproductive Medicine or from cooperating institutions. Past or present coworkers include Dr. Martin Brinkworth, Dr. M. Angelines Castel, Dr. Trevor G. Cooper, Dr. Jorg Gromoll, Dr. Axel Kamischke, Dr. Eckhard Leifke, Priv.-Doz. Dr. Alexander Lerchl, Dr. Carl-Joachim Partsch, Dr. Claus Rolf, Dr. Manuela Simoni, Priv.-Doz. Dr. Gerhard F. Weinbauer, and Dr. Ching-Hei Yeung as well as Priv.-Doz. Dr. Christian De Geyter, Dr. Maria De Geyter, Dr. Sabine Kliesch, Priv.-Doz. Dr. Ulrich A. Knuth, and Dr. Dieter Meschede. Professor David J. Handelsman spent a 9-month sabbatical at our Institute while the book was being written. Intensive cooperation with the Women’s Hospital under the directorship of Professor Dr. Hermann P. G. Schneider is of essential importance for patient care. We are closely connected to the University Urology Clinic, and this cooperation is reflected in the authorship of Professor Dr. Lothar Hertle, Priv.-Doz. Dr. Hermann van Ahlen, and Dr. Frank Oberpenning. Our patients receive psychological counseling from Professor Dr. F.A. Muthny, and Dr. Regina Oberpenning, of the Institute of
Medical Psychology. Professor Dr. Klaus Demmer, a native of Munster, has advised the Institute on ethical questions for many years. Susan Nieschlag, M.A., serves as the Institute’s editor and has contributed editorial input for this volume as well. She has translated some chapters in their entirety and language-edited all others. We hope that the intellectual background shared by the authors will help to present a unified picture of andrology in this book. We thank all authors for their speedy cooperation. Strict adherence to deadlines contributed to the volume’s unified appearance and to its timeliness. The Institute’s secretaries, Kerstin Neuhaus, and Angelika Düthmann deserve a great measure of thanks for word processing. Thanks too go to the members of the Springer Publishing House, Dr. Carol Bacchus, Marga Botsch, and Bernd Reichenhaler, who were responsible for the book’s appearance and prompt handling. We hope that the reader will use this volume to his own advantage and to that of his patients. We are grateful for all comments and criticism.

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Münster
November 1996
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1.1 Definition of Andrology

Andrology is defined as the branches of science and medicine dealing with reproductive functions of the male under physiological and pathological conditions (Statutes of the European Academy of Andrology).

If this definition were to be interpreted in the context of sociobiology, considering reproduction the central task of life to which the entire organism is devoted (e.g., Dawkins 2006), andrology would be a broad field. Generally and also for the purpose of this book, andrology is considered the science and practice of dealing with male reproductive functions and their disturbances in the strict sense. Following the definitions of the WHO, male reproductive health is the subject of andrology.

The central topics of andrology are:
(1) Infertility, (2) hypogonadism, (3) male contraception, (4) erectile dysfunction, and (5) male senescence (Fig. 1.1).

1.2 Andrology, Gynecology, Reproductive Medicine: Reproductive Health

Every layman knows that a man and a woman are necessary to produce offspring. However, a barren couple does not necessarily know whether the affliction lies on the male or the female or both sides. Therefore, it would be sensible for the couples to turn to a physician in a discipline dealing holistically with problems of infertility.
No matter how logical this concept may appear to the patients, medicine has barely offered appropriate solutions. Most often the individual partners of a barren couple continue to consult physicians of different disciplines in order to be diagnosed and treated. For the woman it is relatively easy to find a competent physician, since gynecology is a traditional field of medicine and amply represented. It is much more difficult for the afflicted male. If he suspects problems of infertility on his part, he does not know immediately to whom he should turn. One third first consults the primary health care physician or family practitioner, one quarter turns to (his wife’s) gynecologist and the remaining patients consult urologists (Bruckert 1991) and perhaps endocrinologists. As a firm discipline of medicine andrology is established in very few countries. It is a recognized field only in Poland and Estonia; in Italy it is a speciality, practiced, however, within the frame of endocrinology. In addition, andrology is a speciality in Egypt and Indonesia. Finally, in Germany, in 2003 the Federal Medical Board published guidelines for specialization including andrology and by 2005 andrology was established in all 16 State Medical Boards as a subspeciality of urology, endocrinology/ internal medicine, and dermatology, the qualifications for which can be acquired after an 18-month postgraduate course which can be reduced to 12 months if andrological training had been included in the basic courses.

The European Academy of Andrology (EAA), founded in 1992, has established over 20 training centers in Europe.

These centers offer a 2-year course in which qualified physicians can acquire the specialty training required for the EAA examination. It is the hope of the EAA that this will gradually lead to official recognition of the field throughout Europe. Recent acceptance of the EAA training objectives by the German Federal Medical Board is an acknowledgement of this goal.

From the point of view of the afflicted couple, a specialized interdisciplinary field of reproductive medicine would seem to offer a solution. A few such services are in fact available at universities or in individual practices. It is, however, seldom that both partners of an infertile couple are cared for by one person; usually an interdisciplinary team consisting of an andrologist and a gynecologist working together represent reproductive medicine. At the same time there is a tendency to recognize that, because reproductive medicine has become so complex and comprehensive over recent decades, a discipline encompassing both sexes is imaginable. Especially those gynecologists working in this field have distanced themselves so far from oncology and obstetrics that they can conceive of an independent specialty of reproductive medicine including andrology.

The World Health Organization (WHO) considers the couple as a single entity in its definition of "reproductive health," which it defines as freedom from disease and disturbances of reproductive functions, both in the male and in the female. As part of its concept of reproductive health the WHO postulates that reproduction should take place in an environment of physical, mental and social well-being. In addition, in its demand for self-determination of the number of children by the couple, it assumes that both partners have free access to reliable contraceptive methods. In its research program on human reproduction the WHO devotes itself to problems both in the female and in the male. Whereas in previous years the investigation of female reproductive functions stood in the foreground, more recently studies on male fertility have been given equal weight.

As desirable as care for the infertile couple by only one attending physician may appear, it should not be overlooked that, apart from the initial consultation and those eventually occurring during the course of treatment, the actual investigations of husband and wife do
not necessarily proceed in synchrony. Only when techniques of assisted fertilization, which, however, are still only appropriate for selected couples, are applied is closest cooperation mandatory. Moreover, andrology covers certain aspects of male reproductive functions which can be treated largely without recourse to the partner, e.g., replacement therapy in hypogonadism, delayed pubertal development, erectile dysfunction, contraception and male senescence. For this reason, in addition to gynecology, the part of reproductive medicine dealing with the male, i.e., andrology, is indispensable. Moreover, the field of reproductive gynecology is so comprehensive that it cannot adequately deal with problems of the male as well. While not losing sight of the goal of an integrated field of reproductive medicine, at present, the development of gynecology and andrology as separate fields seems to offer the most advantages, not forgetting, however, that both fields should cooperate most closely in the care of the infertile couple, e.g., within the framework of a center for reproductive medicine. When treatment consists of assisted reproduction, German guidelines (Bundesärztekammer 2006) require that one of a minimum of three physicians must be an andrologist. For practical purposes this means that an andrologist must be part of every center of reproductive medicine.

1.3 Infertility, Subfertility, Sterility, Fecundity: Definition of Terms

When speaking of disturbed fertility, certain concepts must be introduced and defined. It must also be taken into consideration that terminology may change over time.

Fertility refers to the capability to conceive or induce a pregnancy. Fecundity refers to the probability of producing a live birth arising from a given menstrual cycle.

Infertility is the term used when a couple fails to induce a pregnancy within 1 year of regular unprotected intercourse. Primary infertility defines the condition when no pregnancy at all has been achieved, and secondary infertility means no further pregnancies have occurred. The term infertile can be applied to both men and women.

In addition to infertility, the term sterility is also used. Historically, it is an even older term. However, infertility is the more general term which may also include sterility (Templeton 1992). “Infertility” is doubtless the most accurate description for childlessness. “Sterility,” on the other hand, is a term with additional meanings as well (e.g., in the context of hygiene). “Infertility” also has the advantage of making less of a value judgement and avoids terminological ambiguity, for infertility and sterility are not separable nosological entities. The change in usage is reflected by the fact that up to 1982 the database Medline used “sterility”; since then “infertility” has been in use as a headline word (National Library of Medicine 1993).

One objection to general use of the concept of “infertility” as opposed to “fertility” is that what is meant may actually be subfertility, as basically, the ability to sire or conceive may actually exist, e.g., with another partner. However, here too it is difficult to delineate sharply between definitions. The suggestion to drop the term “infertility” and replace it by grades 0–4 and percentage of fertility chances lacks general acceptance as there are no clear criteria to define the percentages (Habbema et al. 2004).

For these reasons in this volume we use the term infertility to refer to disturbed fertility in general and we speak of it when, within 1 year of regular, unprotected intercourse, no pregnancy occurs. One can discriminate between primary and secondary infertility, depending on whether a pregnancy has once been induced or not.

1.4 The Infertile Couple as Target Patients

Even if medical care of the female suffering from disturbed fertility is much better organized than that of the man, an analysis of the distribution of causes of disturbed fertility shows that in up to half of the couples wishing offspring the male may be implicated (Fig. 1.2). Disturbances in fertility may remain latent for years and only become evident when a couple develops a firm desire for a child. It is of particular importance that the suboptimal reproductive capacities of one partner may become evident because of the infertility of the other partner. This demonstrates the
interdependence of male and female reproductive functions, as shown schematically in Fig. 1.3.

In order to evaluate the effects of limited reproductive functions it is important to know the time span within which a “normal” couple of group 1 (Fig. 1.3) will conceive. If a young couple of group 1 plans a pregnancy it will occur within 3 months in 75% of couples (Falk and Kaufmann 1950). In unselected women attending the delivery ward of a larger German municipal hospital 70% conceived within the first 6 months and 90% conceived within the first 12 months of unprotected intercourse (Knuth and Mühlendest 1991).

However, this rate decreases steadily with the age of the female partner. In women older than 25 years pregnancy occurs in 80% of couples only within 20–28 months (Bender 1953). In women whose husbands are azoospermic and who submitted to donor insemination, a rapid decline of fecundity could be found after the age of 30 (Van Noord-Zaadstra et al. 1991). This is attributable to the declining ability of the egg to be fertilized. Results from assisted reproduction show that the pregnancy rates of the female partner clearly decline after the age of 35 (Fig. 1.4). However, the age of the male partner also influences the occurrence of pregnancy. The “time to pregnancy” (TTP), an important parameter for characterizing the fertility of a couple, increases when the male is over 40 independent of the woman’s age (see Chap. 14).

Moreover, the frequency of coitus plays an important role. When both semen parameters and female factors are normal, the interval to conception decreases with the frequency of coitus as long as sperm production is not exhausted. Partners complaining of involuntary childlessness of more than 12 months’ duration and in whom andrological factors have been excluded achieve a maximum conception rate when coitus takes place two to three times per week (McLeod et al. 1955). When sperm production is limited, however, this direct relationship is no longer valid.

Also the timing of coitus is of great importance. Most conceptions occur on the day of ovulation and the two preceding days, few conceptions, if intercourse takes place on days 3–5 before ovulation, but no conceptions after the day of ovulation (Wilcox et al. 1995).

It follows that younger couples should be examined only after they have tried to found a family for at least 1 year. Should the woman be over 30 years and/
or the male partner be over 40, investigations may be initiated earlier. In industrialized nations married childless couples tend to belong to the latter group as the average age at marriage is increasing. Whereas in Germany it was 23.7 for women and 25.9 for men in 1975, by 2005 it had increased to 29.7 for women and 32.6 for men. However, in the meantime 30% of all German children are born to unmarried couples so that the age at marriage no longer corresponds to the age at which parenthood is to be realized. The age of the couples visiting the fertility clinic rises correspondingly. Thus the average age of the female partner at her first visit to our center in 1979 was 28.0 years and 32.4 years in 2005 and her partner’s age was 29.4 and 35.8 years (Fig. 1.5).

The entity represented by the couple with disturbed fertility must not be ignored. For this reason, although this volume deals primarily with andrology, it also provides an overview of diagnosis and therapy of female infertility (see Chap. 20).

### 1.5 Prevalence of Infertility

Information on the prevalence of infertility indicates great variability and only few reliable data are available (review in Schmidt and Münster 1995; Templeton 1992). Infertility shows considerable geographic variation; according to WHO primary infertility is lowest in the Middle East and highest in Central Africa (Farley and Belsey 1988). No absolutely firm data are available for Germany. Estimations assumed a prevalence of (primary and secondary) infertility of up to 15% and more of all couples of reproductive age (Bruckert 1991; Juul et al. 1999). There are marked regional variations within
Europe and even between East and West Germany (Juul et al. 1999). Conversely, little change has occurred in the “time-to-pregnancy” curves which have been constructed over centuries in various populations (Fig. 1.6).

Often it is asked whether the incidence of infertility is increasing. Reports about a presumed decline in sperm numbers contribute to this speculation and are discussed critically in Chap. 19. Whereas some epidemiologists consider the problem as too complex and available data as inadequate (Sallmén et al. 2005), there are solid analyses which find a decline of infertility in the western world. With reference to a 12-month period of infertility from 1982 to 2002 of married American 15–44 year-old women, a representative survey by the USA National Survey of Family Growth found a decline of infertility from 8.5% to 7.2% (Stephen and Chandra 2006). Parallel tendencies are reported from Sweden and Great Britain (Joffe 2000; Scheike et al. 2008). The reasons presumed are improved sexual and general education, a decline in smoking, and the containment or early treatment of venereal diseases. The application of ART has become so widespread that its success also provides demographic impulses (Hoorens et al. 2008; Ziebe and Devroey 2008). Finally, improved upbringing and education of patients play a decisive role so that they are no longer willing to accept their fate but take an active role in searching for solutions and medical aid.

The proportion of couples seeking medical treatment for infertility is estimated at 4–17%. Ultimately 3–4% of all couples remain involuntarily childless at the end of their reproductive life phase (Templeton 1992).

As male causes for infertility are found in half of involuntarily childless couples, it must be assumed...
that about 7% of all men are confronted with the problem of disturbed fertility in the course of their lives. This means that the prevalence of infertility in men clearly exceeds that of diabetes mellitus (types I and II), which is often considered almost endemic.

The incidence of individual disturbances of fertility will be dealt with in connection with the diseases discussed in the following chapters.

1.6 Evidence-Based Andrology

There are many reasons why so much time passed before andrology developed into an independent specialized medical discipline. One important reason is that, until recently, diagnostic and therapeutic measures had not reached a critical mass great enough to justify establishment of an independent field. It is a fact that research efforts investigating the physiology and pathology of male reproductive functions were not undertaken systematically before the 1960s and pathophysiological concepts explaining individual diseases only gradually emerged. One factor contributing to the situation was also that andrological diagnostic techniques lacked standardization and tended to produce vague diagnoses. At least 30% of cases of disturbed male fertility still remain etiologically unclear and are referred to as idiopathic infertility (see Chaps. 4 and 22).

These shortcomings, characterizing andrology as well as other specialties, often meant that the physician’s personal authority and experience tended to become the dominating factor in management decisions. The situation makes it tempting for some physicians to apply innumerable empirical therapeutic procedures whose effectiveness remain uncertain. Many errors in judgement – not only in andrology – can be attributed to this attraction to meddlesome but unproven treatments.

With the advance of basic research and scientific thinking in andrology, the dilemma became obvious to those actively practicing clinical andrology and a “new andrology” operating on scientific thinking and rationally based medical practice was called for. “Evidence-based andrology” developed simultaneously with the beginnings of “evidence-based medicine,” which is increasingly becoming a pervasive force in all fields of medicine. It marks a gradual shift of paradigm in clinical medicine.

The term “evidence-based medicine” signifies that clinical decisions must be based on results from controlled clinical studies and applied statistics and not rely predominantly on intuition, empiricism and traditional protocols (Antes 1998; Cochrane Collaboration, www.cochrane.org).

Whereas they remained rare in the 1960s, today controlled, prospective, randomized and, if possible, double-blind clinical studies are the accepted standard for evaluating the effectiveness of a diagnostic or therapeutic measure. No medication, no interventional measure nor any diagnostic test should be incorporated into clinical practice if its effectiveness has not been proven by appropriate controlled studies. (There will, of course, be exceptions to this, as e.g., hormonal replacement therapy for which the physiological hormone levels in serum represent the target parameters.) The highest degree of evidence is achieved when several controlled studies deliver identical results in a meta-analysis. While the clinical andrologist found it particularly difficult to incorporate this shift of paradigm into the decision-making process, the exponential increase in clinical studies concerning infertility treatment in the 1990s showed that this concept is finally becoming established in andrology as well.

The details of carrying out controlled clinical studies cannot be dealt with here. The most important elements are the studies’ design and statistical evaluation. Over and beyond the problems generally caused by performing controlled studies in other fields of medicine, studies on infertility treatment face the particular difficulty that not one patient is being dealt with, a second participant must not only fulfill strict inclusion criteria, but is in fact the person in whom the end-point, pregnancy, occurs. The fact that pregnancy rates are naturally relatively low and that therefore large numbers of patients must be followed over prolonged periods of time creates special problems in controlled clinical studies on infertility treatment.

“Evidence-based medicine” also subjects pathophysiological concepts, on which diagnosis and therapeutic measures are based, to critical examination and assumes that not all pathophysiological concepts must be correct a priori. This is supported by experience from basic research showing that errors do in fact occur, that
research results may be translated prematurely into clinical strategies, thus giving rise to conceptual “short circuits.” Examples of this are demonstrated by the various ill-founded treatments of idiopathic male infertility (see Chap. 16). Evidence-based medicine demands that translation of a scientific concept into a clinical strategy be provable by rational means and that it stand up under conditions of a controlled clinical study. The goal of this volume is to follow the precepts of evidence-based medicine to the extent possible and thus it is justified to apply the term evidence-based andrology to the message of this book.

One of the important components of evidence-based andrology is **standardized diagnostics**, making results within one laboratory as well as between laboratories comparable. In this respect the **WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edition 2009)** is a standard work and provides the basis for all andrological laboratory diagnosis. Notwithstanding that Chap. 9 of the present volume briefly describes semen analysis as a laboratory technique, the **WHO Manual must be considered as an appendix to this volume.** The methodology described provides the basis for both internal and external quality control in the andrology laboratory which even today remains in its beginning stages. It is to be hoped that other areas of andrological diagnostics will be standardized to further buttress evidence-based andrology.

As long as there is no therapy for the causal treatment of male infertility, the concept of rational andrology remains endangered. When, at the conclusion of diagnostic procedures, only techniques of assisted reproduction (ICSI and TESE) remain as possible solutions, the time and effort required for careful diagnosis may seem exaggerated. This short-sighted conclusion must be rejected emphatically, as many treatable pathologies may be discovered by meticulous investigations. A drastic example are testicular tumors of which 200 were discovered among infertile men at an andrology clinic, but only because thorough diagnosis including ultrasound was performed.

While it is desirable that andrology increasingly be given a firm scientific base and that diagnostic and therapeutic measures be tested by their results, it must not be forgotten that the **patient or couple** requiring care remains the **central point of medical attention.** This includes providing time for extensive counselling, for clarifying physical and pathological facts, for explaining diagnostic findings and therapeutic measures, for answering questions concerning sexuality, for exploring the importance of a child to each partner and to the couple. The patient must be convinced by practice that precisely these aspects are of greatest importance to the physician, whereas scientific validity of his management must be the unspoken precondition of professional expertise underlying patient-doctor interaction.

The **placebo-effect of medical advice and attention** must never be underestimated. This assumes that the **placebo be defined** as a measure lacking a specific effect, but which will nevertheless have a significantly greater influence on the desired outcome than no measure at all (Gotzsche 1994). It must be stressed that the placebo so defined has no negative connotation, of which it is often accused. The meaningfulness of such a placebo-effect becomes clear from results of a controlled study on therapy for varicocele: patients subjected to surgical or angiographic intervention showed the same pregnancy rates as those only counselled and examined at regular intervals (Nieschlag et al. 1998).

Knowing the placebo-effect of medical attention and applying it in treatment strategies is just as much a part of evidence-based andrology as its scientific basis.

When judging the success of therapy it should also be considered that infertility does not represent an absolute diagnosis, but that factors related to time may play an important role. In the course of time pregnancies may occur spontaneously, without any medical intervention. When couples on the Dutch island of Walcheren consulting a primary care center for infertility were left “untreated,” after 2 years the spontaneous pregnancy rate was 40% (Snick et al. 1997). When patients at a tertiary fertility center were treated similarly, after the 2-year observation period the pregnancy rate was 20% (Canadian Infertility Therapy Evaluation Study; Collins et al. 1995) (**Fig. 1.7**). The figures show that the selection of couples plays an important role and that even at a specialized center spontaneous pregnancies occur. Such occurrences must be taken into consideration when judging therapeutic measures; they are the basis for models predicting the chances for pregnancies (Collins et al. 1995).
1 Scope and Goals of Andrology

1.7 Male Contribution to Contraception

Providing male contraceptive methods is one of the tasks of andrology. Here the question arises whether the andrologist (or the specialist for reproductive medicine) is not at odds with himself if, on the one hand, he treats disturbed fertility and contributes to increasing birthrates, and on the other hand, provides contraceptive methods, thus influencing birthrates negatively.

The apparent contradiction is easily resolved as it is a matter of two sides of the same coin. Once the reproductive system has been understood, it can be influenced both positively and negatively. Andrology and reproductive medicine do not in the first instance concern themselves with the politics of population control. Rather they are primarily directed towards the individual and strive to help the individual couple to improve its affected reproductive functions, or to control them if they are not required. In this fashion reproductive medicine should help to reduce the suffering experienced by the couple wanting a child, while simultaneously creating the prerequisites allowing the couple to freely determine the size of its family. Finally, the medical preconditions also provides the means of curbing the world’s overpopulation as a by-product of care for the individual patients and their voluntary rights to reproductive freedom and family planning. As male contraceptive methods in particular are lacking, research leading to the development of such methods appears strongly needed.

Reproduction can be considered as compensation for death. If medical progress allows increasing numbers of people to reach reproductive age, and if, during periods of increasing birthrates the date of death continues to be pushed forward thus leading to overpopulation, then medicine must also provide contraceptive methods in order to maintain or restore a balance between reproduction and death. Andrology must contribute to this goal.

Fig. 1.7 Cumulative pregnancy rates in two populations of diagnosed, but untreated couples in centers of primary care (Walcheren) and of tertiary care (Canadian Infertility Therapy Evaluation Study CITES, Collins et al. 1995). Only pregnancies resulting in live births were computed (From Snick et al. 1997)

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2.1 Functional Organization of the Testis

2.1.1 Interstitial Compartment

The testes produce the male gametes and the male sexual hormones (androgens). The term spermatogenesis describes and includes all the processes involved in the production of gametes, whereas steroidogenesis refers to the enzymatic reactions leading to the production of male steroid hormones. Spermatogenesis and steroidogenesis take place in two compartments morphologically and functionally distinguishable from each other. These are the tubular compartment, consisting of the seminiferous tubules (tubuli seminiferi) and the interstitial compartment (interstitium) between the seminiferous tubules (Figs. 2.1 and 2.2). Although anatomically separate, both compartments are closely connected with each other. For quantitatively and qualitatively normal production of sperm the integrity of both compartments is necessary. The function of the testis and thereby also the function of its compartments are governed by the hypothalamus and the pituitary gland (endocrine regulation). These endocrine effects are mediated and modulated at the testicular level by local control mechanisms (paracrine and autocrine factors).

2.1.1 Interstitial Compartment

The most important cells of this compartment are the Leydig cells. These cells are the source of testicular testosterone and of insulin-like factor 3 (INSL3). Aside from Leydig cells, the interstitial compartment also contains immune cells, blood and lymph vessels, nerves, fibroblasts and loose connective tissue. In experimental animals this compartment comprises...
about 2.6% of the total testicular volume. In the human testis the interstitial compartment represents about 12–15% of the total testicular volume, 10–20% of which is occupied by Leydig cells. Human testes contain approximately $200 \times 10^6$ Leydig cells.

2.1.1.1 Leydig Cells

These cells were first described in 1850 by Franz Leydig (1821–1908). Leydig cells produce and secrete the most important male sexual hormone, testosterone. From the developmental, morphological and functional viewpoint different types of cells can be distinguished: stem Leydig cells as founder cell, progenitor Leydig cells as a committed stem cell, fetal Leydig cells as a terminally differentiated cell in the fetus, and adult Leydig cells as the terminally differentiated Leydig cell (Ge and Hardy 2007). Fetal Leydig cells become neonatal Leydig cells at birth and degenerate thereafter or regress into immature Leydig cells (Prince 2007). Fetal Leydig cells produce testosterone. Immature Leydig cells that mainly produce androstane-3α, 17β-diol instead of testosterone have also been described.

Adult Leydig cells are rich in smooth endoplasmic reticulum and mitochondria with tubular cristae. These physiological characteristics are typical for steroid-producing cells and are very similar to those found in other steroidogenic cells, such as those in the adrenal gland and in the ovary. Other important cytoplasmic components are lipofuscin granules, the final product of endocytosis and lysosomal degradation, and lipid
Fig. 2.2 (a) Schematic representation of the architecture of the human seminiferous epithelium. Note that the tubular wall is composed of several layers of peritubular cells (PT) and a basal lamina (BL). RB = Residual Body, LS = Late/elongating and elongated spermatids, ES = Early/round spermatids, P = Spermatocytes, Ad = A-dark-type spermatogonia (testicular stem cells), Ap = A pale-type spermatogonia; B = B-type spermatogonia, SC = Sertoli cells, JC = junctional complexes constituting the blood-testis barrier built by interconnected Sertoli cells. Modified from Ross (1985)

(b) Depicts the kinetics of the human seminiferous epithelium. Ap spermatogonia are the progenitor stem cells that enter the spermatogenic cycle (color-coded). All descendents of this progenitor cell represent a single clone of germ cells. Ad = A-dark-type spermatogonia, B = B-type spermatogonia, Pl = preleptotene spermatocyte; L = leptotene spermatocyte; Z = zygotene spermatocyte; D = diplotene spermatocyte. It takes 4–4.6 cycles (“generation” on the y-axis, denoted as Start and End) until a sperm (Sd) has developed from a progenitor cell (Sa, Sb, Sc) 2° = 2nd meiotic division. (Modified from Amann 2008)
droplets, in which the preliminary stages of testosterone synthesis take place. Special formations, called Reinke’s crystals, are often found in the adult Leydig cells. These are probably subunits of globular proteins whose functional meaning is not known. The proliferation rate of the Leydig cells in the adult testis is rather low and is influenced by LH. The ontogeny of Leydig cells is not entirely clear and mesonephros, neural crest and coelomic sources have been involved. In the adult testis, Leydig cells develop from perivascular and peritubular mesenchymal-like cells and the differentiation of these cells into Leydig cells is induced by LH but also by growth factors and differentiation factors derived from Sertoli cells.

### 2.1.1.2 Macrophages. Lymphocytes and Nerve Fibers

 Besides Leydig cells, the interstitial compartment also contains cells belonging to the immune system: macrophages and lymphocytes. For every 10–50 Leydig cells one macrophage is to be found. The macrophages probably influence the function of the Leydig cells, in particular their proliferation, differentiation and steroid production, through the secretion of cytokines. Macrophages secrete stimulators and inhibitors of steroidogenesis. Proinflammatory cytokines, reactive oxygen species, nitric oxide and prostaglandins can inhibit Leydig cell function (Hales 2007). There is evidence for an involvement of neurotransmitters and related signalling factors during regulation of Leydig cell function (Mayerhofer et al. 1999). The immunological meaning of these cells for testicular physiology will be discussed under Sect. 2.5.

### 2.1.2 Tubular Compartment

**Spermatogenesis** takes place in the tubular compartment. This compartment represents about 60–80% of the total testicular volume. It contains the germ cells and two different types of somatic cells, the **peritubular cells** and the **Sertoli cells**. The testis is divided by septa of connective tissue into about 250–300 lobules (Fig. 2.1), each one containing 1–3 highly convoluted seminiferous tubules. Overall, the human testis contains about 600 seminiferous tubules. The length of individual seminiferous tubules is about 30–80 cm. Considering an average number of about 600 seminiferous tubules per testis and an average length of the tubuli seminiferi of about 60 cm each, the total length of the tubuli seminiferi is about 360 m per testis, i.e., 720 m of seminiferous epithelium per man.

#### 2.1.2.1 Peritubular Cells

The seminiferous tubules are covered by a lamina propria, which consists of a **basal membrane**, a layer of collagen and the **peritubular cells (myofibroblasts)**. These cells are stratified around the tubulus and form up to concentrical layers that are separated by collagen layers (Fig. 2.1). These characteristics differentiate the human testicle from the majority of the other mammals, whose seminiferous tubules are surrounded only by 2–4 layers of myofibroblasts. Peritubular cells produce several factors that are involved in cellular contractility: **panactin, desmin, gelsolin, smooth muscle myosin and actin** (Holstein et al. 1996). These cells also secrete extracellular matrix and factors typically expressed by connective tissue cells: **collagen, laminin, vimentin, fibronectin, growth factors, fibroblast protein** and adhesion molecules (Albrecht et al. 2006; Schell et al. 2008). The latter work established a human peritubular cell culture system demonstrating secretion of nerve growth factor and pro-inflammatory molecules, e.g., **IL-1β and cyclooxygenase-2** under the influence of **TNF-α** (Schell et al. 2008). Myofibroblasts are poorly differentiated myocytes with the capacity of spontaneous contraction. Mature sperm are transported towards the exit of the seminiferous tubules by contraction of these cells and several regulators of cell contractions are reported, e.g., **oxytocin**, oxytocin-like substances, **prostaglandins**, androgenic steroids, **endothelins**, endothelin converting enzymes and endothelin receptors. Peritubular contractility is mediated by endothelin and this effect is modulated by the relaxant peptide **adrenomedullin** produced by Sertoli cells (Romano et al. 2005). Mice with selective peritubular cell androgen receptor deficiency revealed defects in contractility-related genes, e.g., endothelin-1 and endothelin receptor A and B, adrenomedullin receptor and **vasopressin** receptor 1a (Zhang et al. 2006).

Disturbances of testicular function and decreased or absent spermatogenic activity are associated with a
thickening of the layer of collagen fibres and of the material present between the peritubular cells. When this is the case, the tubular wall becomes fibrotic or – based on the histological appearance – hyalinized. The decrease of testicular volume involves folding of the wall along the length of the tubuli seminiferi, thereby causing an enlargement of the tubular diameter. This becomes particularly evident when fluid is injected into regressed seminiferous tubules. Tubular diameter increases and tubular wall thickness decreases (Schlatt et al. 1999). An interaction between testicular mast cells and peritubular cells leading to fibrotic changes of the seminiferous tubular wall has been suggested (Albrecht et al. 2006). Peritubular and interstitial fibrosis incidence correlated progressively with spermatogenic damage in testis from vasectomized men (Raleigh et al. 2004).

2.1.2.2 Sertoli Cells

Sertoli cells are somatic cells located within the germinal epithelium. In adulthood these cells are mitotically inactive. They are named after Enrico Sertoli (1842–1910), the Italian scientist who first described these cells in 1865 and, due to their prominent cytoplasmatic projections and ramifications called them “cellulae ramificate”. These cells are located on the basal membrane and extend to the lumen of the tubulus seminiferus and, in a broad sense, can be considered as the supporting structure of the germinal epithelium. Along the cell body, extending over the entire height of the germinal epithelium, all morphological and physiological differentiation and maturation of the germinal cell up to the mature sperm take place. Special cytoplasmic structures sustain alignment and orientation of the sperm during differentiation. About 35–40% of the volume of the germinal epithelium is represented by Sertoli cells. The intact testis with complete spermatogenesis contains 800–1200 \( \times 10^6 \) Sertoli cells (Zhengwei et al. 1998a) or approximately \( 25 \times 10^6 \) Sertoli cells per gram testis (Raleigh et al. 2004).

Sertoli cells synthesize and secrete a large variety of factors: proteins, cytokines, growth factors, opioids, steroids, prostaglandins, modulators of cell division etc. The morphology of Sertoli cells is strictly related to their various physiological functions. Cytoplasm contains endoplasmic reticulum both of the smooth (steroid synthesis) and rough type (protein synthesis), a prominent Golgi apparatus (elaboration and transport of secretory products), lysosomal granules (phagocytosis) as well as microtubuli and intermediate filaments (adaptation of the cell shape during the different phases of germ cell maturation). It is generally assumed that Sertoli cells coordinate the spermatogenic process topographically and functionally. On the other hand, more recent data support the contention that germ cells control Sertoli cell functions. At least the time pattern of germ cell transitions and development during the spermatogenic cycle seem to be autonomous as suggested from heterologous germ cell transplantation studies (Nagano et al. 2001). One spermatogenic cycle lasts about 8 days in mice and 12–13 days in rats. Notably, the cycle duration of rat germ cells transplanted into mouse testis remained 12–13 days whereas that of the host germ cells was maintained at 8 days (Franca et al. 1998).

Another important function of Sertoli cells is that they are responsible for final testicular volume and sperm production in the adult. Each individual Sertoli cell is in morphological and functional contact with a defined number of sperm. The number of sperm per Sertoli cell depends on the species. In men we observe about 10 germ cells or 1.5 spermatozoa per each Sertoli cell (Zhengwei et al. 1998a). In comparison, every macaque monkey Sertoli cell is associated with 22 germ cells and 2.7 sperm (Zhengwei et al. 1997, 1998b). This suggests that within a certain species a higher number of Sertoli cells results in a greater production of sperm and testis size, assuming that all the Sertoli cells are functioning normally. In contrast, as determined by flow cytometry, testicular cell numbers were very similar across several primate species, suggesting that testis size is the main determinant of total germ cell output (Luettjens et al. 2005).

Stereological investigations suggest that the number of Sertoli cells in men increases until the 15th year of life. In the prepubertal cynomolgus monkey and the rhesus monkey, Sertoli cells exhibit little mitotic activity, whereas some proliferative activity of A-type spermatogonia occurs in the quiescent testis. Sertoli cell proliferation is markedly activated when exposed to gonadotropin activity (Plant et al. 2005; Schlatt et al. 1995). Both Sertoli cell number and expression of markers of cell division are stimulated by these hormones. The division of Sertoli cells ends when the first germ cells undergo meiotic division and Sertoli cells have built tight junctions between each other, the
connexin-43, a predominant gap-junction protein, prevents Sertoli cell maturation associated with continued division of Sertoli cells and spermatogenic arrest beyond spermatogonial development (Brehm et al. 2007; Sridharan et al. 2007). Expression of Sertoli cells markers such as transferrin, androgen-binding protein and junctional proteins such as N-cadherin, connexin-43, gelsolin, laminin-γ3, occludin, testin, nectin, zyxin and vinculin is androgen-dependent (Zhang et al. 2006). It appears that several of these components are involved in establishing the blood-testis-barrier but also in the release of sperm and subsequent remodelling of the Sertoli cell-germ cell junctions (Yan et al. 2008). In the rat, the experimental prolongation of the division phase of Sertoli cells, produced for example by a deprivation of thyroid hormones, results in an increase of testicular weight and sperm production by about 80%. On the other hand, the decrease of Sertoli cell numbers such as that produced by an antimitotic substance leads to a reduction of testicular volume and sperm production. Patients with Laron dwarfism suffer from a disturbance of thyroid function and growth hormone/IGF-I deficiency, and often have testicles larger than normal.

Through the production and secretion of tubular fluid Sertoli cells create and maintain the patency of the tubulus lumen. More than 90% of Sertoli cell fluid is secreted in the tubular lumen. Special structural elements of the blood-testis barrier prevent reabsorption of the secreted fluid, resulting in pressure that maintains the patency of the lumen. Sperm are transported in the tubular fluid, the composition of which is known in detail only in the rat (Setchell 1999). Unlike blood, the tubular fluid contains a higher concentration of potassium ions and a lower concentration of sodium ions. Other constituents are bicarbonate, magnesium and chloride ions, inositol, glucose, carnitine, glycerophosphorylcholine, amino acids and several proteins. Therefore, the germ cells are immersed in a fluid of unique composition.

The basolateral aspect of neighboring Sertoli cells comprises membrane specializations forming a band sealing the cells to each other and obliterating the intracellular space (occluding tight junctions). The physiological function of the blood-testis barrier has been proven in experiments showing that dyes or lanthanum applied outside the barrier could diffuse only up to the tight junctions without reaching the lumen of the seminiferous tubules. The closure of the blood-testis barrier coincides with the beginning of the first meiosis in the germinal cells (preleptotene, zygotene) and with the arrest of proliferation of Sertoli cells. Through the blood-testis-barrier the seminiferous epithelium is divided into two regions which are anatomically and functionally completely different from each other. Early germ cells are located in the basal region and the later stages of maturing germ cells in the adluminal region. During their development germ cells are displaced from the basal to the adluminal compartment. This is accomplished by a synchronized dissolution and reassembly of the tight junctions above and below the migrating germ cells.

Two important functions are postulated for the blood-testis-barrier: the physical isolation of haploid and thereby antigenic germ cells to prevent recognition by the immune system (prevention of autoimmune orchitis, see Sect. 2.5) and the preparation of a special milieu for the meiotic process and sperm development. In certain seasonal breeders the opening and closure of the barrier depends much more on the activity of the Sertoli cells than on the developmental phase of the germinal epithelium. The constitution of the blood-testis-barrier and its selectivity in excluding certain molecules means that the cells localized in the adluminal compartment have no direct access to metabolites deriving from the periphery or from the interstitium. Therefore, these cells are completely dependent on Sertoli cells for their maintenance. This “nourishing function” could be exercised through different mechanisms: selective transport and transcytosis as well as synthesis and vectorial secretion.

### 2.1.2.3 Germinal Cells

Spermatogenesis starts with the division of stem cells and ends with the formation of mature sperm (Figs. 2.3 and 2.4). The various germ cells are arranged in typical cellular associations within the seminiferous tubules known as spermatogenic stages (Fig. 2.5) and the entire spermatogenic process can be divided into four phases:

1. **Mitotic** proliferation and differentiation of diploid germ cells (spermatogonia) (**spermatogoniogenesis**)
2. **Meiotic** division of tetraploid germ cells (spermatocytes) resulting in haploid germ cells (spermatids)
3. Transformation of spermatids into testicular sperm (**spermiogenesis**)
4. Release of sperm from the germinal epithelium into the tubular lumen (**spermiation**).